WHO Technical Report Series
937

WHO EXPERT COMMITTEE ON SPECIFICATIONS FOR PHARMACEUTICAL PREPARATIONS

Fortieth Report

World Health Organization

Geneva

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Geneva 2006

Typeset in Switzerland
Printed in Switzerland

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Geneva, 24–28 October 2005

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1. Introduction

The WHO Expert Committee on Specifications for Pharmaceutical Preparations met in Geneva from 24 to 28 October 2005. Dr Hans V. Hogerzeil, Director, Policy of Medicines and Standards, welcomed the Committee members and other participants on behalf of the Director-General, Dr LEE Jong-wook, and the Assistant Director-General, Dr Vladimir K. Lepakhin.

In his opening remarks Dr Hogerzeil thanked the Secretariat and members of the Committee for the work done in previous meetings, especially the one held in 2004, and again emphasized the importance of the Committee's work. He indicated that one of the challenges facing the Committee was to identify the global experts who could advise WHO in the field of medicines and related aspects, including standardization of guidelines.

He welcomed all individuals and organizations to the meeting and noted the intensive programme for the week, which included discussions on prequalification, monographs, guidelines on good manufacturing practices (GMP), good distribution practices, bioequivalence and donations and activities relating to strengthening regulatory activities in countries.

He presented the Committee with information on the new structure of the Department as a result of changes in December 2004 and January 2005. Activities and operations were in line with the four-year Medicines Strategy, development and promotion of standards, international treaties, the *WHO Model List of Essential Medicines* and the *WHO Model Formulary*, collection of evidence for medicines policies (including national medicines policies, access to and rational use of medicines and adherence to treatment), and promotion of consistency in pharmaceutical matters in United Nations agencies in a collaborative framework.

Dr Lembit Rägo, Coordinator, Quality Assurance and Safety: Medicines (QSM), welcomed everyone to the meeting. He recognized the contribution of various experts and institutions in the preparation of the documents for the meeting, e.g. the National Institute for the Control of Pharmaceutical and Biological Products (NICPBP), Beijing, People's Republic of China. He also welcomed other organizations and agencies such as the United Nations Industrial Development Organization (UNIDO) and thanked them for their contribution. He referred to the importance of the Committee's work as several guidelines, as well as chemical reference substances, were awaited by many countries. The progress already made was noted.

Dr Rägo remarked that there was a large amount of work to be done and that the Committee had agreed that this meeting be held one year after the previous one. He recommended that the meeting should be held annually in the future to allow the Committee to keep pace with the increasing workload and developments.

2. General Policy

2.1 Cross-cutting pharmaceuticals — quality assurance issues

2.1.1 *Quality assurance*

The Committee was pleased to note that there was good cooperation with other departments and programmes in WHO including those concerned with tuberculosis (TB), human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS), tropical diseases, control of tropical diseases and reproductive health, but was concerned to learn that there were budgetary constraints. Support was being received from the HIV/AIDS department on prequalification, monographs on antiretrovirals and other essential quality-related issues. Funding for prequalification was also available from the Stop TB Partnership, and input was also being received from the Malaria group. The Committee recommended continuation of discussions between QSM and the various programmes related to quality, safety and efficacy issues including on the need to look into products for paediatric use, and for use during pregnancy and breastfeeding.

2.1.2 *Policy, Access and Rational Use*

The Committee was pleased to note the cooperation and collaboration between Policy, Access and Rational Use (PAR) and QSM. The Committee was informed about the usefulness of its work, i.e. in the preparation of guidelines, monographs and good distribution practices and was requested to expedite the deliberations.

2.1.3 *Malaria*

The Committee expressed its appreciation of the immense contribution of various persons and groups, including the NICPBP (People's Republic of China), to the work on the development of monographs for artemisinin combination drugs, including that of artesunate. The Committee was informed of the emerging need for monographs for fixed-dose combinations (FDC) for antimalarial products.

2.1.4 *Biologicals/Vaccines*

The Committee noted that the Expert Committee on Biological Standardization was currently meeting and that an initiative was to be put forward on activities on vaccines, human blood and blood components, in vitro diagnostics and related aspects. It was emphasized that vaccines procured had to meet standards for GMP and comply with the WHO Certification Scheme for pharmaceutical products moving in international commerce. Problem areas to be addressed included the degree of specificity of GMP, conflicting norms (local versus other inspections) and escalating requirements, the need for revision of the WHO GMP, adequate cover of biologicals and the

scope for harmonization. The Committee noted that the Expert Committee on Biological Standardization was planning to review GMP for biologicals and identified the possible need for additional guidelines for blood and plasma-derived products, cell, gene and tissue therapies, computerized systems, animal testing for batch release, and a classification system for GMP deficiencies for biological medicines.

2.1.5 *Production of oral rehydration salts*

The Committee noted that WHO had provided documentation and assistance since the early 1980s in an effort to increase access to oral rehydration salts (ORS), and that this document had to be updated to reflect the revised formulation of the ORS. The United Nations Children's Fund (UNICEF) and several countries had already been procuring the new formulation since 2004. The revised document would be finalized shortly. As agreed at the thirty-ninth meeting of the Committee, *The International Pharmacopoeia* monograph was being rewritten to reflect the revised formulation.

2.1.6 *Other clusters and departments*

Tuberculosis

The Committee endorsed the constructive collaboration between the Stop TB Partnership Secretariat, the Global Drug Facility (GDF) and PSM/QSM, with specific emphasis on prequalification, joint training workshops for manufacturers, preparation of a list of consultants, prequalification of manufacturers of active pharmaceutical ingredients (APIs) (e.g. rifampicin and ethambutol) and quality control (expertise of GDF). The Committee was informed of a problem with the quality of TB products. Only eight out of 100 product dossiers submitted for assessment in the prequalification project had been prequalified to date. Some products had failed on basic aspects including stability. It noted that a new formulation had been developed to ensure that rifampicin was properly absorbed in the presence of isoniazid. Formulations such as triple fixed-dose combinations (3FDCs) were being used in some countries although these products have not yet been included in the *WHO Model List of Essential Medicines*. Training workshops had been organized in India, Malaysia and Ukraine (for countries in the regions). Another workshop was planned for the People's Republic of China in January 2006.

HIV/AIDS department

The Committee noted the information presented by the HIV/AIDS department. The importance of the quality of APIs was stressed, including the necessity for appropriate analytical methodology. It was noted that the development of monographs for APIs and final dosage forms, including fixed-dose combinations (FDCs), together with the introduction of alterna-

tive tests would contribute to better quality of products and would further facilitate technical capability in developing countries.

2.1.7 *International collaboration*

International Atomic Energy Agency

The Committee acknowledged with thanks the collaboration and help that the International Atomic Energy Agency (IAEA) was providing to WHO with the monographs on radiopharmaceuticals for inclusion in *The International Pharmacopoeia*. It noted that a meeting had been held early in 2005 and that model individual monographs to complement the general monograph were discussed. Key products were being looked at as part of a prioritization programme and a list of 30 products had been prepared which will receive priority attention. The Committee agreed to provide input and comments on the format and the contents of the monographs.

United Nations Children's Fund

The Committee noted some of the activities of the United Nations Children's Fund (UNICEF) related to pharmaceuticals. These include qualification of suppliers, specifications for products, contracts with suppliers and the management of warehouses. It was noted that UNICEF uses the WHO lists of prequalified products and manufacturers in the procurement of HIV/AIDS products and vaccines. Due to the lack of prequalified antimalarial products, an interim assessment process was used. Another problem identified was that some products included in the WHO Model List of Essential Medicines were not available on the market.

United Nations Industrial Development Organization

The Committee was informed of the activities of the United Nations Industrial Development Organization (UNIDO). It was reported that although there was a growth in trade, the participation of developing countries had remained marginal. There was a lack of competitive supply, low capability for producing industrial goods according to specifications, and a lack of product standards and testing capabilities. The service module of UNIDO includes capacity building in the area of standards, metrology, testing and accreditation. Competitiveness was enhanced through improvements in quality and productivity, and assistance in global contracting. The Committee noted examples of UNIDO projects. In the last years UNIDO had developed an approach and methodologies for trade capacity building for developing countries. The Committee supported the need for closer cooperation between WHO and UNIDO.

The World Bank

It was noted that the World Bank was actively involved in capacity building of quality control laboratories especially in Africa. The Committee en-

dorsed this programme and recommended closer cooperation between the World Bank and WHO in this area.

2.1.8 *Follow-up report to the Expert Committee*

The Secretariat reported on the progress of work since the last Expert Committee meeting. Some of the achievements and highlights included this additional meeting of the Expert Committee, finalization of specifications, and guidelines that had been prepared directly as a result of the previous meeting.

2.2 Pharmacopoeial Discussion Group

The Committee noted and endorsed the continued participation of WHO as an observer in the work of the Pharmacopoeial Discussion Group (PDG).

2.3 International Conference on Harmonisation

The Committee was informed by the Secretariat that WHO continued to be an observer to the International Conference on Harmonisation (ICH) process, steering committee and global cooperation group. It serves as a link between the ICH and non-ICH parties. Concern was raised about the future status of WHO in ICH due to the lack of resources in WHO. During discussion, the Committee expressed concerns about the universal applicability of the so-called global standards and recommended that attempts by ICH and WHO to reconcile these standards should continue.

2.4 International Conference of Drug Regulatory Authorities

It was noted that this Committee provided a mechanism to implement recommendations from the International Conference of Drug Regulatory Authorities (ICDRA).

The Committee was informed that preparations for the 12th ICDRA were under way and that it would be held in April 2006, in Seoul, Republic of Korea. Recommendations from previous ICDRA meetings were addressed, including those related to fixed-dose combinations.

The pre-ICDRA meeting on counterfeit drugs was mentioned and a follow-up meeting to the pre-ICDRA meeting was planned in order to discuss closer global cooperation in this area.

2.5 Counterfeit drugs

A report was given on the activities being undertaken to combat counterfeit drugs. Strong efforts were being made to promote the concept of improved international collaboration (e.g. a framework convention) in national and international forums, and negotiations to obtain funding and support for an international conference. The conference is planned to be held in Rome in February 2006.

The conference objectives would include:

— an international collaboration mechanism; and
— concrete action to establish an international framework convention on counterfeit medicinal products or a similar mechanism for concerted international action.

Expected outcomes would include:

— recommendations for the World Health Assembly (WHA);
— concrete action to be taken on mechanisms of collaboration;
— administrative tools;
— improved communication; and
— technical support to national authorities.

The Committee received a report on the use of mobile laboratories (vehicles) that were being used in the People's Republic of China in a national programme to curb counterfeit drugs. These vehicles contain both testing equipment (including near infrared (NIR) spectrophotometers) and a comprehensive database (including information on packaging, labelling and quality specifications).

3. Quality control — specifications and tests

3.1 *The International Pharmacopoeia* (Fourth Edition)

The Committee was informed of the progress made since the last meeting and was pleased with the improvements made to the material that had been sent to the publishers for the Fourth Edition of *The International Pharmacopoeia*.

3.1.1 *Dissolution test requirements*

Work was proceeding smoothly on meeting the needs of some monographs where dissolution testing was required. Attempts were being made to incorporate a test, where relevant, in monographs for inclusion in the consolidated Fourth Edition of *The International Pharmacopoeia*. Some of these, however, still lacked related analytical methods, which would, therefore, be added at a later date.

3.2 Pharmacopoeial monographs on antiretrovirals

An update was given on adopted monographs for antiretroviral substances. The Committee was informed that all finalized as well as draft monographs had been made available on the WHO web site.

With respect to new monographs, the normal consultation process had been followed and comments received on these monographs had been discussed during consultations prior to the present Expert Committee meeting. Ad-

ditional specific monographs, information on impurities and the availability of reference substances for antiretrovirals were also discussed.

The following monographs for drug substances were adopted subject to establishing the relevant reference materials:

- abacavir sulfate
- efavirenz
- lamivudine
- stavudine
- zidovudine.

The following monographs for finished products were adopted:

- nelfinavir mesilate tablets
- nelfinavir mesilate oral powder
- saquinavir mesilate capsules.

The Committee recommended that:

- All efforts be made to continue the development of monographs.
- The current approach of using assay methods that did not require quantitative International Chemical Reference Substances (ICRS) should be continued with respect to APIs.
- Less complex methods should be considered in future for the control of related substances and impurities to minimize the reliance on ICRS.
- Technical information concerning the chromatographic columns be made available on the WHO web site.

3.3 Quality specifications for antimalarials

The Committee was reminded that the monographs for various artemisinin derivatives were published in *The International Pharmacopoeia*, Vol. 5, 3rd ed. Proposals for amendment of some of the monographs had been received. The Committee adopted these amendments to the monographs for various artemisinin derivatives.

3.4 Quality specifications for antituberculosis drugs

It was noted that preliminary drafts of monographs for various new antituberculosis drugs had been discussed at previous meetings. The Committee discussed and adopted the monographs for the following finished dosage forms:

- rifampicin tablets
- rifampicin capsules
- rifampicin + isoniazid tablets
- rifampicin + isoniazid + pyrazinamide + ethambutol HCl tablets
- isoniazid + ethambutol HCl tablets
- rifampicin + isoniazid + pyrazinamide tablets.

The Committee noted that dissolution test methods were being developed and agreed that rifampicin should serve as the marker for dissolution testing in the relevant fixed-dose combinations, as it was the least soluble substance. For other products, standard dissolution test methods could be applied.

The Committee decided that in cases where the disintegration time is less than 10 minutes (non-rifampicin-containing products), a dissolution test would normally not be necessary depending on the biopharmaceutics classification system (BCS) category.

3.5 Specifications for other medicines

3.5.1 *Revision of published monograph on oral rehydration salts*

The proposed revision of the published monograph for ORS was presented. Changes to the formula and test methods were noted. The Committee adopted the monograph.

3.5.2 *Monograph on oral powders*

The Committee adopted, in principle, the general monograph on oral powders and noted that it would be circulated for further comments.

3.5.3 *Monographs for excipients*

Progress on the comparison of monographs for excipients published in *The International Pharmacopoeia* and those adopted in the Pharmacopoeial Discussion Group (PDG) process was noted. The Committee was pleased to note the offer of technical assistance by the International Pharmaceutical Excipients Council (IPEC).

3.5.4 *Specifications on herbal medicines*

A need was identified for a revision of some of the general methods included in the *Quality control methods for medicinal plants.* The draft document resulting from consultations was now ready for comment. The Committee adopted the document subject to the inclusion of minor changes in response to comments received.

The Committee was further informed of some of the activities and meetings held on quality assurance and quality control of herbal medicines.

The Committee expressed the need for capacity building in countries to facilitate improved quality assurance and quality control of herbal medicines.

3.6 Basic and screening tests

The Committee acknowledged the significant amount of laboratory studies carried out to develop and validate these tests by the WHO Collaborating Centres in the People's Republic of China, Singapore, Sweden and Thailand;

national laboratories in Norway; and collaborating university laboratories in Denmark, Germany, Ghana, South Africa and Switzerland. The Secretariat informed the Committee that due to internal resource problems these texts had not yet been finalized. The Committee endorsed that the work should continue and be finalized in close cooperation with the Collaborating Centres and that the texts be made available as soon as they are completed.

4. Quality control — International Reference Materials

4.1 International Chemical Reference Substances

The report of the WHO Collaborating Centre for Chemical Reference Substances for 2004 was presented to the Committee. The Committee noted that a number of International Chemical Reference Substances (ICRS) were distributed in 2004. The most frequently requested material was the new reference standard for artesunate (Annex 1).

The Committee recommended that the report be adopted. It also recommended that all efforts be made to maintain this important programme and endorsed the efforts made by the Secretariat to ensure financial support for the activities of the WHO Collaborating Centre for Chemical Reference Substances. It recognized that there was a need to further promote the availability and use of ICRS.

4.2 New International Chemical Reference Substances for antiretrovirals

The Committee adopted new ICRS for didanosine, efavirenz and nevirapine. It noted that work was completed on reference substances for nelfinavir mesilate and saquinavir mesilate, while for others, work was in progress.

4.3 Guidelines for secondary reference substances

The preliminary draft guidelines for the establishment of secondary reference substances were presented to the Committee. The Committee endorsed the general approach and agreed that a definition of a pharmacopoeial reference standard should be included before the text was circulated for comment.

5. Quality control — national laboratories

5.1 External quality assurance assessment scheme

The Committee was informed that the external quality assurance assessment scheme had been ongoing over the last five to six years. An

increased number of laboratories from the six WHO regions were participating in this scheme. In this (the third) series samples were mainly selected from medicines used for treating HIV/AIDS, TB and malaria. The Committee noted that positive feedback had been received from laboratories participating thus far. The Committee noted the reports on Phase 3 (Procedure 1: ultraviolet (UV) visible spectrophotometry and Procedure 2: assay by high performance liquid chromatography (HPLC)). In view of the concerns expressed on the results obtained for the HPLC procedure, the Committee suggested that the scheme should be strengthened by improving the design of the reporting form and conducting a more thorough follow-up, especially in cases where the results were outside the norm.

6. Quality assurance — Good Manufacturing Practices

6.1 Heating, ventilation and air-conditioning

The Committee received the revised second draft of the supplementary guidelines on GMP for heating, ventilation and air-conditioning (HVAC) systems, together with the comments that had been made. After extensive discussion of the comments, the Committee adopted the document, subject to the inclusion of the agreed changes (Annex 2).

6.2 Manufacture of herbal medicines[1]

The Committee was informed that the supplementary guidelines on GMP for the manufacture of herbal medicines had been reviewed and updated over recent years through an extensive consultation process. The Committee adopted the document with minor editorial corrections (Annex 3).

6.3 Validation

The Committee was provided with a revised draft of the supplementary GMP guidelines on validation and the comments received. After extensive discussion of the comments, the Committee adopted the document, subject to the inclusion of the agreed changes (Annex 4).

[1] The term "herbal medicinal products" was replaced by "herbal medicines" in accordance with the terminology used in other WHO publications.

7. Quality assurance — inspection

7.1 Training modules for inspectors

The Committee was informed that much positive feedback had been received from manufacturers, inspectorates and universities using the training modules. A large number of training workshops had been held by WHO in different regions for various countries. The Committee noted that the training materials were being revised to reflect the current GMP. Once this was completed, the materials would be translated and made available.

8. Quality assurance — distribution

8.1 Good distribution practices for pharmaceutical products

The Committee was provided with the background to the document on good distribution practices for pharmaceutical products and the comments received. After discussion of these comments, and appropriate amendments, the document was adopted (Annex 5).

9. Quality assurance — risk analysis

9.1 New approach to inspections and manufacture

The Committee was informed by the European Medicines Agency (EMEA) of a proposed approach to facilitate inspections and to avoid duplication of inspections. A GMP database was being established in the European Union by Member States that would provide information on and outcome of inspections. The database was expected to be released in 2006. Access rights were being discussed with WHO, the Pharmaceutical Inspection Co-operation Scheme (PIC/S), the European Directorate for the Quality of Medicines (EDQM) and other organizations. Different levels of access will exist including one for public access and others for national medicine regulatory authorities, WHO and PIC/S.

The Committee was reminded that WHO had already made available Public Inspection Reports of sites that were inspected as part of the prequalification procedure, where the sites were considered as complying with WHO recommendations at the time of the inspection. It was recommended that links be added between the relevant web sites to enable access to information concerning inspections and inspection outcomes.

Foreign inspections

The Committee noted with appreciation the presentation of a study by the European Federation of Pharmaceutical Industries and Associations (EFPIA) on foreign inspections. The study demonstrated the need for

rationalization of the number of inspections in order to conserve the resources of regulators and manufacturers.

10. Quality assurance — stability

10.1 Stability testing conditions

The Secretariat reminded the Committee that the WHO guidelines had been revised in the light of harmonization efforts in collaboration with ICH. Subsequently focus had been placed within regional harmonization initiatives on the recommendations for hot and humid conditions (referred to as Zone IV). After extensive discussion the Committee reached consensus that the WHO stability guidelines be amended to reflect conditions for Zone IV as follows:

— Zone IVa (30 degrees Celsius and 65% relative humidity); and
— Zone IVb (30 degrees Celsius and 75% relative humidity).

It was agreed that each individual Member State within the former Zone IV would need to indicate whether its territory should be classified as Zone IVa or IVb.

11. Prequalification

11.1 Prequalification of priority medicines

The Secretariat provided an overview of recent developments in the prequalification project. The Committee was informed that at a stakeholders' meeting held on 26 September 2005, the project had been strongly endorsed by both the Director-General and by the stakeholders. The need for streamlining of procedures used in the context of the prequalification process, especially for drugs for malaria and tuberculosis, was recognized. The importance of promoting continued awareness of the prequalification project was emphasized.

It was noted that there was now closer collaboration between WHO and the United States Food and Drug Administration (US FDA) in this area. Under a confidentiality agreement between these two parties, allowing the exchange of information, both US FDA-approved and tentatively approved antiretroviral products will be included in the WHO list of prequalified products and manufacturers. Based on the experience obtained in cooperation with US FDA, the listing through recognition of other similar stringent procedures by regulatory authorities should be considered. It was noted that there were moves in the European Union and Canada towards the implementation of similar procedures.

The Committee stressed the need for it to be kept informed of progress and developments in the prequalification project and encouraged stronger links between the prequalification project and normative work.

11.2 Quality assurance for assessment of procurement agencies — Model Quality Assurance System

As the previous draft of "Quality assurance for assessment of procurement agencies — Model Quality Assurance System" had already been adopted by the Expert Committee at its previous meeting, subject to the inclusion of the recommended changes, the final version was adopted by the Committee (Annex 6).

11.3 Prequalification of quality control laboratories

The Secretariat informed the Committee of the progress made in this area. To date 15 laboratories had expressed an interest in being assessed under this new procedure. Eight laboratories had so far been inspected and two had been listed as prequalified.

A proposal to amend the procedure, to make provision for the review of a Quality Manual (in place of a Laboratory Information File (LIF)) and to include an "inventory audit" was discussed. The Committee agreed that the proposed amended procedure be presented to the WHO Legal Counsel for comments before finalization.

11.4 Procedure for prequalification — manufacturers of active pharmaceutical ingredients

The Committee was informed that there had been a move towards the prequalification of manufacturers of APIs. The focus so far had been on ARVs, antituberculosis and antimalarial substances. A proposed amendment of the WHO GMP guidelines for APIs had been discussed previously but had not been adopted by the Committee. The Committee recommended that:

- the updated procedure for prequalification be prepared as was agreed at the last Expert Committee meeting (including assessment of API manufacturers and contract research organizations (CROs); and
- the WHO GMP guidelines for APIs be reviewed for possible amendment if required.

12. Regulatory guidance on interchangeability for multisource (generic) pharmaceutical products

12.1 Guidelines on registration requirements to establish interchangeability

The Committee noted that this document was a revision of an existing document. It adopted the document in principle, subject to the inclusion of any appropriate minor amendments resulting from comments received by 30 November 2005 (Annex 7).

12.2 Revision/update of the guidance on the selection of comparator pharmaceutical products for equivalence assessment

Subsequent to the recommendations made at the previous meeting of the Committee, the Secretariat took steps towards the revision of the published list of comparator products (published in WHO Technical Report Series, No. 902, Annex 11). The Committee noted that the updates received from the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) had been included by the Secretariat and that the list was also compared with the WHO Model List of Essential Medicines. The list of comparator products had been circulated and comments were awaited by 30 November 2005. The Committee adopted the list, subject to any minor changes based on comments received, and recommended that:

- the list be made available on the web site and kept up to date ("a living list");
- the date of each entry to the list be available on the web site; and
- where printed versions of the list are made available, the list should indicate the date of printing and refer readers to the web site for the current list.

The Committee acknowledged with thanks the cooperation of industry in the preparation of the list.

12.3 List of comparator products for prequalification

The Committee supported the guidance document entitled "Note to applicants on the choice of comparator products for the prequalification project".

12.4 Proposal to waive in vivo bioequivalence requirements for the WHO Model List of Essential Medicines, immediate release, solid oral dosage forms

The revised document was presented to the Committee. It was noted that the tables should be regularly updated to reflect the status of the WHO Model List of Essential Medicines. Minor corrections were recommended and incorporated. The Committee adopted the document (Annex 8).

The Committee recommended that:

- the tables be made available on the web site and kept in line with the WHO Model List of Essential Medicines.

12.5 Additional guidelines for organizations performing in vivo bioequivalence studies

After noting the background to the preparation of this document the Committee adopted the document in principle, subject to the inclusion of any minor changes resulting from comments received by 30 November 2005 (Annex 9).

13. Donations of medicines

13.1 Quality of medicines donated (directly from the manufacturer)

Documentation on products donated by a manufacturer was discussed. UNICEF explained that the procedure and principles it followed for receiving donations were the same as those used for products that were purchased. Donated products should be of the same quality as those purchased. Aspects such as polymorphism, transfer of technology, stability, marketing authorizations and manufacturing authorizations (including GMP compliance) were discussed. The Committee endorsed the principle of ensuring the same standard of quality of donated and purchased products. The Committee supported the approach that general principles of good procurement practices and existing WHO and Interagency Pharmaceutical Coordination (IPC) guidelines on donations should be followed.

14. Regulatory guidance on post-approval changes

14.1 Guidance on variations to a prequalified dossier

The existing guidance on variations to a prequalified dossier was considered by the Committee to be limited. To provide assistance to Member States and to ensure sufficient control over variations, also within the prequalification project, draft guidance was prepared and presented.

The Committee:

- supported the guidance document on variations to a prequalified dossier; and
- recommended that the document be amended to become a general guidance document for Member States. This document should pass through the normal consultative process.

15. Nomenclature and computerized systems

15.1 International Nonproprietary Names

The Secretariat informed the Committee that the revised procedure for the selection of International Nonproprietary Names (INN) was adopted by the WHO Governing Bodies in 2005.

An update on the INN programme was given. The Committee took note of some of the activities and challenges in the INN programme. These included an automated publication process and an Internet-enabled INN submission procedure.

The Committee noted with thanks the report and update by the Secretariat on the activities and revised INN procedure.

15.2 WHO nomenclature used in quality assurance

A new database had been created in which all the definitions used in various documentation on quality assurance had been entered. This database should be regularly updated to include new guidelines as they are adopted. The Committee recognized with thanks the work done and recommended that this information be made available on the web site. An introductory note should be included with an explanation as to the origin and proposed use of the terms. The Committee recommended that working groups should use this document in the preparation of guidelines and similar documents.

16. Summary and recommendations

The areas covered by this Committee are extensive and range from GMP, regulatory guidance texts, e.g. regarding the interchangeability of medicines, prequalification, stability testing and fixed-dose combinations, as well as in the areas of counterfeit and substandard medicines. The Expert Committee made many recommendations in the various specific work areas in quality assurance discussed during the meeting. Detailed recommendations can be found under the relevant sections of the report. Newly developed quality control specifications and International Chemical Reference Substances (ICRS) were discussed, focusing on essential medicines and on those medicines used in the treatment of large populations for which there are often no international quality requirements which are publicly available.

The Expert Committee emphasized the importance of making sufficient resources available for these core normative functions of the Organization. This would enable sustainability and avoid duplication of efforts worldwide. The guidelines, specifications and international nomenclature developed under the aegis of this Expert Committee serve — without always being in the headlines — all Member States and regions and underpin important initiatives, including the Roll Back Malaria Programme, Stop TB and the "3 by 5" initiative launched by the Director-General, Dr LEE Jong-wook.

Making resources available for these activities is very cost-effective as national and regional drug regulatory authorities, as well as major international bodies and institutions, such as the Global Fund, and international organizations such as UNICEF and UNIDO, are the direct beneficiaries of these activities. The Committee was very satisfied that the meeting had been held for the first time on an annual basis to allow it to respond more swiftly to the needs in this area worldwide. The Committee strongly recommended that this frequency should be maintained.

The prequalification of medicines and laboratories (and also possibly of procurement agencies in the future) could not function without the set of guidelines, standards, specifications and new guidance texts adopted by this

Committee after passage through the usual, rigorous consultative process. In return the prequalification programme has provided valuable feedback to the Expert Committee. Practical suggestions for potential revision or the need for additional guidance noted as a result of using the guidelines, specifications, and other materials in the field, can be transmitted directly to the Expert Committee.

Another valuable aspect of the prequalification programme is that participating members of drug regulatory authorities are able to obtain "hands-on" experience in joint inspections and joint regulatory assessment activities, with the participation of both developed and developing countries. This practical experience is later passed on in training workshops, thus allowing even more colleagues to benefit from the programme. Manufacturers and quality control laboratories benefit from the extensive advice given in the inspection reports. National authorities benefit from the availability of these inspection reports and the regulatory information they contain.

In conclusion, the Expert Committee oversees activities in the area of quality assurance that it considers should continue efficiently and swiftly to enable Member States, international organizations, United Nations agencies, regional and interregional harmonization efforts to benefit therefrom. Sustainability of the activities discussed is crucial if WHO is to continue to provide in a worthwhile manner these services laid down in its Constitution.

16.1 New standards and guidelines adopted and recommended for use

1. List of available International Chemical Reference Substances (ICRS) (Annex 1).
2. Supplementary guidelines on good manufacturing practices (GMP) for heating, ventilation and air-conditioning (HVAC) systems (new, Annex 2).
3. Supplementary guidelines on GMP for the manufacture of herbal medicines (revision, Annex 3).
4. Good manufacturing practices: validation (new, Annex 4).
5. Good distribution practices (GDP) for pharmaceutical products (new, Annex 5).
6. Model Quality Assurance System for Assessment of Procurement Agencies (Annex 6).
7. Guidelines on registration requirements to establish interchangeability of multisource (generic) pharmaceutical products (revision, Annex 7).
8. Proposal to waive in vivo bioequivalence requirements for the WHO Model List of Essential Medicines, immediate release, solid dosage forms (Annex 8).
9. Guidelines for organizations performing in vivo bioequivalence studies (Annex 9).

10. Monographs for inclusion in *The International Pharmacopoeia*, subject to establishing the relevant reference materials:

    — abacavir sulfate
    — efavirenz
    — lamivudine
    — stavudine
    — zidovudine

The following monographs for finished products:

— nelfinavir mesilate tablets
— nelfinavir mesilate oral powder
— saquinavir mesilate capsules

And monographs for the following fixed-dose antituberculosis medicines in their finished dosage forms:

— rifampicin tablets
— rifampicin capsules
— rifampicin + isoniazid tablets
— rifampicin + isoniazid + pyrazinamide + ethambutol HCl tablets
— isoniazid + ethambutol HCl tablets
— rifampicin + isoniazid + pyrazinamide tablets

In addition to the above, the Committee adopted:

— the revision of the WHO guide on stability testing;
— a revision of the previously adopted list of comparator products to be published on the web site to facilitate regular updates; and
— a revision of several test methods currently described in the publication entitled "Quality control methods for medicinal plant materials", in collaboration with Traditional Medicine (TRM).

Moreover the Committee has given advice on donations directly from manufacturers.

It also strongly recommended the use of the newly consolidated database on nomenclature used in WHO quality assurance documentation to maintain harmony and consistency in future guidances in this area.

16.2 Activities that should be pursued and progress reported at the next meeting of the Expert Committee

The following activities should be pursued and progress should be reported at the next meeting of the Expert Committee. Development of specifications and guidelines will be carried out using the established international consultative process.

The International Pharmacopoeia

The activities related to *The International Pharmacopoeia* are as follows:

— continuation of development of specifications for medicines included in the *WHO Model List of Essential Medicines* with a focus on priority diseases; and
— continuation of collaboration with IAEA with a view to replacing monographs for radiopharmaceuticals.

Regulatory guidance

The work on regulatory guidance will include:

— continuation of development of guidance on variations to submissions in regulatory dossiers;
— continuation of the development of new guidelines for the development of secondary reference standards; and
— collaboration with EMEA and other national inspectorates to allow exchange of information with the aim of improving risk analysis when planning for foreign inspections.

International Chemical Reference Substances

The Committee strongly recommended that the use of ICRS should be promoted as they are essential to the undertaking of quality control tests.

Prequalification project

The Committee strongly recommended that sufficient resources be made available to enable the prequalification programme to continue, with regard to prequalification of products, quality control laboratories, update of the procedure and requalification as necessary. This work should include:

— update of the prequalificaton procedure to include provision of inspection of API manufacturers and CROs; and
— update of the procedure for prequalification of national quality control laboratories with legal assistance.

16.3 New areas of work suggested

The following new working areas were suggested to be undertaken and progress to be reported to the next Expert Committee.

- Continue the preparatory work of the consolidated *International Pharmacopoeia*, Fourth Edition, both in printed and electronic forms (CD-ROM format).
- Revise general chapters of *The International Pharmacopoeia*, as identified by the group of experts and endorsed by the Expert Committee.

- Continue to update the currently available GMP training modules.
- Proceed with the organization of a workshop to discuss the possibility of establishing an international framework convention to coordinate international strategies to detect and counter counterfeiting.
- Explore WHO's continued participation and proper representation of its Member States at the International Conference on Harmonisation (ICH), an interregional harmonization effort in drug registration of new medicines.
- Continue and strengthen the External Quality Control Laboratory Assessment Scheme.

Acknowledgements

Special acknowledgement was made by the Committee to Mrs W. Bonny, Dr S. Kopp, Mrs A.N. Lo Conte, Ms M.-L. Rabouhans, Dr L. Rägo, and Dr P. Vanbel, Quality Assurance and Safety: Medicines, Department of Medicines Policy and Standards, WHO, Geneva, Switzerland, who were instrumental in the preparation and proceedings of the meeting.

Technical guidance included on this report has been produced with the financial assistance of the European Community.

The Committee also acknowledged with thanks the valuable contributions made to its work by the following institutions and persons:

Bureau of Drug and Narcotics, Department of Medical Sciences, Ministry of Public Health, Nonthaburi, Thailand; Bureau of Food and Drugs, Department of Health, Muntinlupa City, Philippines; Caribbean Regional Drug Testing Laboratory, Kingston, Jamaica; Central Drugs Laboratory, Calcutta, India; Central Laboratory for Quality Control of Medicines of the Ministry of Health of Ukraine, Kiev, Ukraine; Central Quality Control Laboratory, Muscat, Oman; Centre for Quality Assurance of Medicines, Faculty of Pharmacy, University of Potchefstroom, Potchefstroom, South Africa; Departamento de Control Nacional Unidad de control de calidad de productos farmaceúticos del mercado nacional (Control de Estanteria), Santiago de Chile, Chile; Department for Quality Evaluation and Control, National Institute of Pharmacy, Budapest, Hungary; Drug Analysis Division, National Pharmaceutical Control Bureau, Petaling Jaya, Sengalor, Malaysia; Expert Analytic Laboratory, Centre of Drug and Medical Technology Expertise, Yerevan, Armenia; Food and Drug Quality Control Center, Ministry of Health, Vientiane, People's Democratic Republic of Lao; Food and Drugs Board, Quality Control Laboratory, Accra, Ghana; Institute for Quality Control of Medicines, Sarajevo, Bosnia and Herzegovina; Instituto Especializado de Análisis, Universidad de Panamá, República de Panama; Instituto Nacional de Higiene "Rafael Rangel", Caracas, Venezuela; Instituto Nacional de Medicamentos, Buenos Aires, Argentina; Laboratoire Nacional de la Santé du Mali, Bamako, Mali; Laboratoire National de Contrôle des Médicaments, Rabat Instituts, Rabat, Morocco; Laboratoire National de Contrôle des Médicaments, Dakar Étoile, Senegal; Laboratoire National de Contrôle des Médicaments, Bab Saadoun, Tunisia; Laboratoire National de Contrôle des Produits Pharmaceutiques, Alger, Algeria; Laboratoire National de Santé Publique et d'Expertise, Niamey, Niger; Laboratorio Control de Productos MSP, Comisión Para El Control de Calidad de Medicamentos, Montevideo, Uruguay; Laboratorio de Análisis y Asesoría Farmacéutica, San Pedro de Montes de Oca, San José, Costa Rica; Laboratorio de Normas y Calidad de Medicamentos, Caja Costarricense de Seguro Social, Universidad de Costa Rica, San Jose, Costa Rica; LTD Centre for Medicine Quality Control, Tbilisi, Georgia; Medicines Control Authority, Control Laboratory of Zimbabwe, Harare, Zimbabwe; National Drug Quality Assurance Laboratory, Colombo, Sri Lanka; National Institute for the Control of Pharmaceutical and Biological Products, Beijing, People's Republic of China; National Institute of Drug Quality Control, Hanoi, Viet Nam; National Laboratory for Drug Quality Control, Phnom Penh, Cambodia; Provincial Quality Control Laboratory of Drug and Food,

Yogyakarta, Indonesia; Research Institute for Industrial Pharmacy, North-West University, Potchefstroom, South Africa; Royal Drug Research Laboratory, Department of Drug Administration, Kathmandu, Nepal; Tanzania Food and Drugs Authority, Dar-es-Salaam, United Republic of Tanzania; WHO Collaborating Centre for Chemical Reference Substances, Apoteket AB, Central Laboratory, Kungens Kurva, Sweden; WHO Collaborating Centre for Chemical Reference Substances, National Corporation of Swedish Pharmacies, Central Laboratory, Kungens Kurva, Sweden; WHO Collaborating Centre for Drug Quality Control, Therapeutic Goods Administration Laboratories, Woden, Australian Capital Territory, Australia; WHO Collaborating Centre for Drug Quality Assurance, National Institute for the Control of Pharmaceutical and Biological Products, Temple of Heaven, Beijing, People's Republic of China; WHO Collaborating Centre for Biopharmaceutical Aspects of Drug Quality Control, Biopharmaceutical Laboratory, University of Clermont-Ferrand, Clermont-Ferrand, France; WHO Collaborating Centre for Drug Information and Quality Assurance, National Institute of Pharmacy, Budapest, Hungary; WHO Collaborating Centre for Quality Assurance of Essential Drugs, Central Drugs Laboratory, Calcutta, India; WHO Collaborating Centre for Quality Assurance of Essential Drugs, National Quality Control Laboratory of Drug and Food, Directorate General of Drug and Food Control, Ministry of Health, Jakarta, Indonesia; WHO Collaborating Centre for Regulatory Control of Pharmaceuticals, National Pharmaceutical Control Bureau, Jalan University, Ministry of Health, Petaling Jaya, Malaysia; International Pharmaceutical Federation Sections: Industrial Pharmacy, Laboratories and Medicines Control Services, Military Pharmacy and Community Pharmacy, Netherlands; WHO Collaborating Centre for Drug Quality Assurance, Pharmaceutical Laboratory, Centre for Analytical Science, Health Sciences Authority, Singapore; WHO Collaborating Centre for Quality Assurance of Drugs, Potchefstroom University for Christian Higher Education, Potchefstroom, South Africa; WHO Collaborating Centre for International Infrared Reference Spectra, Swiss Federal Institute of Technology, Zurich, Switzerland; WHO Roll Back Malaria Initiative, Geneva, Switzerland; WHO Special Programme for Research and Training in Tropical Diseases, Geneva, Switzerland; WHO Stop TB Department, Geneva, Switzerland; WHO Collaborating Centre for Quality Assurance of Essential Drugs, Department of Medical Sciences, Ministry of Public Health, Nonthaburi, Thailand.

Ms N. Abbasi and Ms Z. Abbasi, Department of Pharmaceutics, Royal Danish School of Pharmacy, Copenhagen, Denmark; Professor I. Abdoulaye, Ministère de la Santé Publique, Cotonou, Benin; Mrs L. Abdul Rahman, Director, Pharmacy and Drug Control, Ministry of Health, Manama, Bahrain; Dr M. Abdullah, P.T. Bio Farma, Bandung, Indonesia; Dr Z. Abeid, Pharmaceutical Department, Ministry of Health and Population, Cairo, Egypt; Dr D. Abhigantaphand, Bureau of Drug and Narcotic, Department of Medical Sciences, Ministry of Public Health, Nonthaburi, Thailand; Dr M. Abuelkhair, Drug Consultant Advisor, General Authority for Health Services, Abu Dhabi, United Arab Emirates; Professor I. Addae-Mensah, University of Ghana, Legon, Ghana; Professor A. Agoumi, Medicines and Pharmacy, Ministry of Health, Rabat-Institute, Rabat, Morocco; Dr M.M. Ahmed, Hamdard WAQF Laboratories, Hamdard Centre, Karachi, Pakistan; Mrs S. Ahmed Jaffar, Directorate General of Pharmaceutical Affairs and Drugs Control, Ministry of Health, Muscat, Oman; Professor J.-M. Aiache, WHO Collaborating Centre for Biopharmaceutical Aspects

of Drug Quality Control, University of Clermont-Ferrand, Clermont-Ferrand, France; Dr W. Akarawut, Department of Medical Science, Ministry of Public Health, Nonthaburi, Thailand; Dr T. Akasah, GMP and Licensing Division, National Pharmaceutical Control Bureau, Ministry of Health, Petaling Jaya, Sengalor, Malaysia; Professor P.I. Akubue, Department of Pharmacology and Toxicology, University of Nigeria, Nsukka, Nigeria; Dr D.N. Akunyili, Director General, National Agency for Food and Drug Administration and Control, Federal Ministry of Health, Wuse-Abuja, Nigeria; Dr E.B.J. Al Mansoori, Director, Drug Control Department, Ministry of Health, Abu Dhabi, United Arab Emirates; Dr A. Al Na'amani, Supreme Board of Drugs and Medical Appliances, Ministry of Public Health, Sana'a, Yemen; Dr M.H.S. Al Yousuf, Zayed, Complex for Herbal Research and Traditional Medicine, General Authority for Health Services, Abu Dhabi, United Arab Emirates; Mr A.H. Al-Abdullah, Ministry of Public Health, Doha, Qatar; Dr A. Albedah, Assistant Director-General, Hospitals, Ministry of Health, Riyadh, Saudi Arabia; Dr R. Alexander, Inspection, Medicines and Healthcare Products Regulatory Agency, Department of Health, London, England; Dr M.I. Al-Hail, Director, Pharmacy and Drug Control Department, Ministry of Public Health, Doha, Qatar; Dr I. Alhobaib, Saudi Food and Drug Authority, Riyadh, Saudi Arabia; Dr S.L. Ali, Zentrallaboratorium Deutscher Apotheker, Eschborn, Germany; Dr R. Allman, Medicines and Medical Devices Safety Authority, Business Unit of the Ministry of Health, Auckland, New Zealand; Dr I. Alshowaier, Drug Sector, Saudi Food and Drug Authority, Riyadh, Saudi Arabia; Dr T. Alves, Communication Manager, International Pharmaceutical Federation, The Hague, Netherlands; Dr M.H. Amal, Director of Inspection and Certification on Cosmetics and Complementary Product, National Agency for Drug and Food Control, Jakarta, Indonesia; Mrs E. Amirejibi, Chairman of the Department of Traditional Medical Activities, Health Care Ministry of Georgia, Tbilisi, Georgia; Dr N. Anand, Lucknow, Uttar Pradesh, India; Dr L. Anderson, Principal Pharmaceutical Officer, Medicines and Healthcare Products Regulatory Agency, Department of Health, London, England; Dr O. Andriollo, Medicopharmaceutical Humanitarian Centre, Clermont-Ferrand, France; Professor M.K. Anglade, Directeur de la Pharmacie et du Médicaments, Abidjan, Côte d'Ivoire; Dr M. Argenti, National Administration of Medicaments, Food and Medical Technology, Buenos Aires, Argentina; Dr A. Artiges, Director, European Directorate for the Quality of Medicines, Council of Europe, Strasbourg, France; Dr L. Bachorik, Senior Advisor for International Policy and Communications, Office of International Programs, US Food and Drug Administration, Rockville, MD, USA; Professor F. Ballereau, Centre Hospitalier Universitaire de Nantes, France; Dr D.M. Barends, Apotheker, Rijksinstituut voor Volksgezondheid en Milieu RIVM, BA Bilthoven, Netherlands; Ms A.C. Baron, European Chemical Industry Council/Active Pharmaceutical Ingredients Committee, CEFIC Sector Group, Brussels, Belgium; Dr C. Barnstein, Drug Information Division, United States Pharmacopeia, Rockville, MD, USA; Professor K.H.C. Baser, Anadolu University, Medicinal & Aromatic Plant and Drug Research Centre, Eskisehir, Turkey; Dr A.K. Bashir, Director, Environmental Division, ERWDA, Abu Dhabi, United Arab Emirates; Dr S. Bawasir, Saudi Food and Drug Authority, Riyadh, Saudi Arabia; Dr P.M. Bazerque, Secretariat for Policies and Health Regulation, Ministry of Health, Buenos Aires, Argentina; Dr M.C. Becerril Martinez, Comisión Permanente de la Farmacopea de los Estados Unidos Mexicanos, Mexico, DF, Mexico; Dr S. Behjat, Coordinator, Traditional

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WHO Technical Report Series, No. 937, 2006

Annex 1

List of available International Chemical Reference Substances and International Infrared Reference Spectra

1. International Chemical Reference Substances

International Chemical Reference Substances (ICRS) are established upon the advice of the WHO Expert Committee on Specifications for Pharmaceutical Preparations. They are supplied primarily for use in physical and chemical tests and assays described in the specifications for quality control of medicines published in *The International Pharmacopoeia* or proposed in draft monographs. The International Chemical Reference Substances are mainly intended to be used as primary standards to calibrate secondary standards.

Directions for use and required analytical data for the intended use in the relevant specifications of *The International Pharmacopoeia* are given in the certificates enclosed with the substances when distributed.

International Chemical Reference Substances may also be used in tests and assays not described in *The International Pharmacopoeia*. However, the responsibility for assessing the suitability of the substances then rests with the user or with the pharmacopoeia commission or other authority that has prescribed this use.

It is generally recommended that the substances should be stored protected from light and moisture and preferably at a temperature of about +5 °C. When special storage conditions are required, this is stated on the label or in the certificate. It is recommended that the user purchase only an amount sufficient for immediate use.

The stability of the ICRS kept at the Collaborating Centre is monitored by regular re-examination and any material that has deteriorated is replaced by new batches when necessary. Lists giving control numbers for the current batches are issued in the annual reports from the Centre and new lists may also be obtained on request or at the web site (see below).

Ordering information

Orders for the International Chemical Reference Substances should be sent to:

WHO Collaborating Centre for Chemical Reference Substances
Apoteket AB
Produktion & Laboratorier
Centrallaboratoriet, ACL
Prismavägen 2
SE-141 75 Kungens Kurva, Sweden
Fax: + 46 8 740 60 40
or e-mail: who.apl@apoteket.se
web site: http://www.apl.apoteket.se/who

The current price for the ICRS is US$ 70 per package. An administration charge of US$ 10 is added to each order to cover costs for handling and dispatch by airmail or air parcel post. If dispatch by air freight is requested, the freight costs will amount to about US$ 200, and these costs have to be paid by the purchaser. Payment should be made according to the invoice. Kindly direct all payments (cheques, bills of exchange, banker's drafts or banker's transfers) to:

Nordea Bank Sweden, SE-105 71 STOCKHOLM
(Apoteket AB/APL/ACL/WHO)
Swift: NDEASESS
Account no: 2 98 40-6
IBAN: SE 65 9500 0099 6026 0029 8406

Invoice number must be quoted when payment is made.

If, however, payment in advance is asked for but not allowed according to the regulations of certain countries, **documentary remittance (cash against documents)** may be used. This means that the invoice is paid at the buyer's bank and against that receipt the parcel is collected at the customs office or, when so agreed, at the bank.

The WHO Centre cannot accept payment by letter of credit (L/C).

Nor can the WHO Centre issue a **Certificate of Origin**, as the bulk material for the ICRS originates from different parts of the world. Also the Centre cannot assist in any legalization of such or other documents sometimes asked for.

On dispatch by air freight, the freight cost is paid directly to the carrier by the purchaser. **In all cases the payment should be net of charge for the WHO Collaborating Centre**.

The administration charge of US$ 10 covers the cost for **handling and dispatch by airmail** (small parcel or air parcel post). If **registered airmail** or **express airmail** is required, an extra charge is added. If safe delivery is possible by means of airmail, this ought to be the preferred method as it is much less expensive for all parties.

ICRS are supplied only in standard packages as indicated in the following list.

Available International Chemical Reference Substances

Catalogue number	Reference substances	Package size	Control number
9930375	*p*-acetamidobenzalazine	25 mg	290042
9930202	acetazolamide	100 mg	186128
9930204	allopurinol	100 mg	287049
9930206	amidotrizoic acid	100 mg	196205
9930191	2-amino-5-nitrothiazole	25 mg	186131
9930194	3-aminopyrazole-4-carboxamide hemisulfate	100 mg	172050
9930193	3-amino-2,4,6-triiodobenzoic acid	100 mg	196206
9930208	amitriptyline hydrochloride	100 mg	181101
9930209	amodiaquine hydrochloride	200 mg	192160
9930210	amphotericin B	400 mg	191153
9930211	ampicillin (anhydrous)	200 mg	390001
9930212	ampicillin sodium	200 mg	388002
9930213	ampicillin trihydrate	200 mg	274003
9930214	anhydrotetracycline hydrochloride	25 mg	180096
9931408	artemether	100 mg	103225
9931406	artemisinin	100 mg	103222
9931407	artemotil	100 mg	103226
9931410	artenimol	100 mg	103223
9931409	artesunate	100 mg	103224
9930215	atropine sulfate	100 mg	183111
9930216	azathioprine	100 mg	172060
9930218	bacitracin zinc	200 mg	192174
9930219	beclometasone dipropionate	200 mg	192175
9930225	benzylpenicillin potassium	200 mg	180099
9930226	benzylpenicillin sodium	200 mg	280047
9930227	bephenium hydroxynaphthoate	100 mg	183112
9930228	betamethasone	100 mg	183113
9930229	betamethasone sodium phosphate	100 mg	196203
9930230	betamethasone valerate	100 mg	190145
9930233	bupivacaine hydrochloride	100 mg	289054
9930234	caffeine	100 mg	181102
9930236	calcium folinate (leucovorin calcium)	100 mg	194188
9930237	captopril	100 mg	197214
9930238	captopril disulfide	25 mg	198216
9930239	carbamazepine	100 mg	189143
9930240	carbenicillin monosodium	200 mg	383043
9930241	chloramphenicol	200 mg	486004
9930242	chloramphenicol palmitate	1 g	286072
9930243	chloramphenicol palmitate (polymorph A)	200 mg	175073
9930199	5-chloro-2-methylaminobenzophenone	100 mg	172061
9930245	chloroquine sulfate	200 mg	195201

Catalogue number	Reference substances	Package size	Control number
9930190	2-(4-chloro-3-sulfamoylbenzoyl)benzoic acid	50 mg	181106
9930246	chlorphenamine hydrogen maleate	100 mg	182109
9930247	chlorpromazine hydrochloride	100 mg	178080
9930248	chlortalidone	100 mg	183114
9930249	chlortetracycline hydrochloride	200 mg	187138
9930250	cimetidine	100 mg	190150
9930256	ciprofloxacin hydrochloride	400 mg	197210
9930252	ciprofloxacin by-compound A	20 mg	198220
9930253	ciprofloxacin desfluoro-compound	20 mg	198219
9930254	ciprofloxacin ethylenediamine-compound	20 mg	198218
9930255	ciprofloxacin fluoroquinolonic acid	20 mg	198217
9930258	cisplatin	100 mg	197207
9930259	clomifene citrate clomifene citrate *Z*-isomer *see* zuclomifene	100 mg	187136
9930261	cloxacillin sodium	200 mg	274005
9930262	colecalciferol (vitamin D_3)	500 mg	190146
9930263	cortisone acetate	100 mg	167006
9930265	dapsone	100 mg	183115
9930266	desoxycortone acetate	100 mg	167007
9930267	dexamethasone	100 mg	388008
9930268	dexamethasone acetate	100 mg	288009
9930269	dexamethasone phosphoric acid	100 mg	192161
9930270	dexamethasone sodium phosphate	100 mg	192158
9930282	diazoxide	100 mg	181103
9930283	dicloxacillin sodium	200 mg	174071
9930285	dicoumarol	100 mg	178077
9931413	didanosine	10 mg	104228
9931414	didanosine for system suitability	10 mg	104230
9930287	diethylcarbamazine dihydrogen citrate	100 mg	181100
9930288	digitoxin	100 mg	277010
9930289	digoxin	100 mg	587011
9930290	dopamine hydrochloride	100 mg	192159
9930292	doxorubicin hydrochloride	100 mg	196202
9931411	efavirenz	100 mg	104229
9930294	emetine hydrochloride	100 mg	187134
9930197	4-epianhydrotetracycline hydrochloride	25 mg	288097
9930198	4-epitetracycline hydrochloride	25 mg	293098
9930295	ergocalciferol (vitamin D_2)	500 mg	190147
9930296	ergometrine hydrogen maleate	50 mg	277012
9930297	ergotamine tartrate	50 mg	385013
9930298	erythromycin	250 mg	191154
9930299	erythromycin B	150 mg	194186

Catalogue number	Reference substances	Package size	Control number
9930300	erythromycin C	25 mg	194187
9930301	estradiol benzoate	100 mg	167014
9930302	estrone	100 mg	279015
9930304	ethambutol hydrochloride	100 mg	179081
9930305	ethinylestradiol	100 mg	301016
9930306	ethisterone	100 mg	167017
9930307	ethosuximide	100 mg	179088
9930309	flucloxacillin sodium	200 mg	195194
9930310	flucytosine	100 mg	184121
9930311	fludrocortisone acetate	200 mg	195199
9930312	fluorouracil	100 mg	184122
9930313	fluphenazine decanoate dihydrochloride	100 mg	182107
9930314	fluphenazine enantate dihydrochloride	100 mg	182108
9930315	fluphenazine hydrochloride	100 mg	176076
9930316	folic acid	100 mg	388019
9930195	3-formylrifamycin	200 mg	202149
9930355	framycetin sulfate (neomycin B sulfate)	200 mg	193178
9930318	furosemide	100 mg	171044
9930319	gentamicin sulfate	100 mg	194183
9930322	griseofulvin	200 mg	280040
9930323	haloperidol	100 mg	172063
9930324	hydrochlorothiazide	100 mg	179087
9930325	hydrocortisone	100 mg	283020
9930326	hydrocortisone acetate	100 mg	280021
9930327	hydrocortisone sodium succinate	200 mg	194184
9930188	(–)-3-(4-hydroxy-3-methoxyphenyl)-2-hydrazino-2-methylalanine (3-*o*-methylcarbidopa)	25 mg	193180
9930189	(–)-3-(4-hydroxy-3-methoxyphenyl)-2-methylalanine (3-*o*-methylmethyldopa)	25 mg	179085
9930328	ibuprofen	100 mg	183117
9930329	imipramine hydrochloride	100 mg	172064
9930330	indometacin	100 mg	178078
9930331	isoniazid	100 mg	185124
9930332	kanamycin monosulfate	12 mg	197211
9930333	lanatoside C	100 mg	281022
9930334	levodopa	100 mg	295065
9930335	levonorgestrel	200 mg	194182

Catalogue number	Reference substances	Package size	Control number
9930336	levothyroxine sodium	100 mg	189144
9930337	lidocaine	100 mg	181104
9930338	lidocaine hydrochloride	100 mg	181105
9930339	liothyronine sodium	50 mg	193179
9930340	loperamide hydrochloride	100 mg	194185
9930341	mebendazole	200 mg	195195
	Melting point reference substances		
9930217	azobenzene (69 °C)	1 g	192168
9930438	vanillin (83 °C)	1 g	299169
9930222	benzil (96 °C)	4 g	294170
9930201	acetanilide (116 °C)	1 g	297171
9930380	phenacetin (136 °C)	1 g	297172
9930221	benzanilide (165 °C)	4 g	192173
9930422	sulfanilamide (166 °C)	1 g	192162
9930423	sulfapyridine (193 °C)	4 g	192163
9930286	dicyanodiamide (210 °C)	1 g	192164
9930411	saccharin (229 °C)	1 g	192165
9930235	caffeine (237 °C)	1 g	299166
9930382	phenolphthalein (263 °C)	1 g	299167
9930345	methotrexate	100 mg	194193
	3-***o***-methylcarbidopa *see* (–)-3-(4-hydroxy-3-methoxyphenyl)-2-hydrazino-2-methylalanine 3-***o***-methylmethyldopa *see* (–)-3-(4-hydroxy-3-methoxyphenyl)-2-methylalanine		
9930346	methyldopa	100 mg	179084
9930347	methyltestosterone	100 mg	167023
9930348	meticillin sodium	200 mg	274024
9930350	metronidazole	100 mg	183118
9930351	nafcillin sodium	200 mg	272025
9930354	neamine hydrochloride (neomycin A hydrochloride) neomycin B sulfate *see* framycetin sulfate	0.5 mg	193177
9930356	neostigmine metilsulfate	100 mg	187135
9931412	nevirapine	100 mg	104227
9930357	nicotinamide	100 mg	200090
9930358	nicotinic acid	100 mg	179091
9930359	nifurtimox	100 mg	194189
9930360	niridazole	200 mg	186129
9930361	niridazole-chlorethylcarboxamide	25 mg	186130
9930366	norethisterone	100 mg	186132
9930367	norethisterone acetate	100 mg	185123
9930369	nystatin	200 mg	300152

Catalogue number	Reference substances	Package size	Control number
9930371	ouabain	100 mg	283026
9930372	oxacillin sodium	200 mg	382027
9930373	oxytetracycline dihydrate	200 mg	189142
9930374	oxytetracycline hydrochloride	200 mg	189141
9930376	papaverine hydrochloride	100 mg	185127
9930377	paracetamol	100 mg	195198
9930378	paromomycin sulfate	75 mg	195197
9930383	phenoxymethylpenicillin	200 mg	179082
9930384	phenoxymethylpenicillin calcium	200 mg	179083
9930385	phenoxymethylpenicillin potassium	200 mg	176075
9930387	phenytoin	100 mg	179089
9930388	piperazine adipate	100 mg	197212
9930389	piperazine citrate	100 mg	197213
9930390	praziquantel	100 mg	194191
9930391	prednisolone	100 mg	389029
9930392	prednisolone acetate	100 mg	289030
9930393	prednisolone hemisuccinate	200 mg	195196
9930394	prednisolone sodium phosphate	200 mg	194190
9930395	prednisone	100 mg	167031
9930396	prednisone acetate	100 mg	169032
9930397	probenecid	100 mg	192156
9930398	procaine hydrochloride	100 mg	183119
9930399	procarbazine hydrochloride	100 mg	184120
9930400	progesterone	100 mg	167033
9930402	propranolol hydrochloride	100 mg	187139
9930403	propylthiouracil	100 mg	185126
9930404	pyrantel embonate (pyrantel pamoate)	500 mg	192157
9930405	pyridostigmine bromide	100 mg	182110
9930406	reserpine	100 mg	186133
9930407	retinol acetate (solution)	5 caps[a]	898038
9930408	riboflavin	250 mg	382035
9930409	rifampicin	300 mg	191151
9930410	rifampicin quinone	200 mg	202148
9930412	sodium amidotrizoate	100 mg	198221
9930413	sodium cromoglicate	100 mg	188140
9930415	spectinomycin hydrochloride	200 mg	193176
9930416	streptomycin sulfate	100 mg	197215
9930417	sulfacetamide	100 mg	196200
9930419	sulfamethoxazole	100 mg	179092
9930420	sulfamethoxypyridazine	100 mg	178079

Catalogue number	Reference substances	Package size	Control number
9930421	sulfanilamide	100 mg	179094
9930424	sulfasalazine	100 mg	191155
9930425	tamoxifen citrate	100 mg	196208
9930426	tamoxifen citrate *E*-isomer	10 mg	196209
9930427	testosterone enantate	200 mg	194192
9930428	testosterone propionate	100 mg	167036
9930429	tetracycline hydrochloride	200 mg	180095
9930430	thioacetazone	100 mg	171046
9930196	4,4' - thiodianiline	50 mg	183116
	thyroxine sodium *see* levothyroxine sodium		
9930431	tolbutamide	100 mg	179086
9930432	tolnaftate	100 mg	176074
9930433	toluene-2-sulfonamide	100 mg	196204
9930434	trimethadione	200 mg	185125
9930435	trimethoprim	100 mg	179093
9930440	vincristine sulfate	9.7 mg/vial	193181
	vitamin A acetate (solution) *see* retinol acetate (solution)		
9930439	warfarin	100 mg	168041
9930260	zuclomifene	50 mg	187137

[a] About 8 mg in 230 mg oil per capsule.

2. List of available International Infrared Reference Spectra

The WHO Collaborating Centre for Chemical Reference Substances is able to supply 69 International Infrared Reference Spectra.

The current price is US$ 5 for a single spectrum and US$ 200 for a set of 50 spectra, including a hardcover binder. The binder can be ordered separately for US$ 10.

An administrative charge of US$ 10 is added to each order to cover the costs of handling and dispatch by airmail or air parcel post.

Orders should be sent to:

WHO Collaborating Centre for Chemical Reference Substances
Apoteket AB
Produktion & Laboratorier
Centrallaboratoriet, ACL
Prismavägen 2
SE-141 75 Kungens Kurva
Sweden
Fax: + 46 8 740 60 40
e-mail: who.apl@apoteket.se
web site: http://www.apl.apoteket.se/who

Payment should be made according to the invoice. Kindly direct all payments to:

Nordea Bank Sweden, SE-105 71 Stockholm
(Apoteket AB/APL/ACL/WHO)
Swift: NDEASESS
Account no: 2 98 40-6
IBAN: SE 65 9500 0099 6026 0029 8406

Invoice number must be quoted when payment is made.

The following International Infrared Reference Spectra are currently available from the Centre:

aceclidine salicylate
acetazolamide
allopurinol
amiloride hydrochloride
amitriptyline hydrochloride
ampicillin trihydrate

beclometasone dipropionate
benzylpenicillin potassium
biperiden
biperiden hydrochloride
bupivacaine hydrochloride

caffeine (anhydrous)
calcium folinate
carbidopa
chlorphenamine hydrogen maleate
clofazimine
cloxacillin sodium

colchicine
cytarabine

dexamethasone
dexamethasone acetate, monohydrate
dextromethorphan hydrobromide
diazepam
dicolinium iodide
dicoumarol
diethylcarbamazine dihydrogen citrate
diphenoxylate hydrochloride

erythromycin ethylsuccinate
erythromycin stearate
etacrynic acid
ethionamide
ethosuximide

furosemide

gallamine triethiodide
glibenclamide

haloperidol
hydrochlorothiazide

ibuprofen
imipramine hydrochloride
indometacin
isoniazid

lidocaine
lidocaine hydrochloride
lindane

metronidazole
miconazole nitrate

niclosamide
nicotinamide
noscapine

oxamniquine

papaverine hydrochloride
phenobarbital
phenoxymethylpenicillin calcium
phenytoin
primaquine phosphate
propylthiouracil
protionamide
pyrimethamine

salbutamol
salbutamol sulfate
sulfadimidine
sulfadoxine
sulfamethoxazole
sulfamethoxypyridazine

tiabendazole
trihexyphenidyl hydrochloride
trimethoprim

valproic acid
verapamil hydrochloride

WHO Technical Report Series, No. 937, 2006

Annex 2

Supplementary guidelines on good manufacturing practices for heating, ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms

1. Introduction

Heating, ventilation and air-conditioning (HVAC) play an important role in ensuring the manufacture of quality pharmaceutical products. A well designed HVAC system will also provide comfortable conditions for operators. These guidelines mainly focus on recommendations for systems for manufacturers of solid dosage forms. The guidelines also refer to other systems or components which are not relevant to solid dosage form manufacturing plants, but which may assist in providing a comparison between the requirements for solid dosage-form plants and other systems.

HVAC system design influences architectural layouts with regard to items such as airlock positions, doorways and lobbies. The architectural components have an effect on room pressure differential cascades and cross-contamination control. The prevention of contamination and cross-contamination is an essential design consideration of the HVAC system. In view of these critical aspects, the design of the HVAC system should be considered at the concept design stage of a pharmaceutical manufacturing plant.

Temperature, relative humidity and ventilation should be appropriate and should not adversely affect the quality of pharmaceutical products during their manufacture and storage, or the accurate functioning of equipment.

This document aims to give guidance to pharmaceutical manufacturers and inspectors of pharmaceutical manufacturing facilities on the design, installation, qualification and maintenance of the HVAC systems. These guidelines are intended to complement those provided in *Good manufacturing practices for pharmaceutical products* (1) and should be read in conjunction with the parent guide. The additional standards addressed by the present guidelines should therefore be considered supplementary to the general requirements set out in the parent guide.

2. Scope of document

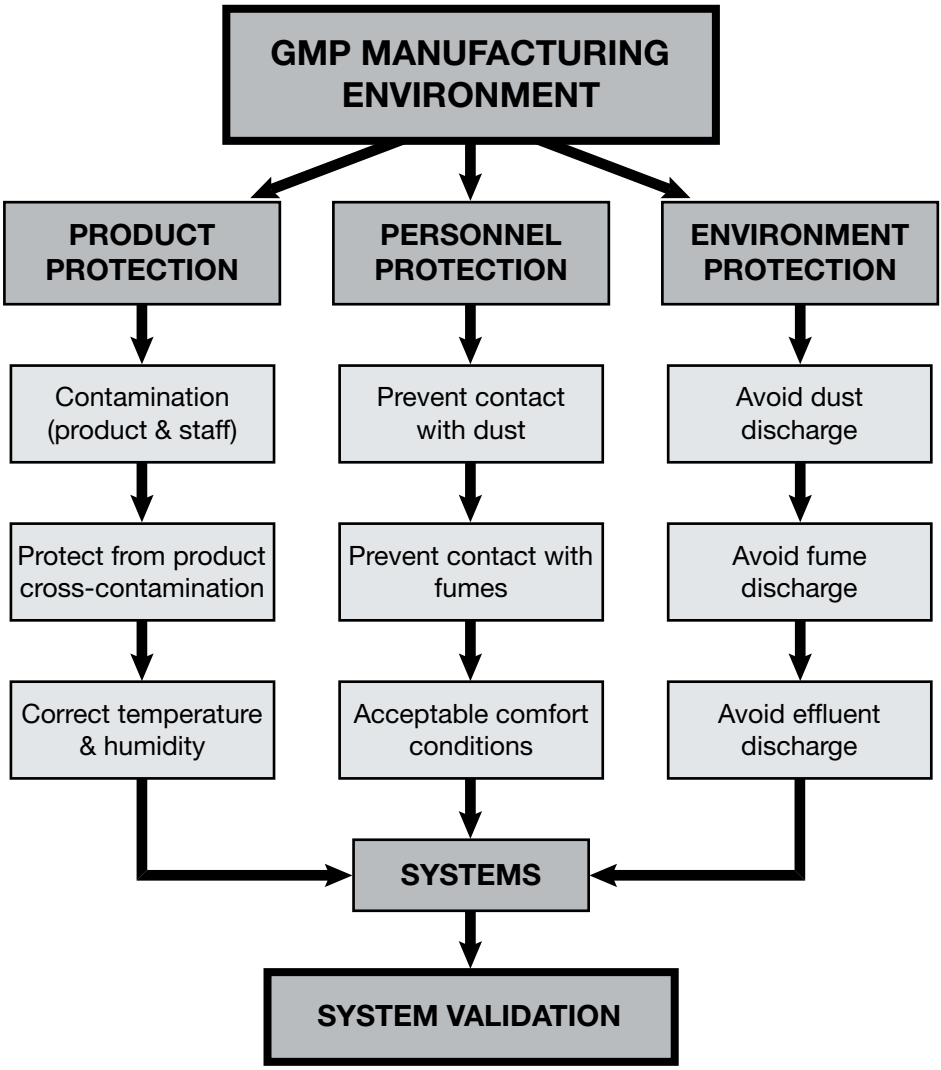
These guidelines focus primarily on the design and good manufacturing practices (GMP) requirements for HVAC systems for facilities for the manufacture of solid dosage forms. Most of the system design principles for facilities manufacturing solid dosage forms also apply to other facilities such as those manufacturing liquids, creams and ointments. These guidelines do not cover requirements for manufacturing sites for the production of sterile pharmaceutical products.

These guidelines are intended as a basic guide for use by GMP inspectors. They are not intended to be prescriptive in specifying requirements and design parameters. There are many parameters affecting a clean area condition and it is, therefore, difficult to lay down the specific requirements for one particular parameter in isolation.

Many manufacturers have their own engineering design and qualification standards and requirements may vary from one manufacturer to the next. Design parameters should, therefore, be set realistically for each project, with a view to creating a cost-effective design, yet still complying with all regulatory standards and ensuring that product quality and safety are not compromised.

The three primary aspects addressed in this manual are the roles that the HVAC system plays in product protection, personnel protection and environmental protection (Fig. 1).

Figure 1
The guidelines address the various system criteria according to the sequence set out in this diagram



GMP, Good manufacturing practice.

3. Glossary

The definitions given below apply to terms used in these guidelines. They may have different meanings in other contexts.

acceptance criteria

Measurable terms under which a test result will be considered acceptable.

action limit

The action limit is reached when the acceptance criteria of a critical parameter have been exceeded. Results outside these limits will require specified action and investigation.

air-handling unit (AHU)

The air-handling unit serves to condition the air and provide the required air movement within a facility.

airlock

An enclosed space with two or more doors, which is interposed between two or more rooms, e.g. of differing classes of cleanliness, for the purpose of controlling the airflow between those rooms when they need to be entered. An airlock is designed for and used by either people or goods (PAL, personnel airlock; MAL, material airlock).

alert limit

The alert limit is reached when the normal operating range of a critical parameter has been exceeded, indicating that corrective measures may need to be taken to prevent the action limit being reached.

as-built

Condition where the installation is complete with all services connected and functioning but with no production equipment, materials or personnel present.

at-rest

Condition where the installation is complete with equipment installed and operating in a manner agreed upon by the customer and supplier, but with no personnel present.

central air-conditioning unit (see *air-handling unit*)

change control

A formal system by which qualified representatives of appropriate disciplines review proposed or actual changes that might affect a validated status. The intent is to determine the need for action that would ensure that the system is maintained in a validated state.

clean area (clean room) [1]

An area (or room) with defined environmental control of particulate and microbial contamination, constructed and used in such a way as to reduce the introduction, generation and retention of contaminants within the area.

commissioning

Commissioning is the documented process of verifying that the equipment and systems are installed according to specifications, placing the equipment into active service and verifying its proper action. Commissioning takes place at the conclusion of project construction but prior to validation.

containment

A process or device to contain product, dust or contaminants in one zone, preventing it from escaping to another zone.

contamination

The undesired introduction of impurities of a chemical or microbial nature, or of foreign matter, into or on to a starting material or intermediate, during production, sampling, packaging or repackaging, storage or transport.

critical parameter or component

A processing parameter (such as temperature or humidity) that affects the quality of a product, or a component that may have a direct impact on the quality of the product.

cross-contamination

Contamination of a starting material, intermediate product or finished product with another starting material or material during production.

design condition

Design condition relates to the specified range or accuracy of a controlled variable used by the designer as a basis for determining the performance requirements of an engineered system.

design qualification (DQ)

DQ is the documented check of planning documents and technical specifications for conformity of the design with the process, manufacturing, GMP and regulatory requirements.

[1] Note: Clean area standards, such as ISO 14644-1 provide details on how to classify air cleanliness by means of particle concentrations, whereas the GMP standards provide a grading for air cleanliness in terms of the condition (at-rest or operational), the permissible microbial concentrations, as well as other factors such as gowning requirements. GMP and clean area standards should be used in conjunction with each other to define and classify the different manufacturing environments.

direct impact system

A system that is expected to have a direct impact on product quality. These systems are designed and commissioned in line with good engineering practice (GEP) and, in addition, are subject to qualification practices.

facility

The built environment within which the clean area installation and associated controlled environments operate together with their supporting infrastructure.

good engineering practice (GEP)

Established engineering methods and standards that are applied throughout the project life-cycle to deliver appropriate, cost-effective solutions.

indirect impact system

This is a system that is not expected to have a direct impact on product quality, but typically will support a direct impact system. These systems are designed and commissioned according to GEP only.

infiltration

Infiltration is the ingress of contaminated air from an external zone into a clean area.

installation qualification (IQ)

IQ is documented verification that the premises, HVAC system, supporting utilities and equipment have been built and installed in compliance with their approved design specification.

no-impact system

This is a system that will not have any impact, either directly or indirectly, on product quality. These systems are designed and commissioned according to GEP only.

non-critical parameter or component

A processing parameter or component within a system where the operation, contact, data control, alarm or failure will have an indirect impact or no impact on the quality of the product.

normal operating range

The range that the manufacturer selects as the acceptable values for a parameter during normal operations. This range must be within the operating range.

operating limits

The minimum and/or maximum values that will ensure that product and safety requirements are met.

operating range

Operating range is the range of validated critical parameters within which acceptable products can be manufactured.

operational condition

This condition relates to carrying out room classification tests with the normal production process with equipment in operation, and the normal staff present in the room.

operational qualification (OQ)

OQ is the documentary evidence to verify that the equipment operates in accordance with its design specifications in its normal operating range and performs as intended throughout all anticipated operating ranges.

oral solid dosage (OSD)

Usually refers to an OSD plant that manufactures medicinal products such as tablets, capsules and powders to be taken orally.

performance qualification (PQ)

PQ is the documented verification that the process and/or the total process related to the system performs as intended throughout all anticipated operating ranges.

point extraction

Air extraction to remove dust with the extraction point located as close as possible to the source of the dust.

pressure cascade

A process whereby air flows from one area, which is maintained at a higher pressure, to another area at a lower pressure.

qualification

Qualification is the planning, carrying out and recording of tests on equipment and a system, which forms part of the validated process, to demonstrate that it will perform as intended.

relative humidity

The ratio of the actual water vapour pressure of the air to the saturated water vapour pressure of the air at the same temperature expressed as a percentage. More simply put, it is the ratio of the mass of moisture in the air, relative to the mass at 100% moisture saturation, at a given temperature.

standard operating procedure (SOP)

An authorized written procedure, giving instructions for performing operations, not necessarily specific to a given product or material, but of a more general nature (e.g. operation of equipment, maintenance and cleaning, validation, cleaning of premises and environmental control, sampling and

inspection). Certain SOPs may be used to supplement product-specific master and batch production documentation.

turbulent flow

Turbulent flow, or non-unidirectional airflow, is air distribution that is introduced into the controlled space and then mixes with room air by means of induction.

unidirectional airflow (UDAF)

Unidirectional airflow is a rectified airflow over the entire cross-sectional area of a clean zone with a steady velocity and approximately parallel streamlines (see also turbulent flow). (Modern standards no longer refer to laminar flow, but have adopted the term unidirectional airflow.)

validation

The documented act of proving that any procedure, process, equipment, material, activity or system actually leads to the expected results.

validation master plan (VMP)

VMP is a high-level document which establishes an umbrella validation plan for the entire project, and is used as guidance by the project team for resource and technical planning (also referred to as master qualification plan).

4. Protection

4.1 Product and personnel

4.1.1 Areas for the manufacture of pharmaceuticals, where pharmaceutical starting materials and products, utensils and equipment are exposed to the environment, should be classified as “clean areas”.

4.1.2 The achievement of a particular clean area classification depends on a number of criteria that should be addressed at the design and qualification stages. A suitable balance between the different criteria will be required in order to create an efficient clean area.

4.1.3 Some of the basic criteria to be considered should include:

- building finishes and structure
- air filtration
- air change rate or flushing rate
- room pressure
- location of air terminals and directional airflow
- temperature
- humidity
- material flow
- personnel flow
- equipment movement

- process being carried out
- outside air conditions
- occupancy
- type of product.

4.1.4 Air filtration and air change rates should ensure that the defined clean area classification is attained.

4.1.5 The air change rates should be determined by the manufacturer and designer, taking into account the various critical parameters. Primarily the air change rate should be set to a level that will achieve the required clean area classification.

4.1.6 Air change rates normally vary between 6 and 20 air changes per hour and are normally determined by the following considerations:

- level of protection required
- the quality and filtration of the supply air
- particulates generated by the manufacturing process
- particulates generated by the operators
- configuration of the room and air supply and extract locations
- sufficient air to achieve containment effect
- sufficient air to cope with the room heat load
- sufficient air to maintain the required room pressure.

4.1.7 In classifying the environment, the manufacturer should state whether this is achieved under "as-built" (Fig. 2), "at-rest" (Fig. 3) or "operational" (Fig. 4) conditions.

Figure 2
"As-built" condition

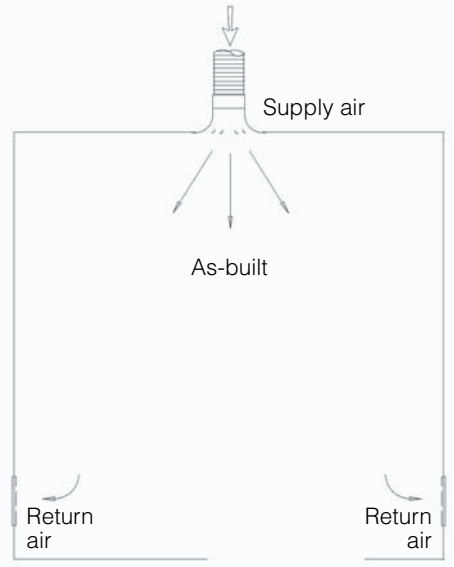


Figure 3
"At-rest" condition

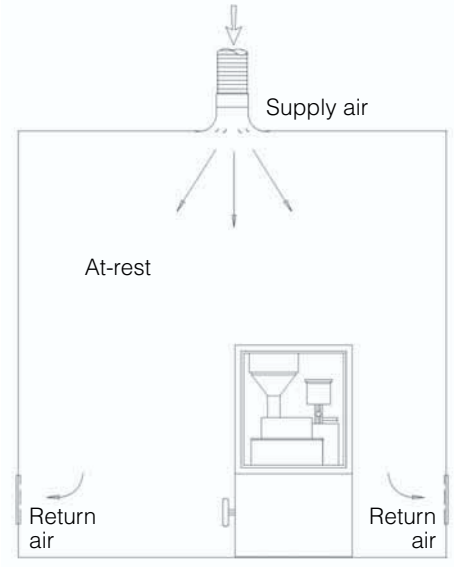
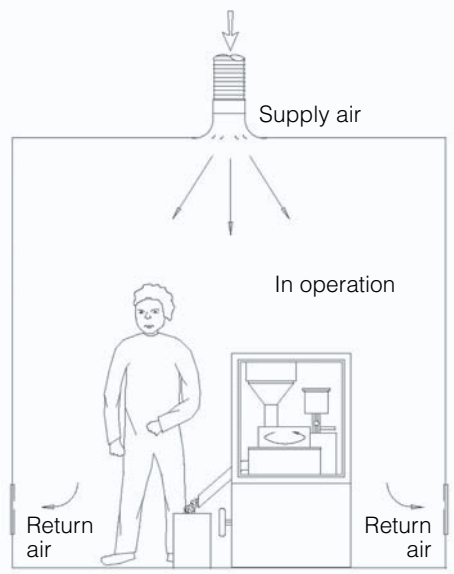


Figure 4
"Operational" Condition



4.1.8 Room classification tests in the "as-built" condition should be carried out on the bare room, in the absence of any equipment or personnel.

4.1.9 Room classification tests in the "at-rest" condition should be carried out with the equipment operating where relevant, but without any operators. Because of the amounts of dust usually generated in a solid dosage facility most clean area classifications are rated for the "at-rest" condition.

4.1.10 Room classification tests in the "operational" condition should be carried out during the normal production process with equipment operating, and the normal number of personnel present in the room. Generally a room that is tested for an "operational" condition should be able to be cleaned up to the "at-rest" clean area classification after a short clean-up time. The clean-up time should be determined through validation and is generally of the order of 20 minutes.

4.1.11 Materials and products should be protected from contamination and cross-contamination during all stages of manufacture (see also section 5.5 for cross-contamination control).
Note: contaminants may result from inappropriate premises (e.g. poor design, layout or finishing), poor cleaning procedures, contaminants brought in by personnel, and a poor HVAC system.

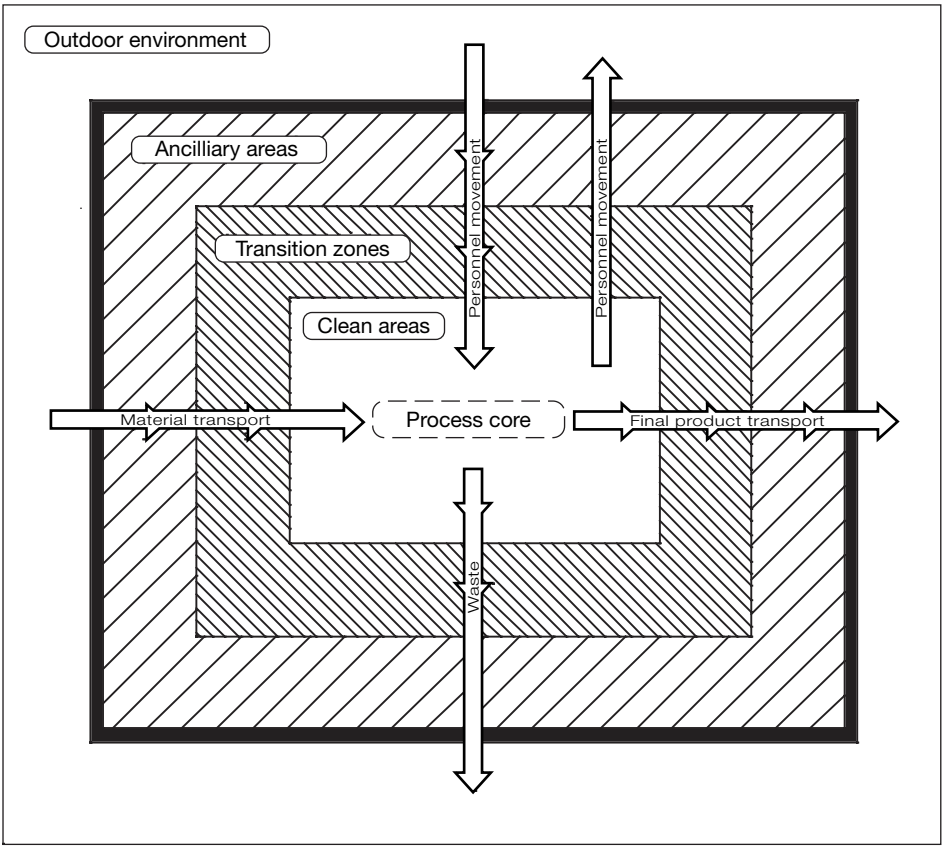
4.1.12 Airborne contaminants should be controlled through effective ventilation.

4.1.13 External contaminants should be removed by effective filtration of the supply air (See Fig. 5 for an example of a shell-like building layout to enhance containment and protection from external contaminants.)

4.1.14 Internal contaminants should be controlled by dilution and flushing of contaminants in the room, or by displacement airflow (See Figs 6 and 7 for examples of methods for the flushing of airborne contaminants.)

4.1.15 Airborne particulates and the degree of filtration should be considered critical parameters with reference to the level of product protection required.

Figure 5
Shell-like containment control concept



Note: The process core is regarded as the most stringently controlled clean zone which is protected by being surrounded by clean areas of a lower classification.

4.1.16 The level of protection and air cleanliness for different areas should be determined according to the product being manufactured, the process being used and the product's susceptibility to degradation (Table 1).

Table 1
Examples of levels of protection

Level	Condition	Example of area
Level 1	General	Area with normal housekeeping and maintenance, e.g. warehousing, secondary packing
Level 2	Protected	Area in which steps are taken to protect the exposed pharmaceutical starting material or product from contamination or degradation, e.g. manufacturing, primary packing, dispensing
Level 3	Controlled	Area in which specific environmental conditions are defined, controlled and monitored to prevent contamination or degradation of the pharmaceutical starting material or product

Figure 6
Turbulent dilution of dirty air

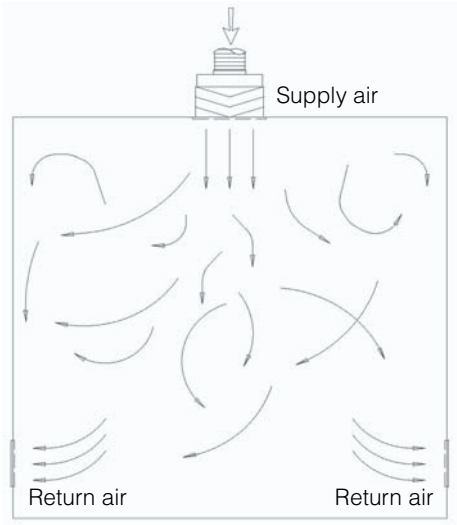
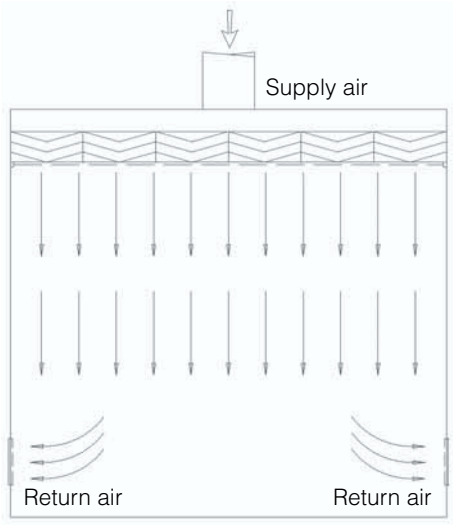


Figure 7
Unidirectional displacement of dirty air



4.2 Air filtration

Note: The degree to which air is filtered plays an important role in the prevention of contamination and the control of cross-contamination.

4.2.1 The type of filters required for different applications depends on the quality of the ambient air and the return air (where applicable) and also on the air change rates. Table 2 gives the recommended filtration levels for different levels of protection in a pharmaceutical facility. Manufacturers should determine and prove the appropriate use of filters.

Table 2
Levels of protection and recommended filtration

Level of protection	Recommended filtration
Level 1	Primary filters only (e.g. EN779 G4 filters)
Level 2 and 3	Production facility operating on 100% outside air: primary plus secondary filters (e.g. EN779 G4 plus F8 filters)
Level 2 and 3	Production facility operating on recirculated plus ambient air, where potential for cross-contamination exists: Primary plus secondary plus tertiary filters (e.g. EN779 G4 plus F8 plus EN1822 H13 filters)

Note: The filter classifications referred to above relate to the EN1822 and EN779 test standards (EN 779 relates to filter classes G1 to F9 and EN 1822 relates to filter classes H10 to U16).

4.2.2 Filter classes should always be linked to the standard test method because referring to actual filter efficiencies can be very misleading (as

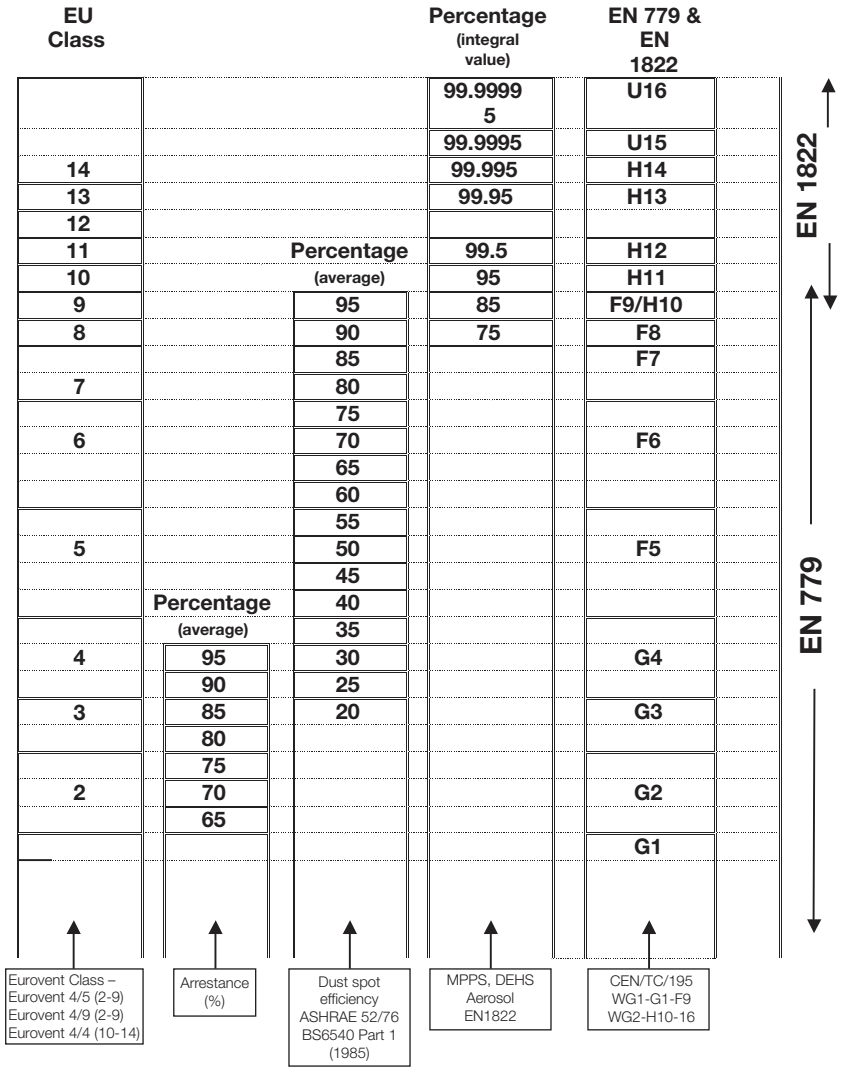
different test methods each result in a different value for the same filter) (Fig. 8).

4.2.3 In selecting filters, the manufacturer should have considered other factors, such as particularly contaminated ambient conditions, local regulations and specific product requirements. Good prefiltration extends the life of the more expensive filters downstream.

Figure 8

Comparison of filter test standards

This figure gives a rough comparison between the different filter standards (filter classes should always be connected to the standard test method).



EN, European norm (Euronorm); EU, European Union.

4.2.4 Materials for components of an HVAC system should be selected with care so that they do not become the source of contamination. Any component with the potential for liberating particulate or microbial contamination into the air stream should be located upstream of the final filters.

4.2.5 Ventilation dampers, filters and other services should be designed and positioned so that they are accessible from *outside* the manufacturing areas (service voids or service corridors) for maintenance purposes.

4.2.6 Personnel should not be a source of contamination.

4.2.7 Directional airflow within production or packing areas should assist in preventing contamination. Airflows should be planned in conjunction with operator locations, so as to minimize contamination of the product by the operator and also to protect the operator from dust inhalation.

4.2.8 HVAC air distribution components should be designed, installed and located to prevent contaminants generated within the room from being spread.

4.2.9 Supply air diffusers of the high induction type (e.g. those typically used for office-type air-conditioning) should where possible not be used in clean areas where dust is liberated. Air diffusers should be of the non-induction type, introducing air with the least amount of induction so as to maximize the flushing effect (see Figs 9–11 for illustrations of the three types of diffuser.)

4.2.10 Whenever possible, air should be exhausted from a low level in rooms to help provide a flushing effect.

Figure 9
Induction diffuser (not recommended)

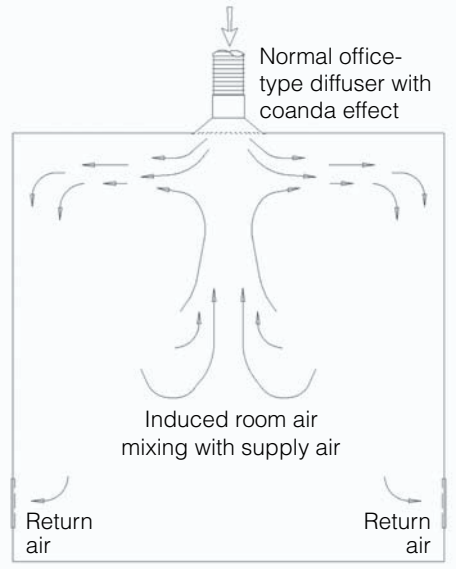
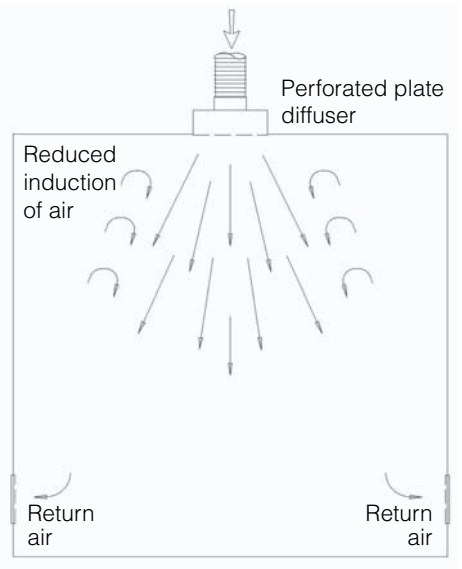


Figure 10
Perforated plate diffuser (recommended)



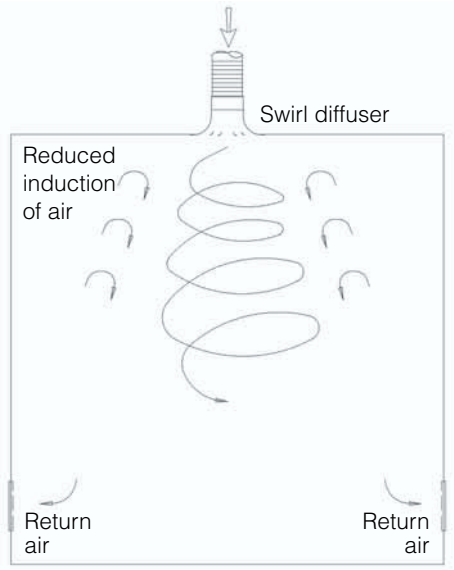
4.3 Unidirectional airflow

4.3.1 Unidirectional airflow (UDAF) should be used where appropriate to provide product protection by supplying a clean air supply over the product, minimizing the ingress of contaminants from surrounding areas.

4.3.2 Where appropriate, the unidirectional airflow should also provide protection to the operator from contamination by the product.

4.3.3 Sampling of materials such as starting materials, primary packaging materials and products, should be carried out in the same environmental conditions that are required for the further processing of the product.

Figure 11
Swirl diffuser (recommended)



4.3.4 In a weighing booth situation, the aim of the design using UDAF should be to provide dust containment.

4.3.5 A dispensary or weighing booth should be provided with unidirectional airflow for protection of the product and operator.

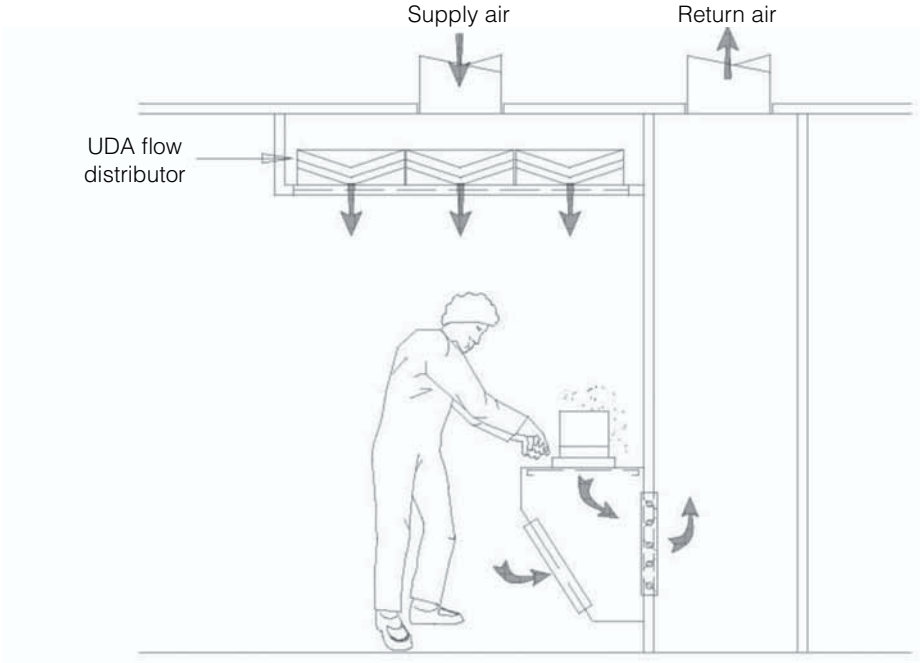
4.3.6 The source of the dust and the position in which the operator normally stands should be determined before deciding on the direction of unidirectional flow.

Example: In Fig. 12 the dust generated at the weighing station is immediately extracted through the perforated worktop, thus protecting the operator from dust inhalation, but at the same time protecting the product from contamination by the operator by means of the vertical unidirectional airflow stream.

4.3.7 The unidirectional flow velocity should be such that it does not disrupt the sensitivity of balances in weighing areas. Where necessary the velocity may be reduced to prevent inaccuracies during weighing, provided that sufficient airflow is maintained to provide containment.

4.3.8 The position in which the operator stands relative to the source of dust liberation and airflow should be determined to ensure that the operator is not in the path of an airflow that could lead to contamination of the product (Fig. 13).

Figure 12
Operator protection at weighing station



UDA, Unidirectional air.

4.3.9 Once the system has been designed and qualified with a specific layout for operators and processes, this should be maintained in accordance with an SOP.

4.3.10 There should be no obstructions in the path of a unidirectional flow air stream that may cause the operator to be exposed to dust.

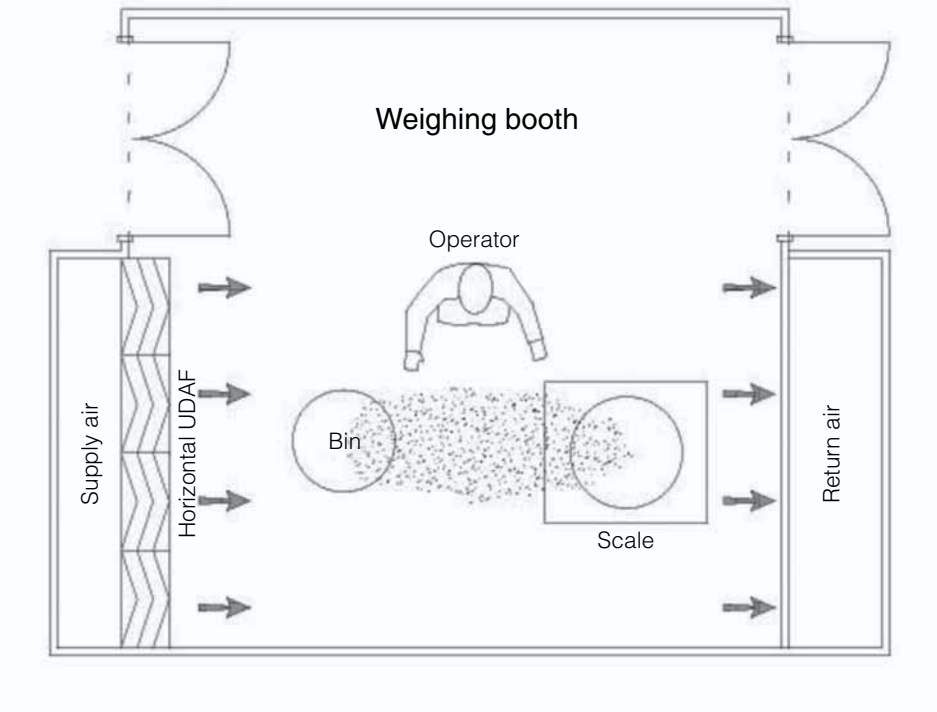
Fig. 14 illustrates the incorrect use of a weighing scale which has a solid back. The back of the weighing scale should not block the return air path as this causes air to rise vertically, resulting in a hazardous situation for the operator.

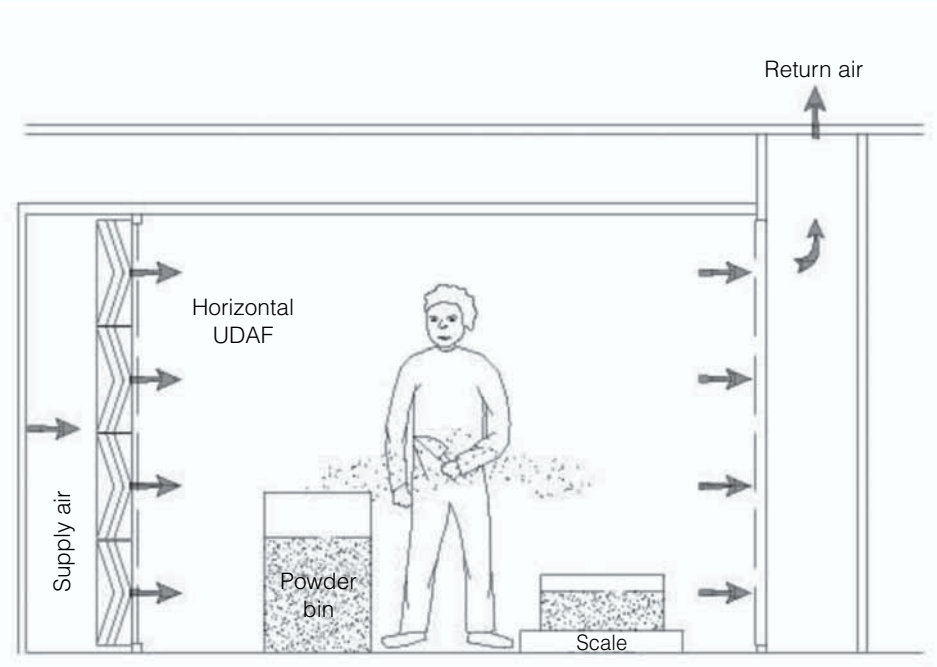
Fig. 15 illustrates a situation where an open bin is placed below a vertical unidirectional flow distributor. The downward airflow should be prevented from entering the bin, and then being forced to rise again, as this would carry dust up towards the operator's face.

Fig. 16 shows that a solid worktop can sometimes cause deflection of the vertical unidirectional airflow resulting in a flow reversal. A possible solution would be to have a 100 mm gap between the back of the table and the wall, with the air being extracted here.

4.3.11 The manufacturer should select either vertical or horizontal unidirectional flow (Fig. 17) and an appropriate airflow pattern to provide the best protection for the particular application.

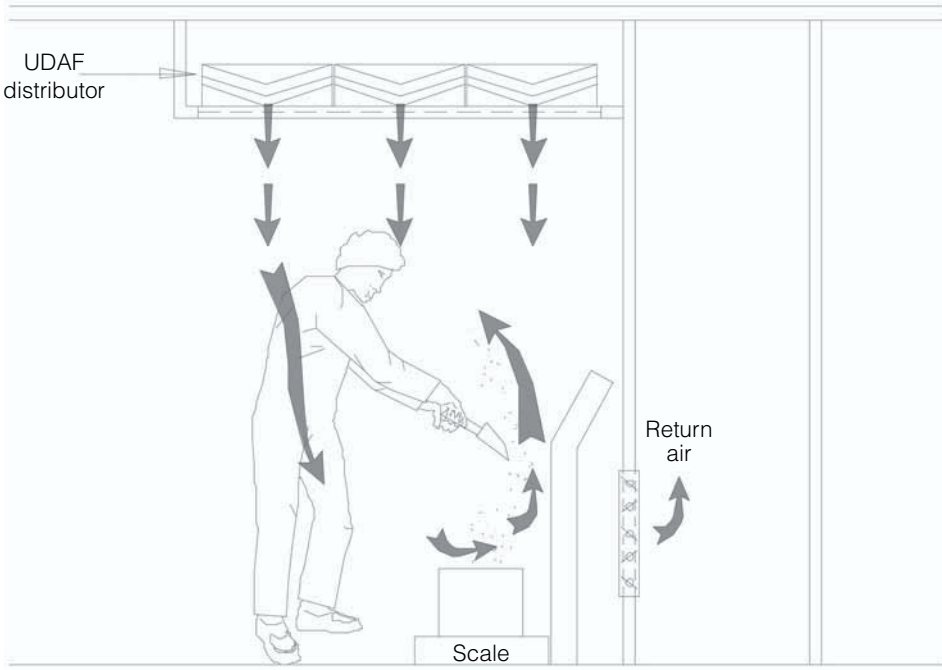
Figure 13
Operator protection by horizontal airflow





UDAF, Unidirectional airflow.

Figure 14
Operator subject to powder inhalation due to obstruction



UDAF, Unidirectional airflow.

4.4 Infiltration

4.4.1 Air infiltration of unfiltered air into a pharmaceutical plant should not be the source of contamination.

4.4.2 Manufacturing facilities should be maintained at a positive pressure relative to the outside, to limit the ingress of contaminants. Where facilities are to be maintained at negative pressures relative to the ambient pressure to prevent the escape of harmful products to the outside (such as penicillin and hormones), special precautions should be taken.

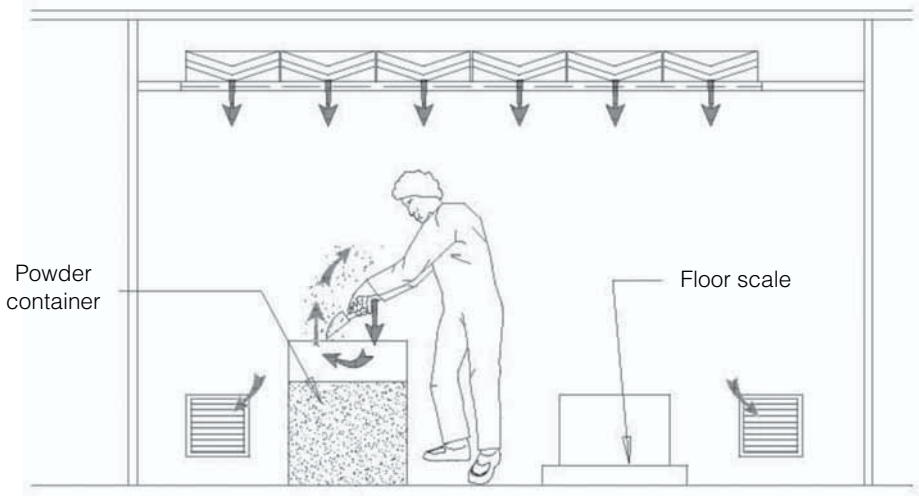
4.4.3 The location of the negative pressure facility should be carefully considered with reference to the areas surrounding it, particular attention being given to ensuring that the building structure is well sealed.

4.4.4 Negative pressure zones should, as far as possible, be encapsulated by surrounding areas with clean air supplies, so that only clean air can infiltrate into the controlled zone.

4.5 Cross-contamination

4.5.1 Where different products are manufactured at the same time, in different areas or cubicles, in a multiproduct OSD manufacturing site, mea-

Figure 15
Operator subject to powder contamination due to airflow reversal in bin



sures should be taken to ensure that dust cannot move from one cubicle to another.

4.5.2 Correct directional air movement and a pressure cascade system can assist in preventing cross-contamination. The pressure cascade should be such that the direction of airflow is from the clean corridor into the cubicles, resulting in dust containment.

4.5.3 The corridor should be maintained at a higher pressure than the cubicles, and the cubicles at a higher pressure than atmospheric pressure.

4.5.4 Containment can normally be achieved by application of the displacement concept (low pressure differential, high airflow), or the pressure differential concept (high pressure differential, low airflow), or the physical barrier concept.

4.5.5 The pressure cascade regime and the direction of airflow should be appropriate to the product and processing method used.

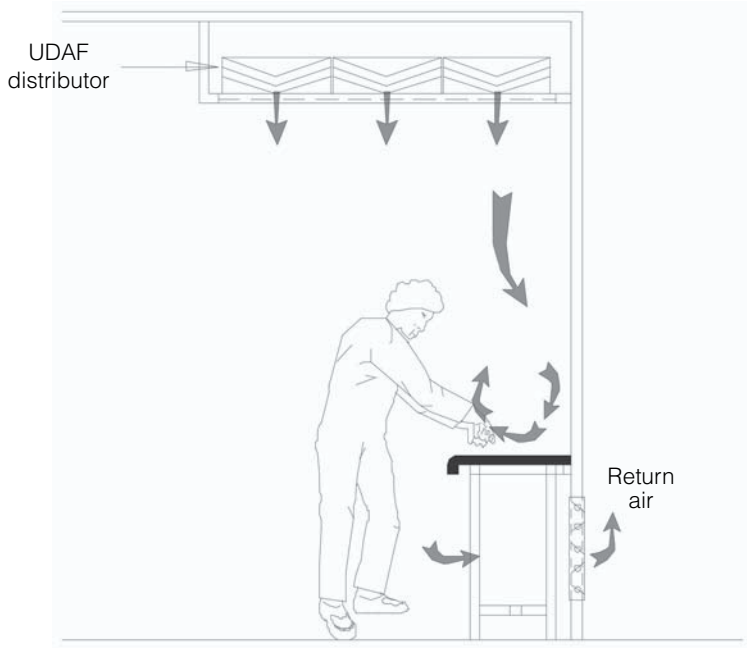
4.5.6 Highly potent products should be manufactured under a pressure cascade regime that is negative relative to atmospheric pressure.

4.5.7 The pressure cascade for each facility should be individually assessed according to the product handled and level of protection required.

4.5.8 Building structure should be given special attention to accommodate the pressure cascade design.

4.5.9 Airtight ceilings and walls, close fitting doors and sealed light fittings should be in place.

Figure 16
Operator subject to powder inhalation due to worktop obstruction



UDAF, Unidirectional airflow.

Displacement concept (low pressure differential, high airflow)

Note: This method of containment is not the preferred method, as the measurement and monitoring of airflow velocities in doorways is difficult. This concept should ideally be applied in production processes where large amounts of dust are generated.

4.5.10 Under this concept the air should be supplied to the corridor, flow through the doorway, and be extracted from the back of the cubicle. Normally the cubicle door should be closed and the air should enter the cubicle through a door grille, although the concept can be applied to an opening without a door.

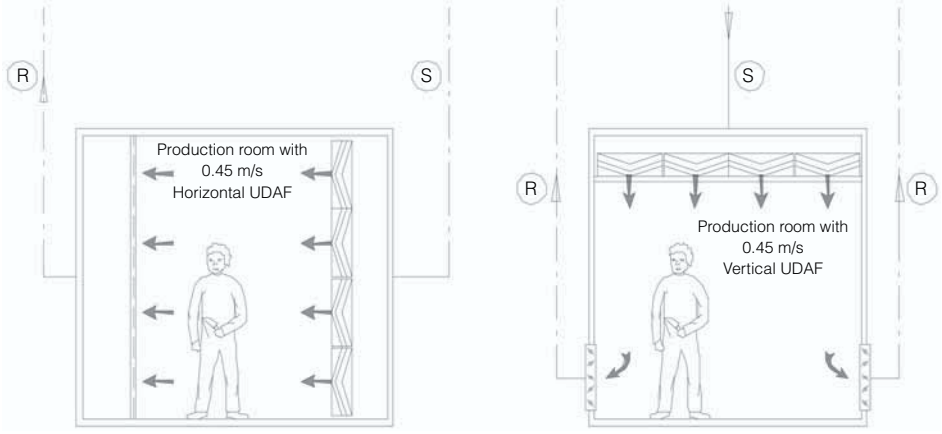
4.5.11 The velocity should be high enough to prevent turbulence within the doorway resulting in dust escaping.

4.5.12 This displacement airflow should be calculated as the product of the door area and the velocity, which generally results in fairly large air quantities.

Pressure differential concept (high pressure differential, low airflow)

Note: The pressure differential concept may normally be used in zones where little or no dust is being generated. It may be used alone or in com-

Figure 17
Diagram indicating horizontal and vertical unidirectional flow



UDAF, Unidirectional airflow.

bination with other containment control techniques and concepts, such as a double door airlock.

4.5.13 The high pressure differential between the clean and less clean zones should be generated by leakage through the gaps of the closed doors to the cubicle.

4.5.14 The pressure differential should be of sufficient magnitude to ensure containment and prevention of flow reversal, but should not be so high as to create turbulence problems.

4.5.15 In considering room pressure differentials, transient variations, such as machine extract systems, should be taken into consideration.

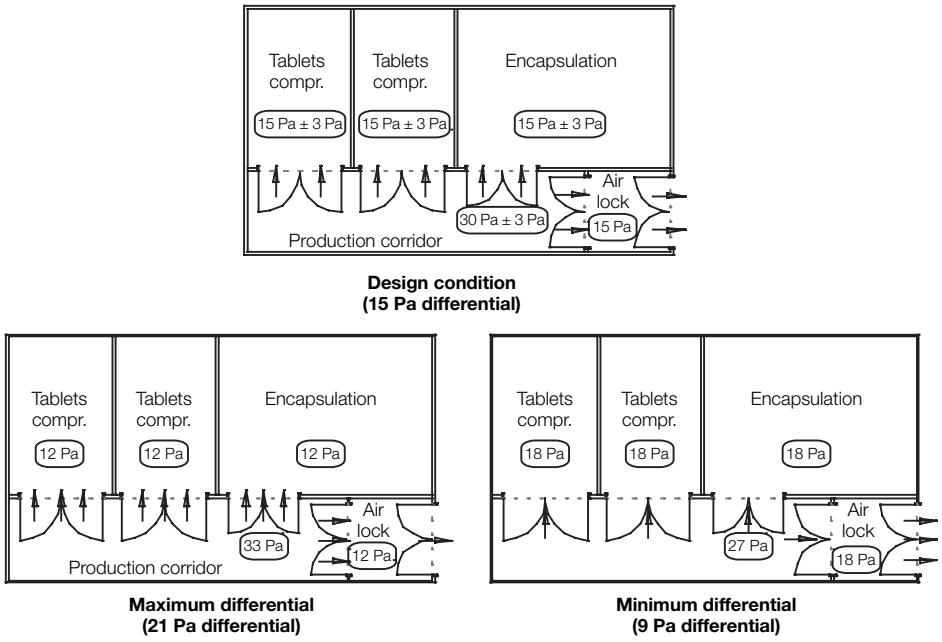
Note: The most widely accepted pressure differential for achieving containment between two adjacent zones is 15 Pa, but pressure differentials of between 5 Pa and 20 Pa may be acceptable. Where the design pressure differential is too low and tolerances are at opposite extremities, a flow reversal can take place. For example, where a control tolerance of ± 3 Pa is specified, the implications of the upper and lower tolerances on containment should be evaluated.

4.5.16 The pressure differential between adjacent rooms could be considered a critical parameter, depending on the outcome of risk analysis. The limits for the pressure differential between adjacent areas should be such that there is no risk of overlap, e.g. 5 Pa to 15 Pa in one room and 15 Pa to 30 Pa in an adjacent room, resulting in no pressure cascade, if the first room is at the maximum tolerance and the second room is at the minimum tolerance.

4.5.17 Low pressure differentials may be acceptable when airlocks (pressure sinks or pressure bubbles) are used.

4.5.18 The effect of room pressure tolerances are illustrated in Fig. 18.

Figure 18
Examples of pressure cascades



4.5.19 The pressure control and monitoring devices used should be calibrated and qualified. Compliance with specifications should be regularly verified and the results recorded. Pressure control devices should be linked to an alarm system set according to the levels determined by a risk analysis,

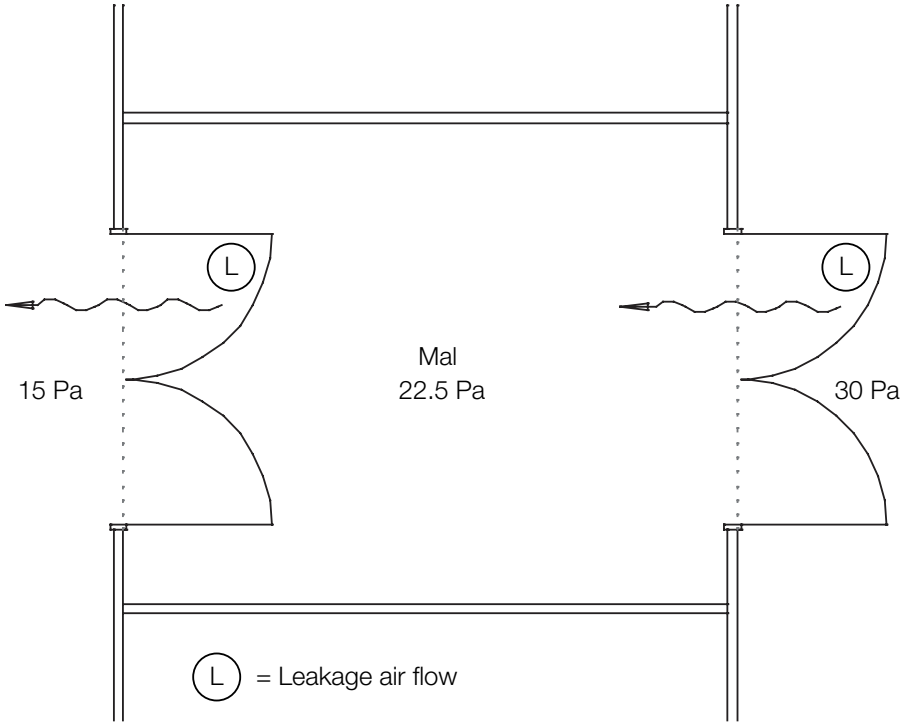
4.5.20 Manual control systems, where used, should be set up during commissioning and should not change unless other system conditions change.

4.5.21 Airlocks can be important components in setting up and maintaining pressure cascade systems.

4.5.22 Airlocks with different pressure cascade regimes include the cascade airlock, sink airlock and bubble airlock (Figs 19–21).

- Cascade airlock: high pressure on one side of the airlock and low pressure on the other.
- Sink airlock: low pressure inside the airlock and high pressure on both outer sides.
- Bubble airlock: high pressure inside the airlock and low pressure on both outer sides.

Figure 19
Example of cascade airlock



MAL, Material airlock.

4.5.23 Doors should open to the high pressure side, and be provided with self-closers. Door closer springs, if used, should be designed to hold the door closed and prevent the pressure differential from pushing the door open. Sliding doors are not recommended.

4.5.24 Central dust extraction systems should be interlocked with the appropriate air handling systems, to ensure that they operate simultaneously.

4.5.25 Room pressure imbalance between adjacent cubicles which are linked by common dust extraction ducting should be prevented.

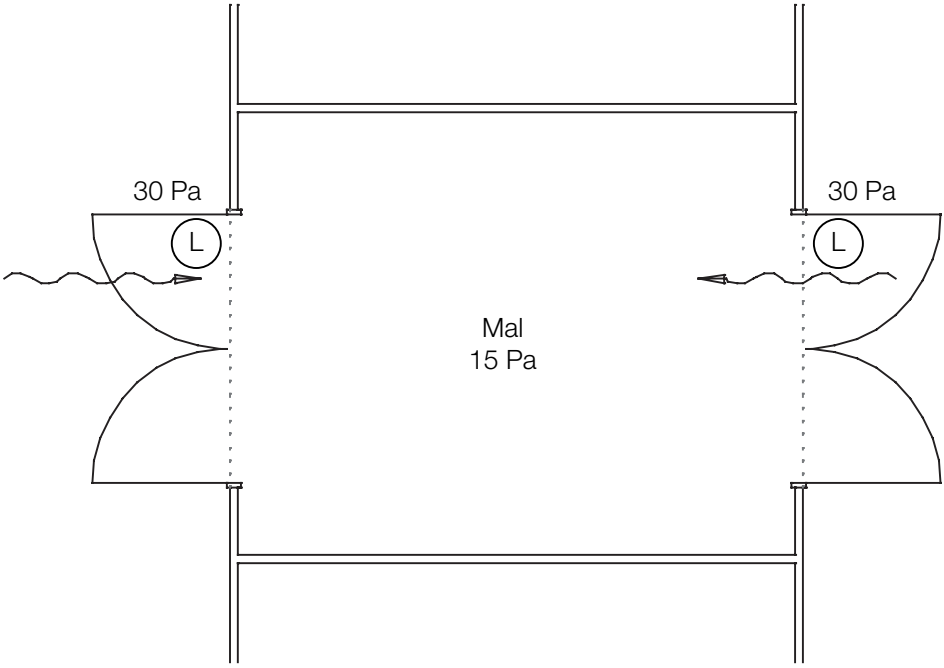
4.5.26 Air should not flow from the room with the higher pressure to the room with the lower pressure, via the dust extract ducting (this would normally occur only if the dust extraction system was inoperative).

Physical barrier concept

4.5.27 Where appropriate, an impervious barrier to prevent cross-contamination between two zones, such as barrier isolators or pumped transfer of materials, should be used.

4.5.28 Spot ventilation or capture hoods may be used as appropriate.

Figure 20
Example of sink airlock



MAL, Material airlock.

4.6 Temperature and relative humidity

4.6.1 Temperature and relative humidity should be controlled, monitored and recorded, where relevant, to ensure compliance with requirements pertinent to the materials and products, and to provide a comfortable environment for the operator where necessary.

4.6.2 Maximum and minimum room temperatures and relative humidity should be appropriate.

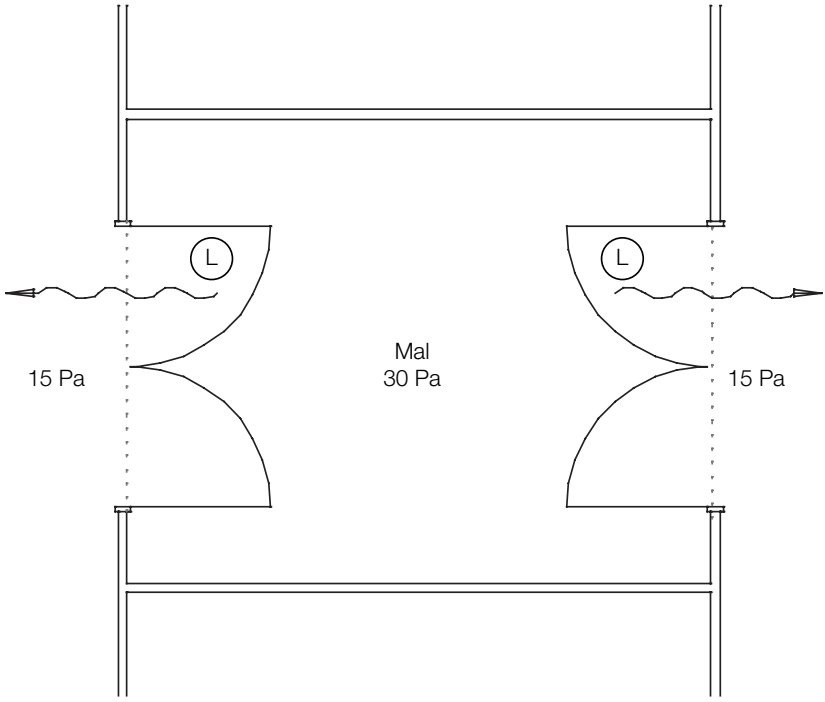
4.6.3 Temperature conditions should be adjusted to suit the needs of the operators while wearing their protective clothing.

4.6.4 The operating band, or tolerance, between the acceptable minimum and maximum temperatures should not be made too close.

4.6.5 Cubicles, or suites, in which products requiring low humidity are processed, should have well-sealed walls and ceilings and should also be separated from adjacent areas with higher humidity by means of suitable airlocks.

4.6.6 Precautions should be taken to prevent moisture migration that increases the load on the HVAC system.

Figure 21
Example of bubble airlock



MAL, Material airlock.

4.6.7 Humidity control should be achieved by removing moisture from the air, or adding moisture to the air, as relevant.

4.6.8 Dehumidification (moisture removal) may be achieved by means of either refrigerated dehumidifiers or chemical dehumidifiers.

4.6.9 Appropriate cooling media for dehumidification such as low temperature chilled water/glycol mixture or refrigerant should be used.

4.6.10 Humidifiers should be avoided if possible as they may become a source of contamination (e.g. microbiological growth). Where humidification is required, this should be achieved by appropriate means such as the injection of steam into the air stream. A product-contamination assessment should be done to determine whether pure or clean steam is required for the purposes of humidification.

4.6.11 Where steam humidifiers are used, chemicals such as corrosion inhibitors or chelating agents, which could have a detrimental effect on the product, should not be added to the boiler system.

4.6.12 Humidification systems should be well drained. No condensate should accumulate in air-handling systems.

4.6.13 Other humidification appliances such as evaporative systems, atomizers and water mist sprays, should not be used because of the potential risk of microbial contamination.

4.6.14 Duct material in the vicinity of the humidifier should not add contaminants to air that will not be filtered downstream.

4.6.15 Air filters should not be installed immediately downstream of humidifiers.

4.6.16 Cold surfaces should be insulated to prevent condensation within the clean area or on air-handling components.

4.6.17 When specifying relative humidity, the associated temperature should also be specified.

4.6.18 Chemical driers using silica gel or lithium chloride are acceptable, provided that they do not become sources of contamination.

5. Dust control

5.1 Wherever possible, the dust or vapour contamination should be removed at source. Point-of-use extraction, i.e. as close as possible to the point where the dust is generated, should be employed.

5.2 Point-of-use extraction should be either in the form of a fixed high velocity extraction point or an articulated arm with movable hood or a fixed extraction hood.

5.3 Dust extraction ducting should be designed with sufficient transfer velocity to ensure that dust is carried away, and does not settle in the ducting.

5.4 The required transfer velocity should be determined: it is dependent on the density of the dust (the denser the dust, the higher the transfer velocity should be, e.g. 15–20 m/s).

5.5 Airflow direction should be carefully chosen, to ensure that the operator does not contaminate the product, and so that the operator is not put at risk by the product.

5.6 Dust-related hazards to which the operators may be subjected should be assessed. An analysis of the type of dust and toxicity thereof should be done and the airflow direction determined accordingly.

5.7 Point extraction alone is usually not sufficient to capture all of the contaminants, and general directional airflow should be used to assist in removing dust and vapours from the room.

5.8 Typically, in a room operating with turbulent airflow, the air should be introduced from ceiling diffusers and extracted from the room at low level to help give a flushing effect in the room.

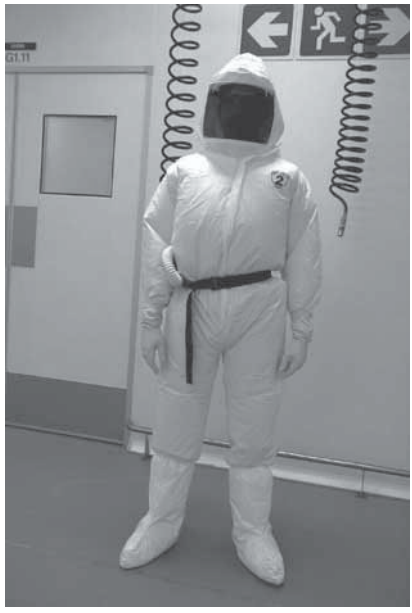
5.9 The low-level extraction should assist in drawing air downwards and away from the operator's face. The extract grilles should be positioned strategically to draw air away from the operator, but at the same time to prevent the operator from contaminating the product.

5.10 When planning the system for the extraction of vapours, the density of the vapour should be taken into account. If the vapour is lighter than air, the extract grilles should be at a high level, or possibly at both high and low levels.

5.11 When dealing with particularly harmful products, additional steps, such as handling the products in glove boxes or using barrier isolator technology, should be used.

5.12 When working with exposed products such as hormones or highly potent products, operators should wear totally enclosed garments, as indicated in Fig. 22. Operators should also be equipped with an air-breathing system that provides a supply of filtered and conditioned air. The air supply to this type of breathing apparatus should normally be through an air compressor. Filtration, temperature and humidity need to be controlled to ensure operator safety and comfort.

Figure 22
Protective garments



5.13 The rates at which fresh air is supplied to the facility should comply with national, regional and/or international regulations, to provide operators with an acceptable level of comfort and safety and also to remove odours or fumes.

5.14 The rate of fresh airflow should also be determined by leakage from the building, for pressure control purposes.

6. Protection of the environment

6.1 Dust in exhaust air

6.1.1 Exhaust air discharge points on pharmaceutical equipment and facilities, such as from fluid bed driers and tablet-coating equipment, and exhaust air from dust extraction systems, carry heavy dust loads and should be provided with adequate filtration to prevent contamination of the ambient air.

6.1.2 Where the powders are not highly potent, final filters on a dust exhaust system should be fine dust filters with a filter classification of F9 according to EN779 filter standards.

6.1.3 Where harmful substances such as penicillin, hormones, toxic powders and enzymes are manufactured, the final filters on the dust exhaust system should be HEPA filters with at least an H12 classification according to EN1822 filter standards, as appropriate.

6.1.4 For exhaust systems where the discharge contaminant is considered particularly hazardous, it may be necessary to install two banks of HEPA filters in series, to provide additional protection should the first filter fail.

6.1.5 When handling hazardous compounds, safe-change filter housings, also called "bag-in-bag-out" filters, should be used.

6.1.6 All filter banks should be provided with pressure differential indication gauges to indicate the filter dust loading.

6.1.7 Filter pressure gauges should be marked with the clean filter resistance and the change-out filter resistance.

6.1.8 Exhaust filters should be monitored regularly to prevent excessive filter loading that could force dust particles through the filter media, or could cause the filters to burst, resulting in contamination of the ambient air.

6.1.9 Sophisticated computer-based data monitoring systems may be installed, with which preventive maintenance is planned by trend logging (This type of system is commonly referred to as a building management system (BMS), building automation system (BAS) or system control and data acquisition (SCADA) system.)

6.1.10 An automated monitoring system should be capable of indicating any out-of-specification condition without delay by means of an alarm or similar system.

6.1.11 Where reverse-pulse dust collectors are used for removing dust from dust extraction systems, they should usually be equipped with cartridge filters containing a compressed air lance, and be capable of continuous operation without interrupting the airflow.

6.1.12 Alternative types of dust collectors (such as those operating with a mechanical shaker, requiring that the fan be switched off when the mechanical shaker is activated) should be used in such a manner that there is no risk of cross-contamination. There should be no disruption of airflow during a production run as the loss of airflow could disrupt the pressure cascade.

6.1.13 Mechanical-shaker dust collectors should not be used for applications where continuous airflow is required.

6.1.14 When wet scrubbers are used, the dust-slurry should be removed by a suitable drainage system.

6.1.15 The quality of the exhaust air should be determined to see whether the filtration efficiency is adequate with all types of dust collectors and wet scrubbers.

6.1.16 Where necessary, additional filtration may be provided downstream of the dust collector.

6.2 Fume removal

6.2.1 The systems for fume, dust and effluent control should be designed, installed and operated in such a manner that they do not become possible sources of contamination or cross-contamination, e.g. an exhaust-air discharge point located close to the HVAC system fresh air inlet.

6.2.2 Fumes should be removed by means of wet scrubbers or dry chemical scrubbers (deep-bed scrubbers).

6.2.3 Wet scrubbers for fume removal normally require the addition of various chemicals to the water to increase the adsorption efficiency.

6.2.4 Deep-bed scrubbers should be designed with activated carbon filters or granular chemical adsorption media. The chemical media for deep-bed scrubbers should be specific to the effluent being treated.

6.2.5 The type and quantity of the vapours to be removed should be known to enable the appropriate filter media, as well as the volume of media required to be determined.

7. HVAC systems and components

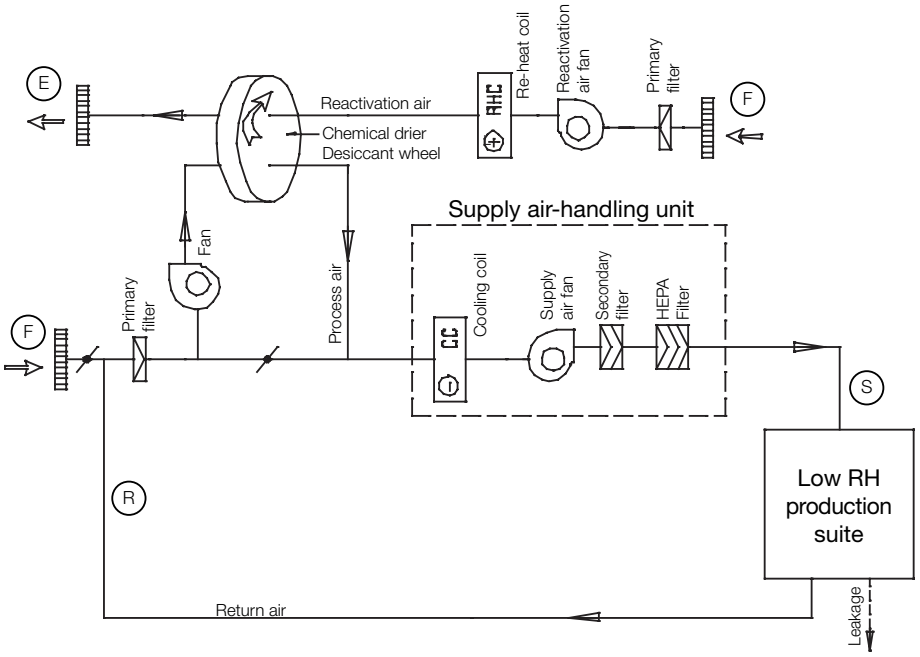
Note: The required degree of air cleanliness in most OSD manufacturing facilities can normally be achieved without the use of high-efficiency particulate air (HEPA) filters, provided the air is not recirculated. Many open product zones of OSD form facilities are capable of meeting ISO 14644-1 Class 8, “at-rest” condition, measured against particle sizes of 0.5 μm and 5 μm, but cleanliness may not be classified as such by manufacturers.

7.1 General

7.1.1 There should be no failure of a supply air fan, return air fan, exhaust air fan or dust extract system fan. Failure can cause a system imbalance, resulting in a pressure cascade malfunction with a resultant airflow reversal.

7.1.2 A schematic diagram of the airflow for a typical system serving a low humidity suite is represented in Fig. 23.

Figure 23
Air-handling system with chemical drying



HEPA, high-efficiency particulate air; RH, relative humidity.

7.1.3 Air should be dried with a chemical drier (e.g. a rotating desiccant wheel which is continuously regenerated by means of passing hot air through one segment of the wheel).

7.1.4 The figure illustrates the chemical drier handling part of the fresh air/return air mixture on a by-pass flow. The location of the chemical drier should be considered in the design phase. Examples of appropriate locations include:

— full flow of fresh/return air;
— partial handling of fresh/return air (by-pass airflow);
— return air only;
— fresh air only; or
— pre-cooled air with any of the above alternatives.

7.1.5 Possible additional components that may be required should be considered depending on the climatic conditions and locations. These may include items such as:

— frost coils on fresh air inlets in very cold climates to preheat the air;
— snow eliminators to prevent snow entering air inlets and blocking airflow;
— dust eliminators on air inlets in arid and dusty locations;
— moisture eliminators in humid areas with high rainfall; and
— fresh air pre-cooling coils for very hot or humid climates.

7.1.6 Appropriate alarm systems should be in place to alert personnel if a critical fan fails.

7.1.7 Low-level return or exhaust air grilles are usually preferred. However, where this is not possible, a higher air change rate may be needed to achieve a specified clean area classification, e.g. where ceiling return air grilles are used.

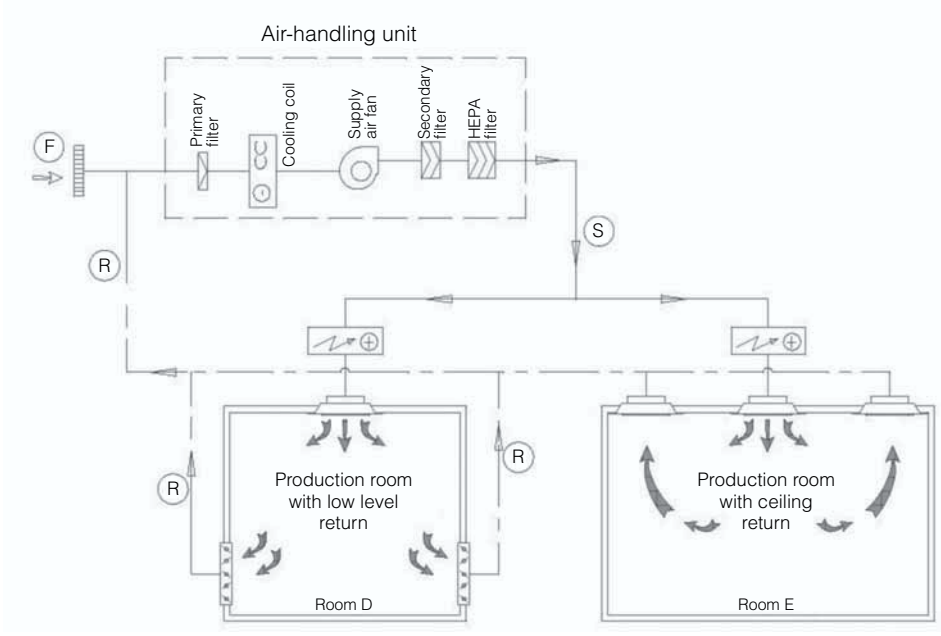
7.1.8 There may be alternative locations for return air. For example, referring to Fig. 24, room D (low-level return air) and room E (ceiling return air).

The airflow schematics of the two systems (Figs 24 and 25) indicate air-handling units with return air or recirculated air, having a percentage of fresh air added. Fig. 25 is a schematic diagram of an air-handling system serving rooms with horizontal unidirectional flow, vertical unidirectional flow and turbulent flow, for rooms A, B and C, respectively.

The airflow diagram in Fig. 24 is an example of a typical system with a lower clean area classification.

Note: There are two basic concepts of air delivery to pharmaceutical production facilities: a recirculation system, and a full fresh air system (100% outside air supply).

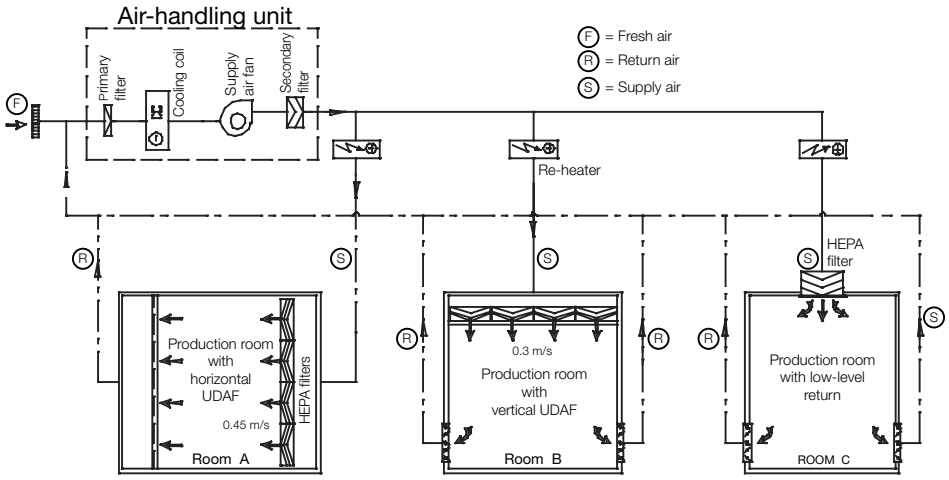
Figure 24
Air-handling system with high-efficiency particulate air filters in air-handling unit



HEPA, high-efficiency particulate air

Figure 25

Horizontal unidirectional flow, vertical unidirectional flow and turbulent flow



UDAF, unidirectional airflow; HEPA, high-efficiency particulate air.

7.2 Recirculation system

7.2.1 There should be no risk of contamination or cross-contamination (including by fumes and volatiles) due to recirculation of air.

7.2.2 Depending on the airborne contaminants in the return-air system it may be acceptable to use recirculated air, provided that HEPA filters are installed in the supply air stream to remove contaminants and thus prevent cross-contamination. The HEPA filters for this application should have an EN1822 classification of H13.

7.2.3 HEPA filters may not be required where the air-handling system is serving a single product facility and there is evidence that cross-contamination would not be possible.

7.2.4 Recirculation of air from areas where pharmaceutical dust is not generated such as secondary packing, may not require HEPA filters in the system.

7.2.5 HEPA filters may be located in the air-handling unit or placed terminally.

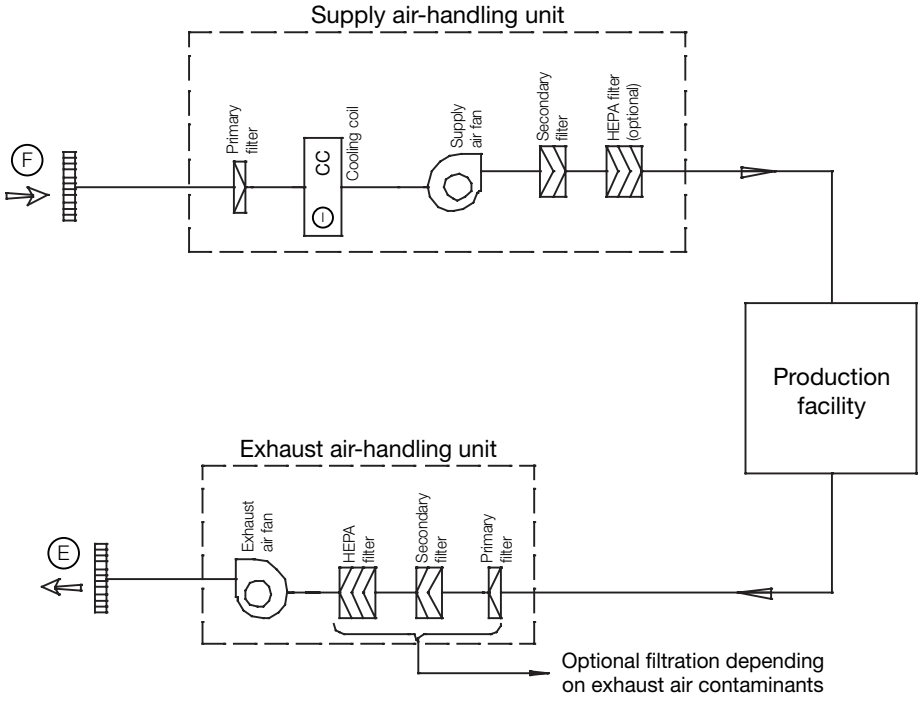
7.2.6 Air containing dust from highly toxic processes should never be recirculated to the HVAC system.

7.3 Full fresh air systems

Fig. 26 indicates a system operating on 100% fresh air and would normally be used in a facility dealing with toxic products, where recirculation of air with contaminants should be avoided.

7.3.1 The required degree of filtration of the exhaust air depends on the exhaust air contaminants and local environmental regulations.

Figure 26.
Full fresh air system



7.3.2 Energy-recovery wheels should normally not be used in multi-product facilities. When such wheels are used they should not become a source of possible contamination (see Fig. 27). *Note*: Alternatives to the energy-recovery wheels, such as crossover plate heat exchangers and water-coil heat exchangers, may be used in multiproduct facilities.

7.3.3 The potential for air leakage between the supply air and exhaust air as it passes through the wheel should be prevented. The relative pressures between supply and exhaust air systems should be such that the exhaust air system operates at a lower pressure than the supply system.

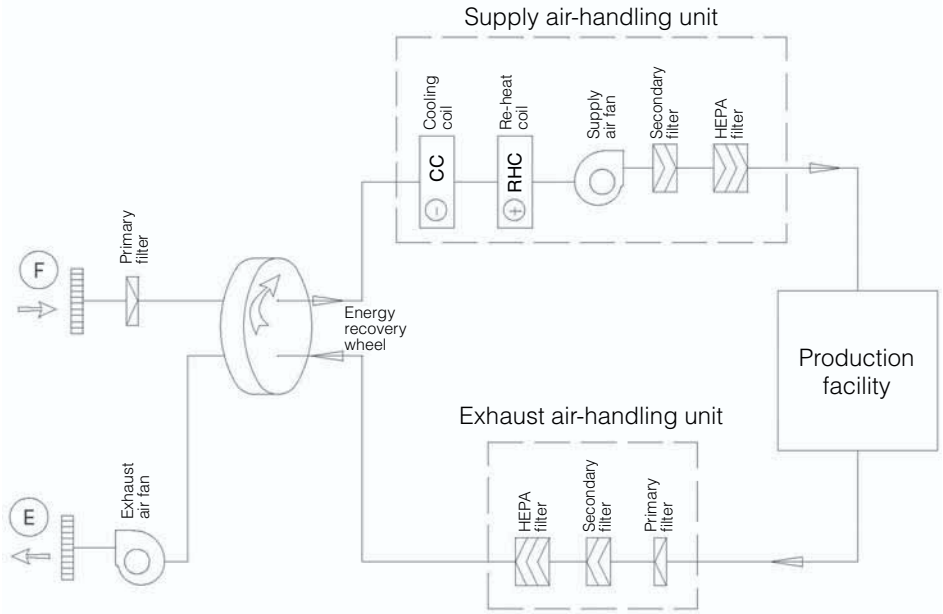
8. Commissioning, qualification and maintenance

8.1 Commissioning

8.1.1 Commissioning should include the setting up, balancing, adjustment and testing of the entire HVAC system, to ensure that it meets all the requirements, as specified in the user requirement specification (URS), and capacities as specified by the designer or developer.

8.1.2 The installation records of the system should provide documented evidence of all measured capacities of the system.

Figure 27
Full fresh-air system with energy recovery



HEPA, high-efficiency particulate air.

8.1.3 The data should include items such as the design and measurement figures for airflows, water flows, system pressures and electrical amperages. These should be contained in the operating and maintenance manuals (O & M manuals).

8.1.4 Acceptable tolerances for all system parameters should be specified prior to commencing the physical installation.

8.1.5 Training should be provided to personnel after installation of the system, and should include operation and maintenance.

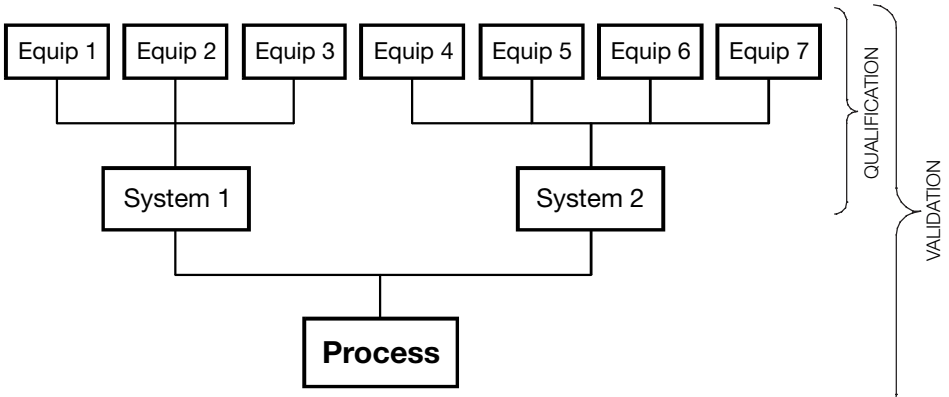
8.1.6 O & M manuals, schematic drawings, protocols and reports should be maintained as reference documents for any future changes and upgrades to the system.

8.1.7 Commissioning should be a precursor to system qualification and process validation.

8.2 Qualification

8.2.1 Validation is a many-faceted and extensive activity and is beyond the scope of these guidelines. Qualification and validation guidelines are included in: *Expert Committee on Specifications for Pharmaceutical Preparations. Fortieth report*. Geneva, World Health Organization, 2005 (WHO Technical Report Series, No. 937), Annex 4 (see also Fig. 28).

Figure 28
Qualification is a part of validation



Equip, equipment.

Manufacturers should qualify HVAC systems using a risk-based approach. The basic concepts of qualification of HVAC systems are set out below.

8.2.2 The qualification of the HVAC system should be described in a validation master plan (VMP).

8.2.3 It should define the nature and extent of testing and the test procedures and protocols to be followed.

8.2.4 Stages of the qualification of the HVAC system should include DQ, IQ, OQ and PQ.

8.2.5 Critical and non-critical parameters should be determined by means of a risk analysis for all HVAC installation components, subsystems and controls.

8.2.6 Any parameter that may affect the quality of the pharmaceutical product, or a direct impact component, should be considered a critical parameter.

8.2.7 All critical parameters should be included in the qualification process.
Note: A realistic approach to differentiating between critical and non-critical parameters is required, to avoid making the validation process unnecessarily complex.
Example:

- *The humidity of the room where the product is exposed should be considered a critical parameter when a humidity-sensitive product is being manufactured. The humidity sensors and the humidity monitoring system should, therefore, be qualified. The heat transfer system, chemical drier or steam humidifier, which is producing the humidity controlled air, is further removed from the product and may not require operational qualification.*

- *A room cleanliness classification is a critical parameter and, therefore, the room air change rates and HEPA filters should be critical parameters and require qualification. Items such as the fan generating the airflow and the primary and secondary filters are non-critical parameters, and may not require operational qualification.*

8.2.8 Non-critical systems and components should be subject to GEP and may not necessarily require qualification.

8.2.9 A change control procedure should be followed when changes are planned to the direct impact HVAC system, its components and controls that may affect critical parameters.

8.2.10 Acceptance criteria and limits should be defined during the design stage.

8.2.11 The manufacturer should define design conditions, normal operating ranges, operating ranges, and alert and action limits.

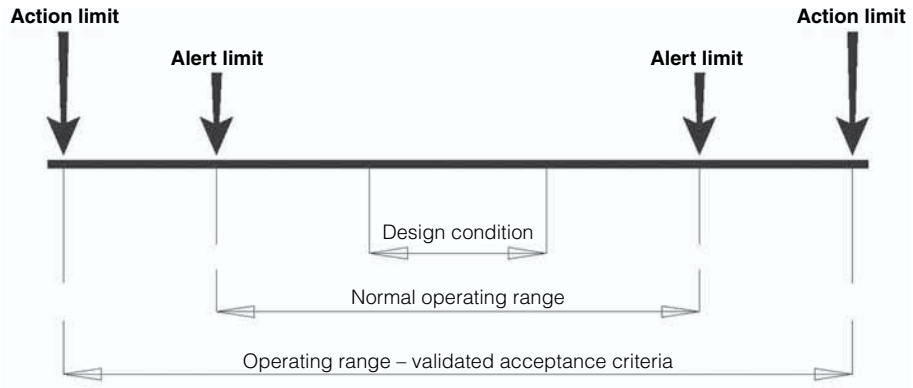
8.2.12 Design condition and normal operating ranges should be identified and set to realistically achievable parameters.

8.2.13 All parameters should fall within the design condition range during system operational qualification. Conditions may go out of the design condition range during normal operating procedures but they should remain within the operating range.

8.2.14 Out-of-limit results (e.g. action limit deviations) should be recorded and form part of the batch manufacturing records.

8.2.15 The relationships between design conditions, operating range and qualified acceptance criteria are given in Fig. 29.

Figure 29
System operating ranges



8.2.16 A narrow range of relative humidities coupled with a wide range of temperatures is unacceptable as changes in temperature will automatically give rise to variations in the relative humidity.

8.2.17 For a pharmaceutical facility, based on a risk assessment, some of the typical HVAC system parameters that should be qualified may include:

— temperature
— relative humidity
— supply air quantities for all diffusers
— return air or exhaust air quantities
— room air change rates
— room pressures (pressure differentials)
— room airflow patterns
— unidirectional flow velocities
— containment system velocities
— HEPA filter penetration tests
— room particle counts
— room clean-up rates
— microbiological air and surface counts where appropriate
— operation of de-dusting
— warning/alarm systems where applicable.

8.2.18 The maximum time interval between tests should be defined by the manufacturer. The type of facility under test and the product level of protection should be considered.
Note: Table 3 gives intervals for reference purposes only. The actual test periods may be more frequent or less frequent, depending on the product and process.

8.2.19 Periodic requalification of parameters should be done at regular intervals, e.g. annually.

8.2.20 Requalification should also be done when any change, which could affect system performance, takes place.

8.2.21 Clean-up or recovery times normally relate to the time it takes to "clean up" the room from one condition to another, e.g. the relationship between "at-rest" and "operational" conditions in the clean area may be used as the criteria for clean-up tests. Therefore, the clean-up time can be expressed as the time taken to change from an "operational" condition to an "at rest" condition.

8.3 Maintenance

8.3.1 There should be a planned preventive maintenance programme, procedures and records for the HVAC system. Records should be kept.

8.3.2 Maintenance personnel should receive appropriate training.

Table 3

Part A: schedule of tests to demonstrate compliance (for reference purposes only)

Schedule of tests to demonstrate continuing compliance			
Test parameter	Clean room class	Max. time interval	Test procedure
Particle count test (Verification of cleanliness)	All classes	6 months	Dust particle counts to be carried out and printouts of results produced. No. of readings and positions of tests to be in accordance with ISO 14644-1 Annex B
Air pressure difference (To verify absence of cross-contamination)	All classes	12 months	Log of pressure differential readings to be produced or critical plants should be logged daily, preferably continuously. A 15 Pa pressure differential between different zones is recommended. In accordance with ISO 14644-3 Annex B5*
Airflow volume (To verify air change rates)	All classes	12 months	Airflow readings for supply air and return air grilles to be measured and air change rates to be calculated. In accordance with ISO 14644-3 Annex B13*
Airflow velocity (To verify laminar flow or containment conditions)	All Classes	12 Months	Air velocities for containment systems and laminar flow protection systems to be measured. In accordance with ISO 14644-3 Annex B4*

8.3.3 HEPA filters should be changed either by a specialist or a trained person.

8.3.4 Any maintenance activity should be assessed critically to determine any impact on product quality including possible contamination.

8.3.5 Maintenance activities should normally be scheduled to take place outside production hours, and any system stoppage should be assessed with a view to the possible need for requalification of an area as a result of an interruption of the service.

Part B: recommended optional strategic tests (ISO 14644)

Schedule of tests to demonstrate continuing compliance			
Test parameter	Clean room class	Max. time interval	Test procedure
Filter leakage tests (To verify filter integrity)	All classes	24 months	Filter penetration tests to be carried out by a recognized authority to demonstrate filter media and filter seal integrity. Only required on HEPA filters. In accordance with ISO 14644-3 Annex B6*
Containment leakage (To verify absence of cross-contamination)	All classes	24 months	Demonstrate that contaminant is maintained within a room by means of: • airflow direction smoke tests • room air pressures. In accordance with ISO 14644-3 Annex B4*
Recovery (To verify clean-up time)	All classes	24 months	Test to establish time that a clean room takes to return from a contaminated condition to the specified clean room condition. This should not take more than 15 min. In accordance with ISO 14644-3 Annex B13*
Airflow visualization (To verify required airflow patterns)	All classes	24 months	Tests to demonstrate airflows: • from clean to dirty areas • do not cause cross-contamination • uniformly from laminar flow units. Demonstrated by actual or video-taped smoke tests. In accordance with ISO 14644-3 Annex B7*

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Annex 3

Supplementary guidelines on good manufacturing practices for the manufacture of herbal medicines

Introduction

Following the publication of the last revised WHO guidelines on *Good manufacturing practices for pharmaceutical products: main principles* (*1*), supporting and supplementary guidelines were developed to address specific issues connected with the manufacture of certain types of pharmaceutical product. As part of this series, the WHO *Supplementary guidelines for the manufacture of herbal medicinal products* (*2*) were issued in 1996. The guidelines were also reproduced in the second volume of the WHO compendium on *Quality assurance of pharmaceuticals* (*3*). Related WHO documents such as *Guidelines for the assessment of herbal medicines* (*4*), *General Guidelines for methodologies on research and evaluation of traditional medicine* (*5*), *Quality control methods for medicinal plant materials* (*6*), *Guidelines on good agricultural and collection practices for medicinal plants* (*7*) were also issued.

WHO's *Good manufacturing practices: main principles for pharmaceutical products* were updated in 2003 (*1, 8*). Around the turn of the millenium, various product-specific good manufacturing practice (GMP) guidelines covering herbal medicines were developed by several WHO Member States, and by the European Union. They covered several issues relevant to the production and quality control of herbal medicines in more detail. For this reason, within the framework of the *WHO Traditional Medicine Strategy: 2000–2005*, revision of the present supplementary guidelines was considered desirable; this was also endorsed by the WHO Expert Committee on Pharmaceutical Specifications at its meetings in 2002, 2003 and 2004.

These guidelines are intended to complement those provided in *Good manufacturing practices for pharmaceutical products* (*1*) and should be read in conjunction with the parent guide. The additional standards addressed by the present guidelines should therefore be considered supplementary to the general requirements set out in (*1*). They relate specifically to the production and control of herbal medicines, insofar as they mainly focus on identifying the critical steps needed to ensure good quality. Therefore the structure of these supplementary guidelines follows that of WHO's GMP main principles.

The supplementary guidelines are intended to provide WHO Member States with general and minimum technical requirements for quality assurance and control in the manufacture of herbal medicines. Each Member State should develop its own national GMP for manufacturing herbal medicines that are appropriate to the country's actual situation.

These supplementary guidelines deal exclusively with herbal medicines. Combination of herbal materials with animal materials, mineral materials, chemicals and other substances is not covered in these guidelines.

General

Unlike conventional pharmaceutical products, which are usually produced from synthetic materials by means of reproducible manufacturing techniques and procedures, herbal medicines are prepared from materials of herbal origin, which are often obtained from varied geographical and/or commercial sources. As a result it may not always be possible to ascertain the conditions to which they may have been subjected. In addition, they may vary in composition and properties. Furthermore, the procedures and techniques used in the manufacture and quality control of herbal medicines are often substantially different from those employed for conventional pharmaceutical products.

Because of the inherent complexity of naturally grown medicinal plants and the often variable nature of cultivated ones, the examples of contamination with toxic medicinal plants and/or plant parts and the number and small quantity of defined active ingredients, the production and primary processing has a direct influence on the quality of herbal medicines. For this reason, application of GMPs in the manufacture of herbal medicines is an essential tool to assure their quality.

Glossary

Established terms such as batch, bulk, intermediate product, qualification, starting material and validation are used as defined in the *WHO Good manufacturing practices for pharmaceutical products* (*1*).

The definitions given below apply to the terms as used in these guidelines. These terms and their definitions have been selected and adopted from other WHO documents and guidelines that are widely used by the WHO Member States (*1, 2, 5, 7, 8*). However, they may have different meanings in other contexts.

It should be noted that, as a consequence of the various types of "herbal medicines", the same type of material may be classified, depending on the case, in different ways (e.g. powdered plant material may be both *herbal material* and *herbal preparation* or, in a packed form, *herbal medicinal product*).

active ingredients (5)

The herbal material(s) or the herbal preparation(s) will be considered to be active ingredient(s) of a herbal medicine(s). However, if constituents with known therapeutic activities are known, the active ingredients should be standardized to contain a defined amount of this/ these constituent(s).

blending

Blending is the process of combining materials or different batches to produce a homogeneous intermediate or finished product.

constituents with known therapeutic activity (5)

Constituents with known therapeutic activity are substances or groups of substances which are chemically defined and known to contribute to the therapeutic activity of a herbal material or of a preparation.

herbal medicines (5)

Herbal medicines include *herbs, herbal materials, herbal preparations* and *finished herbal products.*

> *Herbs* include crude materials which could be derived from lichen, algae, fungi or higher plants, such as leaves, flowers, fruit, fruiting bodies, seeds, stems, wood, bark, roots, rhizomes or other parts, which may be entire, fragmented or powdered.
>
> *Herbal materials* include, in addition to herbs, fresh juices, gums, fixed oils, essential oils, resins and dry powders of herbs. In some countries, these materials may be processed by various local procedures, such as steaming, roasting or stir-baking with honey, alcoholic beverages or other materials (*5*).
>
> *Herbal preparations* are the basis for finished herbal products and may include comminuted or cut herbal materials, or extracts, tinctures and fatty oils of herbal materials. They are produced by extraction, fractionation, purification, concentration, or other physical or biological processes. They also include preparations made by steeping or heating herbal materials in alcoholic beverages and/or honey, or in other materials.
>
> *Finished herbal products* consist of herbal preparations made from one or more herbs. If more than one herb is used, the term "mixture herbal product" can also be used. Finished herbal products and mixture herbal products may contain excipients in addition to the active ingredients. However, finished herbal products or mixture herbal products to which chemically defined active substances have been added, including synthetic compounds and/or isolated constituents from herbal materials, are not considered to be herbal (*5*).

markers

Markers are chemically defined constituents of a herbal material utilized for control purposes. They may or may not contribute to the clinical efficacy. When they contribute to the clinical efficacy, however, evidence that they are solely responsible for the clinical efficacy may or may not be available. Markers are generally employed when constituents of known therapeutic activity are not known or are not clearly identified, and may be used to identify the herbal material or preparation or calculate their quantity in the finished product.

medicinal plant (2)

Medicinal plants are plants (wild or cultivated) used for medicinal purposes.

medicinal plant materials see *herbal materials (2)*

therapeutic activity (5)

Therapeutic activity refers to the successful prevention, diagnosis and treatment of physical and mental illnesses, improvement of symptoms of illnesses, as well as beneficial alteration or regulation of the physical and mental status of the body and development of a sense of general well-being.

1. Quality assurance in the manufacture of herbal medicines

In addition to the use of modern analytical techniques (especially high-performance thin-layer chromatography (HPTLC), gas chromatography (GC), high-performance liquid chromatography (HPLC), capillary electrophoresis (CE), mass spectrometry (MS) and atomic absorption (AA) to characterize herbal medicines, quality assurance also requires the control of starting materials, storage and processing. For this reason, an appropriate quality assurance system should be applied in the manufacture of herbal medicines.

Note: The methods of choice may depend on the country's infrastructure.

2. Good manufacturing practice for herbal medicines

2.1 The general principles of GMP are set out in the parent guidelines (*1*). Cultivation and collection of medicinal plants, as the starting materials for herbal medicines, are covered by other guidelines (7). The first critical step of their production where the application of GMP starts should be clearly designated (see subsection 16.1). This is of particular importance for those products which consist solely of comminuted or powdered herbal materials.

3. Sanitation and hygiene

3.1 Because of their origin, herbal materials may contain microbiological contaminants. Furthermore, during the course of harvesting and processing, herbal products that may be especially prone to microbiological contamination are produced. To avoid alterations and to reduce contamination in general, a high level of sanitation and hygiene during manufacture is necessary (for guidelines on personal hygiene see section 11, and for those on sanitation see section 12).

3.2 Water supply to the manufacturing unit should be monitored, and, if necessary treated appropriately to ensure consistency of quality.

3.3 Waste from the manufacturing unit should be disposed of regularly so as to maintain a high standard of hygiene in the manufacturing area. Clearly marked waste-bins should be available, emptied and cleaned as needed, but at least daily.

4. Qualification and validation

4.1 Qualification of critical equipment, process validation and change control are particularly important in the production of herbal medicines with unknown therapeutically active constituents. In this case, the reproducibility of the production process is the main means for ensuring consistency of quality, efficacy and safety between batches.

4.2 The written procedure should specify critical process steps and factors (such as extraction time, temperature and solvent purity) and acceptance criteria, as well as the type of validation to be conducted (e.g. retrospective, prospective or concurrent) and the number of process runs.

4.3 A formal change control system should be established to evaluate the potential effects of any changes on the quality of the herbal medicines, particu-larly content of the active ingredients. Scientific judgement should be used to determine which additional testing and validation studies are appropriate to justify a change in a validated process.

5. Complaints

5.1 The person responsible for handling complaints and deciding on the measures to be taken to deal with them should have appropriate training and/or experience in the specific features of the quality control of herbal medicines.

5.2 There are basically two types of complaint, product quality complaints and adverse reactions/events.

5.3 The first type of complaint may be caused by problems such as faulty manufacture, product defects or deterioration as well as, particular to herbal medicines, adulteration of the herbal material. These complaints should be recorded in detail and the causes thoroughly investigated (e.g. by comparison with the reference samples kept from the same batch). There should also be written procedures to describe the action to be taken.

5.4 To address the second type of complaint, reports of any adverse reaction/event should be entered in a separate register in accordance with national and international requirements. An investigation should be conducted to find out whether the adverse reaction/event is due to a quality problem and whether such reactions/events have already been reported in the literature or whether it is a new observation. In either case, complaint records

should be reviewed regularly to detect any specific or recurring problems requiring special attention and possible recall of marketed products. The *WHO guidelines on safety monitoring of herbal medicines in pharmacovigilance systems* deal with specific issues relating to adverse reactions and adverse events following treatment with herbal medicines (*9*).

5.5 The licensing authority should be kept informed of any complaints leading to a recall or restriction on supply and the records should be available for inspection.

6. Product recalls

6.1 The product recall procedure depends very much on the national regulations. There should be a standard operating procedure (SOP) for storage of recalled herbal medicines in a secure segregated area, complying with the requirements specified under subsection 12.1 (Storage areas), while their fate is decided.

7. Contract production and analysis

7.1 The contract partner should have adequate premises and equipment for the production of herbal medicines according to GMP. Validated methods should be applied for cleaning the equipment and premises carefully before using them to produce different herbal medicinal, food or cosmetic products. In the case of raw materials used for producing food, it is realistic to require manufacturing departments to be separated from those where the plant raw material will be cut or powdered for use in the preparation of medicines.

7.2 Technical aspects of the contract should be drawn up by competent persons suitably knowledgeable on the specific characteristics of herbal medicines, including their production and quality control testing.

8. Self-inspection

8.1 At least one member of the self-inspection team should possess a thorough knowledge of herbal medicines.

9. Personnel

9.1 General guidance in relation to personnel involved in the manufacture of medicinal products is given in the parent guide (*1*).

9.2 The release of herbal medicines should be authorized by a person who has been trained in the specific features of the processing and quality control of herbal materials, herbal preparations and finished herbal products.

9.3 Personnel dealing with the production and quality control of herbal medicines should have adequate training in the specific issues relevant to herbal medicines.

10. Training

10.1 The personnel should have adequate training in appropriate fields such as pharmaceutical technology, taxonomic botany, phytochemistry, pharmacognosy, hygiene, microbiology and related subjects (such as traditional use of herbal medicines).

10.2 Training records should be maintained and periodic assessments of the effectiveness of training programmes should be made.

11. Personal hygiene

11.1 Personnel entrusted with the handling of herbal materials, herbal preparations and finished herbal products should be required to have a high degree of personal hygiene and to have received adequate training in maintaining appropriate standards of hygiene. The personnel should not work if they have infectious diseases or skin diseases. Written procedures listing the basic hygiene requirements should be made available.

11.2 Personnel must be protected from contact with toxic irritants and potentially allergenic plant materials by means of adequate protective clothing. They should wear suitable gloves, caps, masks, work suits and shoes throughout the whole procedure from plant processing to product manufacture.

12. Premises

12.1 As a general principle, premises should be designed, located, constructed, adapted and maintained to suit the operations to be carried out according to GMP (*1*).

12.2 Because of their potential for degradation and infestation with certain pests as well as their sensitivity to microbiological contamination, production, and particularly storage, of herbal materials and herbal preparations assume special importance.

Storage areas

12.3 Storage areas should be well organized and tidy. Special attention should be paid to cleanliness and good maintenance. Any accidental spillage should be cleaned up immediately using methods that minimize the risk of cross-contamination of other materials, and should be reported.

12.4 The set-up of storage areas depends on the type of materials stored. The areas should be well labelled and materials stored in a such a way as to

avoid any risk of cross-contamination. An area should be identified for the quarantine of all incoming herbal materials.

12.5 Storage areas should be laid out to permit effective and orderly segregation of the various categories of materials stored, and to allow rotation of stock. Different herbal materials should be stored in separate areas.

12.6 To protect the stored material, and reduce the risk of pest attacks, the duration of storage of any herbal material in unpacked form should be kept to a minimum.

12.7 Incoming fresh herbal materials should be processed, unless specified otherwise, as soon as possible. If appropriate, they should be stored between 2 °C and 8 °C, whereas frozen materials should be stored below –18 °C.

12.8 Where materials are stored in bulk, to reduce the risk of mould formation or fermentation it is advisable to store them in aerated rooms or containers using natural or mechanical aeration and ventilation. These areas should also be equipped in such a way as to protect against the entry of insects or animals, especially rodents. Effective measures should be taken to limit the spread of animals and microorganisms brought in with the plant material and to prevent cross-contamination.

12.9 Herbal materials, even when stored in fibre drums, bags or boxes, should be stored off the floor and suitably spaced to permit cleaning and inspection.

12.10 The storage of plants, extracts, tinctures and other preparations may require special conditions of humidity and temperature or protection from light; appropriate steps should be taken to ensure that these conditions are provided, maintained, monitored and recorded.

12.11 Herbal materials, including raw herbal materials, should be kept in a dry area protected from moisture and processed following the principle of "first in, first out" (FIFO).

Production areas

12.12 Production areas should comply with the general requirements of GMP (*1*). As a rule, campaign work in their processing is necessary. However, if feasible, the use of dedicated premises is encouraged. Moreover, the special nature of the production of herbal medicines requires that particular attention be given to processing products that generate dust. When heating or boiling of the materials is necessary, a suitable air exhaust mechanism should be employed to prevent accumulation of fumes and vapours.

12.13 To facilitate cleaning and to avoid cross-contamination, adequate precautions should be taken during the sampling, weighing, mixing and processing of medicinal plants, e.g. by use of dust extraction and air-handling systems to achieve the desired differential pressure and net airflow.

13. Equipment

13.1 Processing of herbal materials may generate dust or material which is susceptible to pest-infestation or microbiological contamination and cross-contamination. Effective cleaning of the equipment is therefore particularly important.

13.2 Vacuum or wet-cleaning methods are preferred. If wet-cleaning is done, the equipment should be dried immediately after cleaning to prevent the growth of microorganisms. Cleaning with compressed air and brushes should be used with care and avoided if possible, as these methods increase the risk of product contamination.

13.3 Non-wooden equipment should be used unless tradition demands wooden material. Where it is necessary to use traditional equipment (such as wooden implements, clay pots, pallets, hoppers, etc.), this should be dedicated, unless otherwise justified. When such equipment is used, it is advisable that it does not come into direct contact with chemicals or contaminated material. If the use of wooden equipment is unavoidable, special consideration must be given to its cleaning as wooden materials may retain odours, be easily discoloured and are easily contaminated.

14. Materials

14.1 All incoming herbal materials should be quarantined and stored under appropriate conditions that take into account the degradability of herbal materials and herbal preparations.

14.2 Only permitted substances should be used for fumigation, and allowable limits for their residues together with specifications for the apparatus used should be set according to the national regulations.

Reference samples and standards

14.3 The reference standard for a herbal medicine may be a botanical sample of the herbal material; a sample of the herbal preparation, e.g. extract; or a chemically defined substance, e.g. a known active constituent, a marker substance or a known impurity. The reference standard should be of a quality appropriate to its purpose. If the herbal medicine is not described in a recognized pharmacopoeia, a herbarium sample of the flowering or fruiting top of the whole medicinal plant or part of the medicinal plant (e.g. if the whole medicinal plant is a tree) should be available. All reference standards should be stored under appropriate conditions to prevent degradation. Their expiry and/or revalidation date should be determined and indicated.

15. Documentation

15.1 The general principles for documentation are set out in the parent guidelines (*1*).

Specifications

15.2 The specifications for herbal starting materials, for herbal preparations and finished herbal products are primarily intended to define the quality rather than to establish full characterization, and should focus on those characteristics found to be useful in ensuring safety and efficacy. Consistent quality for herbal medicines (finished herbal products) can only be assured if the starting herbal materials are defined in a rigorous and detailed manner. In some cases more detailed information may be needed on aspects of collection or agricultural production. For instance, the selection of seeds, conditions of cultivation and harvesting are important aspects in producing a reproducible quality of herbal medicines (*7*). Their characterization (which also includes a detailed evaluation of the botanical and phytochemical aspects of the medicinal plant, manufacture of the herbal preparation and the finished herbal product) is therefore essential to allow the establishment of specifications which are both comprehensive and relevant.

15.3 For this reason, in addition to the data called for in (*1*), the specifications for herbal materials should as far as possible include, as a minimum, the following information:

15.4 *Herbal materials*

- The family and botanical name of the plant used according to the binomial system (genus, species, variety and the authority, i.e. the reference to the originator of the classification, e.g. Linnaeus). It may also be appropriate to add the vernacular name and the therapeutic use in the country or region of origin of the plant.
- Details of the source of the plant, such as country and/or region (also state and province, if applicable) of origin, whether it was cultivated or collected from the wild and, where applicable, method of cultivation, dates and conditions of harvesting (e.g. whether there was extreme weather), collection procedures, collection area, and brand, quantity and date of pesticide application, as required by the *WHO Guideline on good agricultural and collection practices* (*7*).
- Whether the whole plant or only a part is used. In the latter case, which part of the plant is used and its state, e.g. whole or reduced. For dried plant material, the drying system should be specified, if applicable.
- A description of the plant material based on visual (macroscopic) and/or microscopic examination.

- Suitable identity tests including, where appropriate, identification tests (such as TLC or other chromatographic fingerprint) for known active ingredients or markers. A reference sample should be available for identification purposes.
- Details of the assay, where appropriate, of active constituents or markers.
- Limit tests such as dry residue of liquids, ash value (total ash, and ash insoluble in hydrochloric acid), water-soluble extractives, moisture/water content and loss on drying (taking into account the presence of essential oils if any).
- Suitable methods for the determination of possible pesticide contamination and the acceptable limits for such contamination in herbal materials or herbal preparations used in the manufacture of herbal medicines.
- Tests for toxic metals and for likely contaminants, foreign materials and adulterants.
- Tests for fungal and/or microbiological contamination, fumigant residues (if applicable), mycotoxins, pest-infestations, radioactivity and their acceptable limits.
- Other appropriate tests (e.g. particle size, swelling index and residual solvents in herbal preparations and biological fingerprints such as induced fluorescent markers).

15.5 Specifications for starting materials (and also of primary or printed packaging materials) should include, if applicable, reference to a pharmacopoeial monograph.

15.6 If the herbal material for processing does not comply with its quality specifications, the rules that apply for its rejection, and to storage and disposal of the rejected herbal material should be included.

15.7 Starting materials derived from or comprising genetically modified organisms should comply with existing national or international regulations and the label should include this information. Chemical protection of herbal materials should be in accordance with national and/or international regulations (*7*).

15.8 Qualitative and quantitative information on the active ingredients or constituents with known therapeutic activity in herbal materials and herbal preparations should be given as described in subsection 17.5 (labelling).

15.9 *Finished herbal products*

- Tests for microbiological contamination and tests for other toxicants.
- Uniformity of weight (e.g. for tablets, single-dose powders, suppositories, capsules and herbal tea in sachets), disintegration time (for tablets, capsules, suppositories and pills), hardness and friability (for example, uncoated tablets), viscosity (for internal and external fluids), consis-

tency (semisolid preparations), and dissolution (tablets or capsules), if applicable.
- Physical appearance such as colour, odour, form, shape, size and texture.
- Loss on drying, or water content.
- Identity tests, qualitative determination of relevant substances of the plants (e.g. fingerprint chromatograms).
- Quantification of relevant active ingredients, if they have been identified, and the analytical methods that are available.
- Limit tests for residual solvents.

15.10 The control tests and specifications for the finished herbal product should be such as to allow the qualitative and quantitative determination of the main active constituents. If the therapeutic activity of constituents is known, these constituents should be indicated in the documentation. If such substances are not known (e.g. because they are part of a complex mixture), the constituents useful for assessing the quality should be identified as markers. In both cases, the assay (i.e. quantitative determination) specifications should be defined. When the therapeutic activity of the constituents cannot be determined quantitatively, specifications should be based on the determination of markers.

15.11 If either the final product or the herbal preparation contains several herbal materials and a quantitative determination of each active ingredient is not feasible, the mixture of several active ingredients may be determined. The need for such a procedure should be justified.

15.12 The concept of different acceptance criteria for release versus shelf-life specifications applies to finished herbal medicines only and not to herbal materials and herbal preparations. Adequate retest periods should be established for the latter. Examples where this may be applicable include assay and impurity (degradation product) levels.

15.13 *Herbal preparations*

The specifications of herbal preparations consist, depending on the preparation in question, of the relevant items of the specifications for herbal materials or for finished herbal products as outlined above.

Processing instructions

15.14 The processing instructions should describe the different operations to be performed on the plant material, such as drying, crushing, milling and sifting. They should also include the time and, if applicable, temperatures required in the drying process, and the methods to be used to control fragment or particle size. Instructions on removing foreign matters and other unwanted materials should also be given.

15.15 The drying conditions chosen should be appropriate to the type of plant material processed. These depend on both the character of the active ingredients (e.g. essential oils) and the type of plant part collected (e.g. root, leaf or flower). Drying by direct exposure to sunlight, if not specifically contraindicated, is possible, but drying on the ground should be avoided. If the plant should be processed fresh, without drying, the reasons and criteria determining the use of fresh material should be stated.

15.16 For the production of processed extracts, the instructions should specify details of any vehicle or solvent that may be used, the durations and temperatures needed for extraction, and any concentration stages and methods that may be required.

15.17 The permissible environmental conditions e.g. temperature, humidity and standard of cleanliness, should be stated.

15.18 Any treatment, such as fumigation, used to reduce fungal or microbiological contamination or other infestation, together with methods of determining the extent of such contamination and potential residues, should be documented. Instructions on the conduct of such procedures should be available and should include details of the process, tests and allowable limits for residues together with specifications for apparatus used.

15.19 Steps in the processes of blending and adjustment to reach defined contents of pharmacologically active constituents should be clearly documented.

15.20 The rules that apply to the disposal of spent herbal material after processing should also be elaborated.

16. Good practices in production

16.1 To ensure not only the quality, but also the safety and efficacy of complex products of biological origin such as herbal medicines, it is essential that the steps in their production are clearly defined.

Selection of the first production step covered by these guidelines

16.2 For medicinal plants — which are either cultivated or collected from the wild, and which may be used in crude form or subjected to simple processing techniques (such as cutting or comminuting) — the first critical step of their production, i.e. where the application of these guidelines starts, should be clearly designated. The rationale for this designation should be stated and documented. Guidance is provided below. However, for processes such as extraction, fermentation and purification, this rationale should be established on a case-by-case basis.

- Collection/cultivation and/or harvesting of medicinal plants should follow other relevant guidance such as the *WHO Guideline on good agri-*

culture and collection practices (GACP) for medicinal plants (*7*) or a national guideline.

- Generally, postharvest processing including primary cutting is (or should be) covered by GACP. If further comminuting is carried out in the manufacturing processing, it should be covered by GMP, or by these supplementary guidelines. If cutting and comminuting considerably reduce the probability of detection of adulteration or mix-up of herbal materials, application of these supplementary guidelines may be extended to encompass these steps.
- When the active ingredient, as defined in the Glossary, consists exclusively of comminuted or powdered herbs, application of these guidelines starts at the physical processing following primary cutting and comminuting, and includes packaging.
- When herbal extracts are used, the principles of these guidelines should apply to any production step following postharvest processing.
- In the case of finished herbal products manufactured by fermentation, application of GMP should cover any production step following primary cutting and comminuting. Particular attention should be given to the introduction of cells from a cell bank into the fermentation process.

General considerations

16.3 Materials should be handled in a fashion that is not detrimental to the product. On arrival at the processing facility, the herbal material should be promptly unloaded and unpacked. During this operation, the herbal material should not come into direct contact with the soil. Moreover, it should not be exposed directly to the sun (except in cases where this is a specific requirement, e.g. sun-drying) and it should be protected from rain and microbiological contamination.

16.4 Attention should be paid to "classification" of clean area requirements taking into account the possible high degree of initial microbial contamination of herbal materials. Classification of premises as applied to sites for the production of other pharmaceutical substances may not be applicable to processing of herbal materials. Specific and detailed requirements should be developed to cover microbial contamination of equipment, air, surfaces and personnel, and also for rest rooms, utilities, ancillary and supporting systems (e.g. water and compressed air).

16.5 Care should be taken to choose cleaning methods appropriate to the characteristics of the herbal materials being processed. Washing dried herbal materials with water is generally inappropriate. When it is necessary to clean them, an air duster or air shower should be employed. In cases when immersion of herbal materials in water or other appropriate agents (such as disinfectants) for cleaning is unavoidable (e.g. to eliminate suspected coliform bacteria), it should be kept to a minimum.

16.6 The presence of plant materials from different species and varieties, or different plant parts should be controlled during the entire production process to avoid contamination, unless it is assured that these materials are equivalent.

16.7 If time limits are specified in the master production instructions, these limits should not be exceeded, to ensure the quality of intermediates and finished products. The less is known about the constituents responsible for the therapeutic activity, the more strictly this rule should be obeyed. Such time limits, however, may be inappropriate when processing to achieve a target value (e.g. drying to a predetermined specification) because completion of processing steps is determined by in-process sampling and testing.

Mixing of batches and blending

16.8 Herbal medicines with constituents of known therapeutic activity are often standardized (i.e. adjusted to a defined content of such constituents). The methods used to achieve such standardization should be documented. If another substance is added for these purposes, it is necessary to specify, as a range, the quantity that may be added. Blending different batches of a specific herbal material (e.g. before extraction) or by mixing different lots of similar herbal preparations may also be acceptable. Records should be maintained to ensure traceability. The blending process should be adequately controlled and documented and the blended batch should be tested for conformity with established specifications where appropriate.

16.9 Batches should be mixed only if it can be guaranteed that the mixture will be homogeneous. Such processes should be well documented.

16.10 Out-of-specification batches of herbal medicines should not be blended with other batches for the purpose of meeting specifications, except for standardization of the content of constituents with known pharmaceutical therapeutic effect. Every batch incorporated into the blend should have been manufactured using an established process and should have been individually tested and found to meet appropriate specifications prior to blending.

16.11 Where particular physical attributes of the material are critical, blending operations should be validated to show uniformity of the combined batch. Validation should include testing of critical attributes (e.g. particle size distribution, bulk density and tap density) that may be affected by the blending process.

16.12 The expiry date of the blended batch should be chosen according to the date of manufacture of the oldest batch in the blend.

17. Good practices in quality control

17.1 General

17.1.1 The personnel of quality control units should have the necessary expertise in herbal medicines to enable them to carry out identification tests and recognize adulteration, the presence of fungal growth or infestations and lack of uniformity in a consignment of herbal materials.

17.1.2 The quality control of the herbal material, herbal preparations and finished herbal products should establish their quality but does not imply the control of every single constituent.

17.2 Sampling

17.2.1 Because herbal materials are an aggregate of individual plants and/or different parts of the same plant and thus have an element of heterogeneity, sampling should be carried out with special care by personnel with the necessary expertise.

17.2.2 Further advice on sampling and visual inspection is given in the WHO docu-ment *Quality control methods for medicinal plant materials* (*6*).

17.3 Testing

17.3.1 The identity and quality of herbal material, herbal preparations and of finished herbal products should be tested as described in the *Quality control methods for medicinal plant materials* (*6*). The minimum requirement for the technical equipment is for instruments to perform the tests described in (*6*). Moreover, each country should develop this basic requirement for technical equipment further, according to the country's needs.

17.3.2 Herbal material, herbal preparations (including extracts) and finished herbal products can be categorized as follows:

a. the active constituents are identified, and may be quantified as such;
b. the main group of components which contribute to the activity (i.e. the constituents with known therapeutic activity) are known and can be quantified as a total (e.g. essential oils) or calculated using a representative substance belonging to the group (e.g. flavonoids);
c. the former are not identified and/or not quantifiable, but marker substances are;
d. others, where quantification (i.e. specification for a certain quantity of a constituent) is not applicable or feasible.

17.3.3 Identification methods may be based on:

- physical and, if applicable, macroscopic (organoleptic) and microscopic tests;

- chromatographic procedures (TLC, HPLC, HPTLC or gas–liquid chromatography (GLC)), spectrometric techniques (ultraviolet-visible (UV-VIS), IR, nuclear magnetic resonance (NMR), MS); and/or
- chemical reactions.

17.3.4 The identification test methods should be specific for the herbal material, herbal preparation or finished herbal product and ideally should be capable of discriminating between the required herbal material and potential substitutes or adulterants that are likely to occur. The identification methods used for groups a and b should be capable of detecting the said active ingredients and at least the main ingredients should be stated on the label. For group c, the analytical procedure should be based on characteristic constituents, if any.

17.3.5 Reference samples of herbal materials should be made available for use in comparative tests, e.g. visual and microscopic examination and chromatography.

17.3.6 Quantitative determination of known active components for members of groups a and b and of markers for members of group c is necessary.

17.3.7 The development and execution of quality control methods for herbal materials, herbal preparations and the finished herbal products should be in line with subsection 15.1 (Specifications). Tests and quality requirements that are characteristic of the given analyte should be selected.

17.3.8 Particularly for herbal materials in group d and for finished herbal products containing such materials, characteristic chromatograms (and/or fingerprint chromatograms) may be applicable. Using these methods may ensure that the main constituents can be easily followed throughout the production process. Caution is necessary, however, for every delivery of herbal materials and every batch of herbal preparations (including extracts) will have slightly different chromatograms/fingerprints resulting from differences in chemical compositions caused by intrinsic or extrinsic factors.

17.4 Stability studies

17.4.1 If the expiry date for a herbal material or herbal preparation is given, some stability data to support the proposed shelf-life under the specified storage conditions should be available. Stability data are always required to support the shelf-life proposed for the finished herbal products.

17.4.2 Finished herbal products may contain several herbal materials or herbal preparations, and it is often not feasible to determine the stability of each active ingredient. Moreover, because the herbal material, in its entirety, is regarded as the active ingredient, a mere determination of the stability of the constituents with known therapeutic activity will not usually be sufficient. Chromatography allows tracing of changes which may occur during storage of a complex mixture of biologically active substances contained in

herbal materials. It should be shown, as far as possible, e.g. by comparisons of appropriate characteristic/fingerprint chromatograms, that the identified active ingredient (if any) and other substances present in the herbal material or finished herbal product are likewise stable and that their content as a proportion of the whole remains within the defined limits.

17.4.3 The fingerprint methods used for the stability studies should be as similar as possible to those used for quality control purposes.

17.4.4 For identified active ingredients, constituents with known therapeutic activi-ty and markers, widely used general methods of assay, and physical and sensory or other appropriate tests may be applied.

17.4.5 To determine the shelf-life of finished herbal products, strong emphasis should also be placed on other tests in subsection 15.1 (Specifications), such as moisture content, microbial contamination and general dosage form control tests.

17.4.6 The stability of preservatives and stabilizers should be monitored. When these are not used, alternative tests should be done to ensure that the product is self-preserving over its shelf-life.

17.4.7 Samples used for stability studies should be stored in the containers intended for marketing.

17.4.8 Normally the first three commercial production batches should be included in the stability-monitoring programme to confirm the expiry date. However, where data from previous studies, including pilot batches, show that the product is expected to remain stable for at least two years, fewer than three batches can be used. The testing frequency depends on the characteristics of the herbal medicinal products and should be determined on a case-by-case basis.

17.4.9 The protocol for ongoing stability studies should be documented. This would normally involve one batch per year being included in a stability-monitoring programme.

17.5 Packaging materials and labelling

17.5.1 All packaging materials, such as bottles and other materials, should be stored properly. Controls on the issue and use of these packaging materials should be adequate to ensure that incorrect labels and cartons are not used.

17.5.2 All containers and closures should be thoroughly cleaned and dried before being used to pack the products.

17.5.3 There should be adequate information on the label (or the package insert) to inform the users of the composition of the product (in addition to the brand name, if any), indications or actions, directions for use, cautions and adverse reactions if any, and the expiry date.

17.5.4 Finished herbal products may contain several herbal materials and/or herbal preparations. Unless otherwise fully justified, the full quantitative composition of the herbal ingredients should be stated on the product label. If this is not possible, at least the main ingredients should be stated on the label while the full qualitative composition could appear on the package insert.

17.5.5 The qualitative and quantitative particulars of the active ingredients in herbal materials and herbal preparations should be expressed in the following ways:

- For herbal materials and herbal preparations consisting of comminuted or powdered herbal materials:
  a. the quantity of the herbal material must be stated or, if constituents with known therapeutic activity are unidentified, the quantity of the herbal material/herbal preparation should be stated; or
  b. the quantity of the herbal material/herbal preparation should be given as a range, corresponding to a defined quantity of constituents with known therapeutic activity (see examples).

Examples:

(a)

Name of the active ingredient or active plant materials	*Quantity of constituent*
Valerianae radix	900 mg

(b)

Name of the active ingredient or active herbal materials	*Quantity of constituent*
Sennae folium	415–500 mg, corresponding to 12.5 mg of hydroxyanthracene glycosides, calculated as sennoside B

- For herbal preparations produced by steps, which exceed comminution, the nature and concentration of the solvent and the physical state of the extract should be given. Furthermore, the following should be indicated:
  a. the equivalent quantity or the ratio of a herbal material to herbal preparation must be stated if therapeutic activity of the constituents is unknown (this does not apply to fatty or essential oils); or
  b. if the therapeutic activity of the constituents is known, the quantity of the herbal preparation may be given as a range, corresponding to a defined quantity of the constituents with known therapeutic activity (see examples).

Examples:

(a)

Name of the active substance or active herbal materials	*Quantity of constituent*
Valerianae radix	25 mg dry ethanolic (96% v/v) extract (8:1) or 125 mg ethanolic (96% v/v) extract, equivalent to 1000 mg of *Valerianae radix*
other ingredient	
Dextrin	20–50 mg

(b)

Name of the active substance or active herbal materials	*Quantity of constituent*
Sennae folium	100–130 mg dry ethanolic (96% v/v) extract (8:1), corresponding to 25 mg of hydroxyanthracene glycosides, calculated as sennoside B
other ingredient	
Dextrin	20–50 mg

17.5.6 The composition of any solvent or solvent mixture used and the physical state of the extract should be identified.

17.5.7 If any other substance is added during the manufacture of the herbal preparation to adjust the level of constituents of known therapeutic activity, or for any other purpose, the added substance(s) should be described as such or as "other ingredients" and the genuine extract as the "active ingredient". However, where different batches of the same extract are used to adjust constituents with known therapeutic activity to a defined content or for any other purpose, the final mixture should be regarded as the genuine extract and listed as the "active ingredient" in the unit formula.

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WHO Technical Report Series, No. 937, 2006

Annex 4

Supplementary guidelines on good manufacturing practices: validation

1. Introduction

Validation is an essential part of good manufacturing practices (GMP). It is, therefore, an element of the quality assurance programme associated with a particular product or process. The basic principles of quality assurance have as their goal the production of products that are fit for their intended use. These principles are as follows:

- Quality, safety and efficacy must be designed and built into the product.
- Quality cannot be inspected or tested into the product.
- Each critical step of the manufacturing process must be validated. Other steps in the process must be under control to maximize the probability that the finished product consistently and predictably meets all quality and design specifications.

Validation of processes and systems is fundamental to achieving these goals. It is by design and validation that a manufacturer can establish confidence that the manufactured products will consistently meet their product specifications.

Documentation associated with validation includes:

— standard operating procedures (SOPs)
— specifications
— validation master plan (VMP)
— qualification protocols and reports
— validation protocols and reports.

The implementation of validation work requires considerable resources such as:

- *Time:* generally validation work is subject to rigorous time schedules.
- *Financial:* validation often requires the time of specialized personnel and expensive technology.
- *Human:* validation requires the collaboration of experts from various disciplines (e.g. a multidisciplinary team, comprising quality assurance, engineering, manufacturing and other disciplines, depending on the product and process to be validated).

These guidelines aim to give guidance to inspectors of pharmaceutical manufacturing facilities and manufacturers of pharmaceutical products on the requirements for validation. The main part covers the general principles of validation and qualification. In addition to the main part, appendices on validation and qualification (e.g. cleaning, computer and computerized systems, equipment, utilities and systems, and analytical methods) are included.

2. Scope

2.1 These guidelines focus mainly on the overall concept of validation and are intended as a basic guide for use by GMP inspectors and manufac-

turers. It is not the intention to be prescriptive in specific validation requirements. This document serves as general guidance only, and the principles may be considered useful in its application in the manufacture and control of active pharmaceutical ingredients (APIs) and finished pharmaceutical products. Validation of specific processes and products, for example in sterile product manufacture, requires much more consideration and a detailed approach that is beyond the scope of this document.

2.2 There are many factors affecting the different types of validation and it is, therefore, not intended to define and address all aspects related to one particular type of validation here.

2.3 Manufacturers should plan validation in a manner that will ensure regulatory compliance and ensuring that product quality, safety and consistency are not compromised.

2.4 The general text in the main part of these guidelines may be applicable to validation and qualification of premises, equipment, utilities and systems, and processes and procedures. More specific principles of qualification and validation are addressed in the appendices. Semi-automatic or fully automatic clean-in-place (CIP) systems and other special cases should be treated separately.

3. Glossary

The definitions given below apply to the terms used in these guidelines. They may have different meanings in other contexts.

calibration

The set of operations that establish, under specified conditions, the relationship between values indicated by an instrument or system for measuring (for example, weight, temperature and pH), recording, and controlling, or the values represented by a material measure, and the corresponding known values of a reference standard. Limits for acceptance of the results of measuring should be established.

computer validation

Documented evidence which provides a high degree of assurance that a computerized system analyses, controls and records data correctly and that data processing complies with predetermined specifications.

commissioning

The setting up, adjustment and testing of equipment or a system to ensure that it meets all the requirements, as specified in the user requirement specification, and capacities as specified by the designer or developer. Commissioning is carried out before qualification and validation.

concurrent validation

Validation carried out during routine production of products intended for sale.

cleaning validation

Documented evidence to establish that cleaning procedures are removing residues to predetermined levels of acceptability, taking into consideration factors such as batch size, dosing, toxicology and equipment size.

design qualification (DQ)

Documented evidence that the premises, supporting systems, utilities, equipment and processes have been designed in accordance with the requirements of GMP.

good engineering practices (GEP)

Established engineering methods and standards that are applied throughout the project life-cycle to deliver appropriate, cost-effective solutions.

installation qualification (IQ)

The performance of tests to ensure that the installations (such as machines, measuring devices, utilities and manufacturing areas) used in a manufacturing process are appropriately selected and correctly installed and operate in accordance with established specifications.

operational qualification (OQ)

Documented verification that the system or subsystem performs as intended over all anticipated operating ranges.

performance qualification (PQ)

Documented verification that the equipment or system operates consistently and gives reproducibility within defined specifications and parameters for prolonged periods. (In the context of systems, the term "process validation" may also be used.)

process validation

Documented evidence which provides a high degree of assurance that a specific process will consistently result in a product that meets its predetermined specifications and quality characteristics.

prospective validation

Validation carried out during the development stage on the basis of a risk analysis of the production process, which is broken down into individual steps; these are then evaluated on the basis of past experience to determine whether they may lead to critical situations.

qualification

Action of proving and documenting that any premises, systems and equipment are properly installed, and/or work correctly and lead to the expected results. Qualification is often a part (the initial stage) of validation, but the individual qualification steps alone do not constitute process validation.

retrospective validation

Involves the evaluation of past experience of production on the condition that composition, procedures, and equipment remain unchanged.

revalidation

Repeated validation of an approved process (or a part thereof) to ensure continued compliance with established requirements.

standard operating procedure (SOP)

An authorized written procedure giving instructions for performing operations not necessarily specific to a given product or material but of a more general nature (e.g. equipment operation, maintenance and cleaning; validation; cleaning of premises and environmental control; sampling and inspection). Certain SOPs may be used to supplement product-specific master batch production documentation.

validation

Action of proving and documenting that any process, procedure or method actually and consistently leads to the expected results.

validation protocol (or plan) (VP)

A document describing the activities to be performed in a validation, including the acceptance criteria for the approval of a manufacturing process — or a part thereof — for routine use.

validation report (VR)

A document in which the records, results and evaluation of a completed validation programme are assembled and summarized. It may also contain proposals for the improvement of processes and/or equipment.

validation master plan (VMP)

The VMP is a high-level document that establishes an umbrella validation plan for the entire project and summarizes the manufacturer's overall philosophy and approach, to be used for establishing performance adequacy. It provides information on the manufacturer's validation work programme and defines details of and timescales for the validation work to be performed, including a statement of the responsibilities of those implementing the plan.

verification

The application of methods, procedures, tests and other evaluations, in addition to monitoring, to determine compliance with the GMP principles.

worst case

A condition or set of conditions encompassing the upper and lower processing limits for operating parameters and circumstances, within SOPs, which pose the greatest chance of product or process failure when compared to ideal conditions. Such conditions do not necessarily include product or process failure.

4. Relationship between validation and qualification

Validation and qualification are essentially components of the same concept. The term qualification is normally used for equipment, utilities and systems, and validation for processes. In this sense, qualification is part of validation.

5. Validation

5.1 Approaches to validation

5.1.1 There are two basic approaches to validation — one based on evidence obtained through testing (prospective and concurrent validation), and one based on the analysis of accumulated (historical) data (retrospective validation). Whenever possible, prospective validation is preferred. Retrospective validation is no longer encouraged and is, in any case, not applicable to the manufacturing of sterile products.

5.1.2 Both prospective and concurrent validation, may include:

- extensive product testing, which may involve extensive sample testing (with the estimation of confidence limits for individual results) and the demonstration of intra- and inter-batch homogeneity;
- simulation process trials;
- challenge/worst case tests, which determine the robustness of the process; and
- control of process parameters being monitored during normal production runs to obtain additional information on the reliability of the process.

5.2 Scope of validation

5.2.1 There should be an appropriate and sufficient system including organizational structure and documentation infrastructure, sufficient personnel and financial resources to perform validation tasks in a timely manner. Management and persons responsible for quality assurance should be involved.

5.2.2 Personnel with appropriate qualifications and experience should be responsible for performing validation. They should represent different departments depending on the validation work to be performed.

5.2.3 There should be proper preparation and planning before validation is performed. There should be a specific programme for validation activities.

5.2.4 Validation should be performed in a structured way according to the documented procedures and protocols.

5.2.5 Validation should be performed:

— for new premises, equipment, utilities and systems, and processes and procedures;
— at periodic intervals; and
— when major changes have been made.

(Periodic revalidation or periodic requalification may be substituted, where appropriate, with periodic evaluation of data and information to establish whether requalification or revalidation is required.)

5.2.6 Validation should be performed in accordance with written protocols. A written report on the outcome of the validation should be produced.

5.2.7 Validation should be done over a period of time, e.g. at least three consecutive batches (full production scale) should be validated, to demonstrate consistency. Worst case situations should be considered.

5.2.8 There should be a clear distinction between in-process controls and validation. In-process tests are performed during the manufacture of each batch according to specifications and methods devised during the development phase. Their objective is to monitor the process continuously.

5.2.9 When a new manufacturing formula or method is adopted, steps should be taken to demonstrate its suitability for routine processing. The defined process, using the materials and equipment specified, should be shown to result in the consistent yield of a product of the required quality.

5.2.10 Manufacturers should identify what validation work is needed to prove that critical aspects of their operations are appropriately controlled. Significant changes to the facilities or the equipment, and processes that may affect the quality of the product should be validated. A risk assessment approach should be used to determine the scope and extent of validation required.

6. Qualification

6.1 Qualification should be completed before process validation is performed. The process of qualification should be a logical, systematic process and should start from the design phase of the premises, equipment, utilities and equipment.

6.2 Depending on the function and operation of the equipment, utility or system, only installation qualification (IQ) and operational qualification (OQ) may be required, as the correct operation of the equipment, utility or system could be considered to be a sufficient indicator of its performance (refer to Section 11 for IQ, OQ and performance qualification (PQ)). (The equipment, utility and system should then be maintained, monitored and calibrated according to a regular schedule.)

6.3 Major equipment and critical utilities and systems, however, require IQ, OQ and PQ.

7. Calibration and verification

7.1 Calibration and verification of equipment, instruments and other devices, as applicable, used in production and quality control, should be performed at regular intervals.

7.2 Personnel who carry out calibration and preventive maintenance should have appropriate qualifications and training.

7.3 A calibration programme should be available and should provide information such as calibration standards and limits, responsible persons, calibration intervals, records and actions to be taken when problems are identified.

7.4 There should be traceability to standards (e.g. national, regional or international standards) used in the calibration.

7.5 Calibrated equipment, instruments and other devices should be labelled, coded or otherwise identified to indicate the status of calibration and the date on which recalibration is due.

7.6 When the equipment, instruments and other devices have not been used for a certain period of time, their function and calibration status should be verified and shown to be satisfactory before use.

8. Validation master plan

The validation master plan (VMP) should reflect the key elements of the validation programme. It should be concise and clear and contain at least the following:

— a validation policy
— organizational structure of validation activities
— summary of facilities, systems, equipment and processes validated and to be validated
— documentation format (e.g. protocol and report format)
— planning and scheduling

— change control
— references to existing documents.

9. Qualification and validation protocols

9.1 There should be qualification and validation protocols describing the qualification and validation study to be performed.

9.2 As a minimum the protocols should include the following significant background information:

— the objectives of the study
— the site of the study
— the responsible personnel
— description of SOPs to be followed
— equipment to be used; standards and criteria for the relevant products and processes
— the type of validation
— the processes and/or parameters
— sampling, testing and monitoring requirements
— predetermined acceptance criteria for drawing conclusions.

9.3 There should be a description of the way in which the results will be analysed.

9.4 The protocol should be approved prior to use. Any changes to a protocol should be approved prior to implementation of the change.

10. Qualification and validation reports

10.1 There should be written reports on the qualification and validation performed.

10.2 Reports should reflect the protocols followed and include at least the title and objective of the study; reference to the protocol; details of material, equipment, programmes and cycles used; procedures and test methods.

10.3 The results should be evaluated, analysed and compared against the pre-determined acceptance criteria. The results should meet the acceptance criteria; deviations and out-of-limit results should be investigated. If these deviations are accepted, this should be justified. Where necessary further studies should be performed.

10.4 The departments responsible for the qualification and validation work should approve the completed report.

10.5 The conclusion of the report should state whether or not the outcome of the qualification and/or validation was considered successful.

10.6 The quality assurance department should approve the report after the final review. The criteria for approval should be in accordance with the company's quality assurance system.

10.7 Any deviations found during the validation process should be acted upon and documented as such. Corrective actions may be required.

11. Qualification stages

11.1 There are four stages of qualification:

— design qualification (DQ);
— installation qualification (IQ);
— operational qualification (OQ); and
— performance qualification (PQ).

11.2 All SOPs for operation, maintenance and calibration should be prepared during qualification.

11.3. Training should be provided to operators and training records should be maintained.

Design qualification

11.4 Design qualification should provide documented evidence that the design specifications were met.

Installation qualification

11.5 Installation qualification should provide documented evidence that the installation was complete and satisfactory.

11.6 The purchase specifications, drawings, manuals, spare parts lists and vendor details should be verified during installation qualification.

11.7 Control and measuring devices should be calibrated.

Operational qualification

11.8 Operational qualification should provide documented evidence that utilities, systems or equipment and all its components operate in accordance with operational specifications.

11.9 Tests should be designed to demonstrate satisfactory operation over the normal operating range as well as at the limits of its operating conditions (including worst case conditions).

11.10 Operation controls, alarms, switches, displays and other operational components should be tested.

11.11 Measurements made in accordance with a statistical approach should be fully described.

Performance qualification

11.12 Performance qualification should provide documented evidence that utilities, systems or equipment and all its components can consistently perform in accordance with the specifications under routine use.

11.13 Test results should be collected over a suitable period of time to prove consistency.

Requalification

11.14 Requalification should be done in accordance with a defined schedule. The frequency of requalification may be determined on the basis of factors such as the analysis of results relating to calibration, verification and maintenance.

11.15 There should be periodic requalification, as well as requalification after changes (such as changes to utilities, systems, equipment; maintenance work; and movement). (See also point 5.2.5 above and section 12 below.)

11.16 Requalification should be considered as part of the change control procedure.

Revalidation

11.17 Processes and procedures should be revalidated to ensure that they remain capable of achieving the intended results.

11.18 There should be periodic revalidation, as well as revalidation after changes. (See also points 5.2.5 above, point 11.21 below and section 12 below.)

11.19 Revalidation should be done in accordance with a defined schedule.

11.20 The frequency and extent of revalidation should be determined using a risk-based approach together with a review of historical data.

Periodic revalidation

11.21 Periodic revalidation should be performed to assess process changes that may occur gradually over a period of time, or because of wear of equipment.

11.22 The following should be considered when periodic revalidation is performed:

— master formulae and specifications;
— SOPs;
— records (e.g. of calibration, maintenance and cleaning); and
— analytical methods.

Revalidation after change

11.23 Revalidation should be performed following a change that could have an effect on the process, procedure, quality of the product and/or the product characteristics. Revalidation should be considered as part of the change control procedure.

11.24 The extent of revalidation will depend on the nature and significance of the change(s).

11.25 Changes should not adversely affect product quality or process characteristics.

11.26 Changes requiring revalidation should be defined in the validation plan and may include:

- changes in starting materials (including physical properties, such as density, viscosity or particle size distribution that may affect the process or product);
- change of starting material manufacturer;
- transfer of processes to a different site (including change of facilities and installations which influence the process);
- changes of primary packaging material (e.g. substituting plastic for glass);
- changes in the manufacturing process (e.g. mixing times or drying temperatures);
- changes in the equipment (e.g. addition of automatic detection systems, installation of new equipment, major revisions to machinery or apparatus and breakdowns);
- production area and support system changes (e.g. rearrangement of areas, or a new water treatment method);
- appearance of negative quality trends;
- appearance of new findings based on current knowledge, e.g. new technology;
- support system changes.

Changes of equipment which involve the replacement of equipment on a "like-for-like" basis would not normally require a revalidation. For example, installation of a new centrifugal pump to replace an older model would not necessarily require revalidation.

12. Change control

12.1 Changes should be controlled in accordance with a SOP as changes may have an impact on a qualified utility, system or piece of equipment, and a validated process and/or procedure.

12.2 The procedure should describe the actions to be taken, including the need for and extent of qualification or validation to be done.

12.3 Changes should be formally requested, documented and approved before implementation. Records should be maintained.

13. Personnel

13.1 Personnel should demonstrate that they are appropriately qualified, where relevant.

13.2 Personnel requiring qualification include, for example:

— laboratory analysts;
— personnel following critical procedures;
— personnel doing data entry in computerized systems; and
— risk assessors.

Appendix 1

Validation of heating, ventilation and air-conditioning systems

1. General
2. Commissioning
3. Qualification
4. Reference

1. General

1.1 The heating, ventilation and air-conditioning (HVAC) system plays an important role in the protection of the product, the personnel and the environment.

1.2 For all HVAC installation components, subsystems or parameters, critical parameters and non-critical parameters should be determined.

1.3 Some of the parameters of a typical HVAC system that should be qualified include:

— room temperature and humidity;
— supply air and return air quantities;
— room pressure, air change rate, flow patterns, particle count and clean-up rates; and
— unidirectional flow velocities and HEPA filter penetration tests.

2. Commissioning

2.1 Commissioning should involve the setting up, balancing, adjustment and testing of the entire HVAC system, to ensure that the system meets all the requirements, as specified in the user requirement specification, and capacities as specified by the designer or developer.

2.2 The installation records of the system should provide documented evidence of all measured capacities of the system.

2.3 The data should include items such as the design and measured figures for airflows, water flows, system pressures and electrical amperages. These should be contained in the operating and maintenance manuals (O & M manuals).

2.4 Acceptable tolerances for all system parameters should be specified prior to commencing the physical installation.

2.5 Training should be provided to personnel after installation of the system, and should include how to perform operation and maintenance.

2.6 O & M manuals, schematic drawings, protocols and reports should be maintained as reference documents for any future changes and upgrades to the system.

2.7 Commissioning should be a precursor to system qualification and validation.

3. Qualification

3.1 Manufacturers should qualify HVAC systems using a risk-based approach. The basic concepts of qualification of HVAC systems are set out in Fig. 1 below.

3.2 The qualification of the HVAC system should be described in a validation master plan (VMP).

3.3 The validation master plan should define the nature and extent of testing and the test procedures and protocols to be followed.

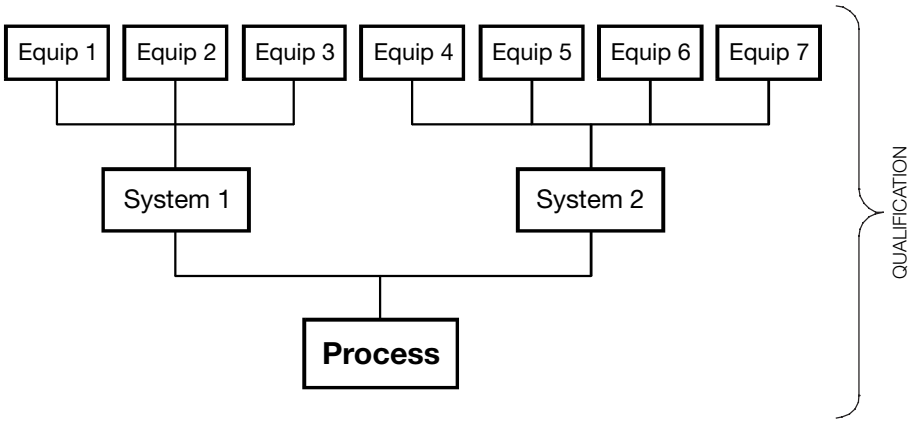
3.4 Stages of the qualification of the HVAC system should include design qualification (DQ), installation qualification (IQ), operational qualification (OQ), and performance qualification (PQ).

3.5 Critical and non-critical parameters for all HVAC installation components, subsystems and controls should be determined by means of a risk analysis.

3.6 Any parameter that may affect the quality of the pharmaceutical product should be considered a critical parameter.

3.7 All critical parameters should be included in the qualification process.

Figure 1
Qualification is a part of validation



Note: A realistic approach to differentiating between critical and non-critical parameters is required, to avoid making the validation process unnecessarily complex.

Example:

- *The humidity of the room where the product is exposed should be considered a critical parameter when a humidity-sensitive product is being manufactured. The humidity sensors and the humidity monitoring system should, therefore, be qualified. The heat transfer system, chemical drier or steam humidifier, which is producing the humidity-controlled air, is further removed from the product and may not require operational qualification.*
- *A room cleanliness classification is a critical parameter and, therefore, the room air-change rates and high-efficiency particulate air (HEPA) filters should be critical parameters and require qualification. Items such as the fan generating the airflow and the primary and secondary filters are non-critical parameters, and may not require operational qualification.*

3.8 Non-critical systems and components should be subject to good engineering practice (GEP) and may not necessarily require full qualification.

3.9 A change control procedure should be followed when changes are planned to the HVAC system, its components, and controls, that may affect critical parameters.

3.10 Acceptance criteria and limits should be defined during the design stage.

3.11 The manufacturer should define design conditions, normal operating ranges, operating ranges, and alert and action limits.

3.12 Design condition and normal operating ranges should be identified and set to realistically achievable parameters.

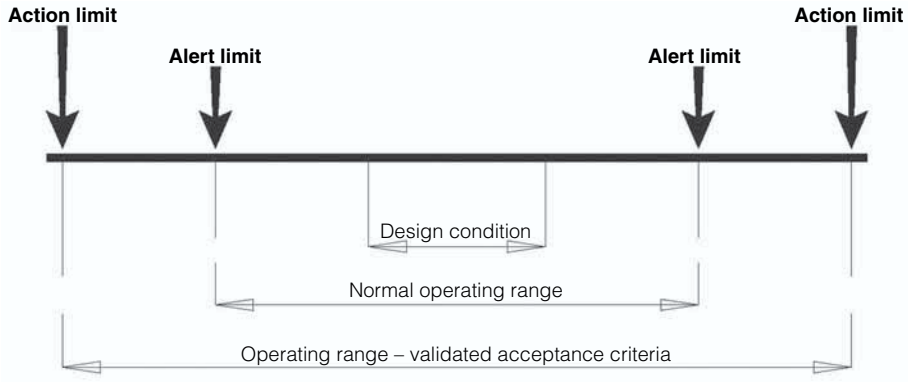
3.13 All parameters should fall within the design condition range during system operational qualification. Conditions may go out of the design condition range during normal operating procedures but they should remain within the operating range.

3.14 Out-of-limit results (e.g. action limit deviations) should be recorded and form part of the batch manufacturing records.

3.15 The relationships between design conditions, operating range and qualified acceptance criteria are given in Figure 2.

3.16 A narrow range of relative humidities coupled with a wide range of temperatures is unacceptable as changes in temperature will automatically give rise to variations in the relative humidity.

Figure 2
System operating ranges



3.17 Some of the typical HVAC system parameters that should be qualified for a pharmaceutical facility may include:

— temperature
— relative humidity
— supply air quantities for all diffusers
— return air or exhaust air quantities
— room air-change rates
— room pressures (pressure differentials)
— room airflow patterns
— unidirectional flow velocities
— containment system velocities
— HEPA filter penetration tests
— room particle counts
— room clean-up rates
— microbiological air and surface counts where appropriate
— operation of de-dusting
— warning/alarm systems where applicable.

3.18 The maximum time interval between tests should be defined by the manufacturer. The type of facility under test and the product level of protection should be considered.
Note: Table 1 gives intervals for reference purposes only. The actual test periods may be more or less frequent, depending on the product and process.

3.19 Periodic requalification of parameters should be done at regular intervals, e.g. annually.

3.20 Requalification should also be done when any change, which could affect system performance, takes place.

3.21 Clean-up times normally relate to the time it takes to "clean up" the room from one condition to another, e.g. the relationship between "at-rest"

Table 1.
Strategic tests (for reference purposes only)

Schedule of tests to demonstrate continuing compliance			
Test parameter	Clean area class	Max. time interval	Test procedure
Particle count test (verification of cleanliness)	All classes	6 months	Dust particle counts to be carried out and printouts of results produced. No. of readings and positions of tests to be in accordance with ISO 14644-1 Annex B
Air pressure difference (To verify absence of cross-contamination)	All classes	12 months	Log of pressure differential readings to be produced or critical plants should be logged daily, preferably continuously. A 15 Pa pressure differential between different zones is recommended. In accordance with ISO 14644-3 Annex B5
Airflow volume (To verify air change rates)	All classes	12 months	Airflow readings for supply air and return air grilles to be measured and air change rates to be calculated. In accordance with ISO 14644-3 Annex B13
Airflow velocity (To verify unidirectional flow or containment conditions)	All classes	12 months	Air velocities for containment systems and unidirectional flow protection systems to be measured. In accordance with ISO 14644-3 Annex B4

Source: ISO 14644 Standard, given for reference purposes only.

and "operational" conditions in the clean area may be used as the criteria for clean-up tests. Therefore, the clean-up time can be expressed as the time taken to change from an "operational" condition to an "at-rest" condition.

4. Reference

1. Supplementary guidelines on good manufacturing practices for heating, ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fortieth report.* Geneva, World Health Organization, 2006 (WHO Technical Report Series, No. 937), Annex 2.

Appendix 2

Validation of water systems for pharmaceutical use

1. General

1.1 All water-treatment systems should be subject to planned maintenance, validation and monitoring.

1.2 Validation of water systems should consist of at least three phases: Phase 1: investigational phase; Phase 2: short-term control; and Phase 3: long-term control.

1.3 During the period following phase 3 (typically running for one year) the objective should be to demonstrate that the system is under control over a long period of time. Sampling may be reduced from, e.g. daily to weekly.

1.4 The validation performed and revalidation requirements should be included in the "Water quality manual".

2. Start-up and commissioning of water systems

2.1 Planned, well-defined, successful and well-documented commissioning is an essential precursor to successful validation of water systems. The commissioning work should include setting to work, system set-up, controls, loop tuning and recording of all system performance parameters. If it is intended to use or refer to commissioning data within the validation work then the quality of the commissioning work and associated data and documentation must be commensurate with the validation plan requirements.

3. Qualification

3.1 Water for pharmaceutical use (WPU), purified water (PW), highly purified water (HPW) and water for injections (WFI) systems are all considered to be direct impact, quality critical systems that should be qualified. The qualification should follow the validation convention of design review or design qualification (DQ), installation qualification (IQ), operational qualification (OQ) and performance qualification (PQ).

3.2 This guidance does not define the standard requirements for the conventional validation stages DQ, IQ and OQ, but concentrates on the particular PQ approach that should be used for WPU systems to demonstrate

their consistent and reliable performance. A three-phase approach should be used to satisfy the objective of proving the reliability and robustness of the system in service over an extended period.

Phase 1. A test period of 2–4 weeks should be spent monitoring the system intensively. During this period the system should operate continuously without failure or performance deviation. The following procedures should be included in the testing approach.

- Undertake chemical and microbiological testing in accordance with a defined plan.
- Sample the incoming feed-water to verify its quality.
- Sample after each step in the purification process daily.
- Sample at each point of use and at other defined sampling points daily.
- Develop appropriate operating ranges.
- Develop and finalize operating, cleaning, sanitizing and maintenance procedures.
- Demonstrate production and delivery of product water of the required quality and quantity.
- Use and refine the standard operating procedures (SOPs) for operation, maintenance, sanitization and troubleshooting.
- Verify provisional alert and action levels.
- Develop and refine the test-failure procedure.

Phase 2. A further test period of 2–4 weeks should be spent carrying out further intensive monitoring while deploying all the refined SOPs after the satisfactory completion of phase 1. The sampling scheme should be generally the same as in phase 1. Water can be used for manufacturing purposes during this phase. The approach should also:

— demonstrate consistent operation within established ranges; and
— demonstrate consistent production and delivery of water of the required quantity and quality when the system is operated in accordance with the SOPs.

Phase 3. Phase 3 typically runs for one year after the satisfactory completion of phase 2. Water can be used for manufacturing purposes during this phase which has the following objectives and features:

- Demonstrate extended reliable performance.
- Ensure that seasonal variations are evaluated.
- The sample locations, sampling frequencies and tests should be reduced to the normal routine pattern based on established procedures proven during phases 1 and 2.

Reference

1. *WHO good manufacturing practices: water for pharmaceutical use.* Geneva, World Health Organization 2005 (WHO Technical Report Series, No. 929), Annex 3.

Appendix 3

Cleaning validation

1. Principle

1.1 The objectives of good manufacturing practices (GMP) include the prevention of possible contamination and cross-contamination of pharmaceutical starting materials and products.

1.2 Pharmaceutical products can be contaminated by a variety of substances such as contaminants associated with microbes, previous products (both active pharmaceutical ingredients (API) and excipient residues), residues of cleaning agents, airborne materials, such as dust and particulate matter, lubricants and ancillary material, such as disinfectants, and decomposition residues from:

— product residue breakdown occasioned by, e.g. the use of strong acids and alkalis during the cleaning process; and
— breakdown products of the detergents, acids and alkalis that may be used as part of the cleaning process.

1.3 Adequate cleaning procedures play an important role in preventing contamination and cross-contamination. Validation of cleaning methods provides documented evidence that an approved cleaning procedure will provide clean equipment, suitable for its intended use.

1.4 The objective of cleaning validation is to prove that the equipment is consistently cleaned of product, detergent and microbial residues to an acceptable level, to prevent possible contamination and cross-contamination.

1.5 Cleaning validation is not necessarily required for non-critical cleaning such as that which takes place between batches of the same product (or different lots of the same intermediate in a bulk process), or of floors, walls, the outside of vessels, and following some intermediate steps.

1.6 Cleaning validation should be considered important in multiproduct facilities and should be performed among others, for equipment, sanitization procedures and garment laundering.

2. Scope

2.1 These guidelines describe the general aspects of cleaning validation, excluding specialized cleaning or inactivation that may be required, e.g. for removal of viral or mycoplasmal contaminants in the biological manufacturing industry.

2.2 Normally cleaning validation would be applicable for critical cleaning such as cleaning between manufacturing of one product and another, of surfaces that come into contact with products, drug products and API.

3. General

3.1 There should be written SOPs detailing the cleaning process for equipment and apparatus. The cleaning procedures should be validated.

3.2 The manufacturer should have a cleaning policy and an appropriate procedure for cleaning validation, covering:

- surfaces that come into contact with the product;
- cleaning after product changeover (when one pharmaceutical formulation is being changed for another, completely different formulation);
- between batches in campaigns (when the same formula is being manufactured over a period of time, and on different days);
- bracketing products for cleaning validation. (This often arises where products contain substances with similar properties (such as solubility) or the same substance in different strengths. An acceptable strategy is to first manufacture the more dilute form (not necessarily the lowest dose) and then the most concentrated form. There are sometimes "families" of products which differ slightly as to actives or excipients.); and
- periodic evaluation and revalidation of the number of batches manufactured between cleaning validations.

3.3. At least three consecutive applications of the cleaning procedure should be performed and shown to be successful to prove that the method is validated.

4. Cleaning validation protocols and reports

4.1 Cleaning validation protocols

4.1.1 Cleaning validation should be described in cleaning validation protocols, which should be formally approved, e.g. by the quality control or quality assurance unit.

4.1.2 In preparing the cleaning validation protocol, the following should be considered:

— disassembly of system;
— precleaning;
— cleaning agent, concentration, solution volume, water quality;
— time and temperature;
— flow rate, pressure and rinsing;
— complexity and design of the equipment;
— training of operators; and
— size of the system.

4.1.3 The cleaning validation protocol should include:

- the objectives of the validation process;
- the people responsible for performing and approving the validation study;
- the description of the equipment to be used, including a list of the equipment, make, model, serial number or other unique code;
- the interval between the end of production and the commencement of the cleaning procedure (interval may be part of the validation challenge study itself)
  — the maximum period that equipment may be left dirty before being cleaned as well as the establishment of the time that should elapse after cleaning and before use;
- the levels of microorganisms (bioburden);
- the cleaning procedures (documented in an existing SOP, including definition of any automated process) to be used for each product, each manufacturing system or each piece of equipment;
- all the equipment used for routine monitoring, e.g. conductivity meters, pH meters and total organic carbon analysers;
- the number of cleaning cycles to be performed consecutively;
- the sampling procedures to be used (direct sampling, rinse sampling, in-process monitoring and sampling locations) and the rationale for their use;
- the data on recovery studies (efficiency of the recovery of the sampling technique should be established);
- the analytical methods (specificity and sensitivity) including the limit of detection and the limit of quantification;
- the acceptance criteria (with rationale for setting the specific limits) including a margin for error and for sampling efficiency;

- the choice of the cleaning agent should be documented and approved by the quality unit and should be scientifically justified on the basis of, e.g.
  - — the solubility of the materials to be removed;
  - — the design and construction of the equipment and surface materials to be cleaned;
  - — the safety of the cleaning agent;
  - — the ease of removal and detection;
  - — the product attributes;
  - — the minimum temperature and volume of cleaning agent and rinse solution; and
  - — the manufacturer's recommendations;
- revalidation requirements.

4.1.4 Cleaning procedures for products and processes which are very similar do not need to be individually validated. A validation study of the "worst case" may be considered acceptable. There should be a justified validation programme for this approach referred to as "bracketing", addressing critical issues relating to the selected product, equipment or process.

4.1.5 Where "bracketing" of products is done, consideration should be given to type of products and equipment.

4.1.6 Bracketing by product should be done only when the products concerned are similar in nature or property and will be processed using the same equipment. Identical cleaning procedures should then be used for these products.

4.1.7 When a representative product is chosen, this should be the one that is most difficult to clean.

4.1.8 Bracketing by equipment should be done only when it is similar equipment, or the same equipment in different sizes (e.g. 300-l, 500-l and 1000-l tanks). An alternative approach may be to validate the smallest and the largest sizes separately.

4.2 Cleaning validation reports

4.2.1 The relevant cleaning records (signed by the operator, checked by production and reviewed by quality assurance) and source data (original results) should be kept. The results of the cleaning validation should be presented in cleaning validation reports stating the outcome and conclusion.

5. Personnel

5.1 Personnel or operators who perform cleaning routinely should be trained and should be effectively supervised.

6. Equipment

6.1 Normally only procedures for the cleaning of surfaces of the equipment that come into contact with the product need to be validated. Consideration should be given to "non-contact" parts of the equipment into which product or any process material may migrate. Critical areas should be identified (independently from method of cleaning), particularly in large systems employing semi-automatic or fully automatic clean-in-place systems.

6.2 Dedicated equipment should be used for products which are difficult to clean, equipment which is difficult to clean, or for products with a high safety risk where it is not possible to achieve the required cleaning acceptance limits using a validated cleaning procedure.

6.3 Ideally, there should be one process for cleaning a piece of equipment or system. This will depend on the products being produced, whether the cleaning occurs between batches of the same product (as in a large campaign) or whether the cleaning occurs between batches of different products.

6.4 The design of equipment may influence the effectiveness of the cleaning process. Consideration should therefore be given to the design of the equipment when preparing the cleaning validation protocol, e.g. V-blenders, transfer pumps or filling lines.

7. Detergents

7.1 Detergents should facilitate the cleaning process and be easily removable. Detergents that have persistent residues such as cationic detergents which adhere very strongly to glass and are difficult to remove, should be avoided where possible.

7.2 The composition of the detergent should be known to the manufacturer and its removal during rinsing, demonstrated.

7.3 Acceptable limits for detergent residues after cleaning should be defined. The possibility of detergent breakdown should also be considered when validating cleaning procedures.

7.4 Detergents should be released by quality control and, where possible, should meet local food standards or regulations.

8. Microbiology

8.1 The need to include measures to prevent microbial growth and remove contamination where it has occurred should be considered.

8.2 There should be documented evidence to indicate that routine cleaning and storage of equipment does not allow microbial proliferation.

8.3 The period and conditions for storage of unclean equipment before cleaning, and the time between cleaning and equipment reuse, should form part of the validation of cleaning procedures.

8.4 Equipment should be stored in a dry condition after cleaning. Stagnant water should not be allowed to remain in equipment after cleaning.

8.5 Control of the bioburden through adequate cleaning and appropriate storage of equipment is important to ensure that subsequent sterilization or sanitization procedures achieve the necessary assurance of sterility, and the control of pyrogens in sterile processing. Equipment sterilization processes may not be adequate to achieve significant inactivation or removal of pyrogens.

9. Sampling

9.1 General

9.1.1 Equipment should normally be cleaned as soon as possible after use. This may be especially important for operations with topical products, suspensions and bulk drug or where the drying of residues will directly affect the efficiency of a cleaning procedure.

9.1.2 Two methods of sampling are considered to be acceptable. These are direct surface sampling and rinse samples. A combination of the two methods is generally the most desirable.

9.1.3 The practice of resampling should not be used before or during cleaning and operations and is acceptable only in rare cases. Constant retesting and resampling can show that the cleaning process is not validated because these retests actually document the presence of unacceptable residue and contaminants resulting from an ineffective cleaning process.

9.2 Direct surface sampling (direct method)

Note: This method of sampling is the most commonly used and involves taking an inert material (e.g. cotton wool) on the end of a probe (referred to as a "swab") and rubbing it methodically across a surface. The type of sampling material used and its potential impact on the test data is important as the sampling material may interfere with the test. (For example, the adhesive used in swabs has been found to interfere with the analysis of samples.)

9.2.1 Factors that should be considered include the supplier of the swab, area swabbed, number of swabs used, whether they are wet or dry swabs, swab handling and swabbing technique.

9.2.2 The location from which the sample is taken should take into consideration the composition of the equipment (e.g. glass or steel) and the

location (e.g. blades, tank walls or fittings). Worst case locations should be considered. The protocol should identify the sampling locations.

9.2.3 Critical areas, i.e. those hardest to clean, should be identified, particularly in large systems that employ semi-automatic or fully automatic clean-in-place systems.

9.2.4 The sampling medium and solvent used should be appropriate to the task.

9.3 Rinse samples (indirect method)

Note: This method allows sampling of a large surface, of areas that are inaccessible or that cannot be routinely disassembled and provides an overall picture. Rinse samples may give sufficient evidence of adequate cleaning where accessibility of equipment parts can preclude direct surface sampling, and may be useful for checking for residues of cleaning agents, e.g. detergents.

9.3.1 Rinse samples should be used in combination with other sampling methods such as surface sampling.

9.3.2. There should be evidence that samples are accurately recovered. For example, a recovery of > 80% is considered good, > 50% reasonable and < 50% questionable.

9.4 Batch placebo method

Note: This method relies on the manufacture of a placebo batch which is then checked for carry-over of the previous product. It is an expensive and laborious process. It is difficult to provide assurance that the contaminants will be dislodged from the equipment surface uniformly. Additionally, if the particles of the contaminant or residue are large enough, they may not be uniformly dispersed in the placebo batch.

9.4.1 The batch placebo method should be used in conjunction with rinse and/or surface sampling method(s).

9.4.2 Samples should be taken throughout the process of manufacture. Traces of the preceding products should be sought in these samples. (Note that the sensitivity of the assay may be greatly reduced by dilution of the contaminant.)

10. Analytical methods

10.1 The analytical methods should be validated before the cleaning validation is performed.

10.2 The methods chosen should detect residuals or contaminants specific for the substance(s) being assayed at an appropriate level of cleanliness (sensitivity).

10.3 Validation of the analytical method should include as appropriate:

— precision, linearity and selectivity (the latter if specific analytes are targeted);
— limit of detection (LOD);
— limit of quantitation (LOQ);
— recovery, by spiking with the analyte; and
— reproducibility.

10.4 The detection limit for each analytical method should be sufficiently sensitive to detect the established acceptable level of the residue or contaminants.

10.5 Suitable methods that are sensitive and specific should be used where possible and may include chromatographic methods (e.g. high pressure liquid chromotography (HPLC), gas chromotography (GC), and high pressure thin-layer chromatography (HPTLC)). Other methods may include (alone or in combination) measurement of total organic carbon (TOC), pH, or conductivity; ultraviolet (UV) spectroscopy; and enzyme-linked immunosorbent assay (ELISA).

11. Establishing acceptable limits

Note: uniform distribution of contaminants is not guaranteed.

11.1 The acceptance criteria established for contaminant levels in the sample should be practical, achievable and verifiable. The rationale for the residue limits established should be logical, and based on the knowledge of the materials involved.

11.2 Each situation should be assessed individually. The manner in which limits are established should be carefully considered. In establishing residual limits it may not be adequate to focus only on the principal reactant, because other chemical variations may be more difficult to remove.

11.3 Where necessary, screening using thin-layer chromatography should be performed in addition to chemical analyses.

11.4 There should be no residue from the previous product, from reaction by-products and degradants, or from the cleaning process itself (e.g. detergents or solvents).

11.5 The limit-setting approach can:

- be product-specific;
- group products into families and choose a worst case product;

- group products into groups according to risk, e.g. very soluble products, products with similar potency, highly toxic, or difficult to detect products;
- use different safety factors for different dosage forms based on physiological response (this method is essential for potent materials).

11.6 Limits may be expressed as a concentration in a subsequent product (ppm), limit per surface area (mcg/cm^2), or in rinse water as ppm.

11.7 The sensitivity of the analytical methods should be defined to enable reasonable limits to be set.

11.8 The rationale for selecting limits for carry-over of product residues should meet defined criteria.

11.9 The three most commonly used criteria are:

- visually clean. (No residue should be visible on equipment after cleaning.) Spiking studies should determine the concentration at which most active ingredients are visible. This criterion may not be suitable for high-potency, low-dosage drugs;
- no more than 10 ppm of one product will appear in another product (basis for heavy metals in starting materials); and
- no more than 0.1% of the normal therapeutic dose of one product will appear in the maximum daily dose of a subsequent product.

11.10 The most stringent of three options should be used.

11.11 Certain allergenic ingredients (e.g. penicillins and cephalosporins) and highly potent material (e.g. anovulent steroids, potent steroids and cytotoxics) should be undetectable by the best available analytical methods. (In practice this may mean that dedicated manufacturing facilities should be used for the manufacturing and processing of such products.)

Appendix 4

Analytical method validation

1. Principle

1.1 This appendix presents some information on the characteristics that should be considered during validation of analytical methods. Approaches other than those specified in this appendix may be followed and may be acceptable. Manufacturers should choose the validation protocol and procedures most suitable for testing of their product.

1.2 The manufacturer should demonstrate (through validation) that the analytical procedure is suitable for its intended purpose.

1.3 Analytical methods, whether or not they indicate stability, should be validated.

1.4 The analytical method should be validated by research and development before being transferred to the quality control unit when appropriate.

2. General

2.1 There should be specifications for both, materials and products. The tests to be performed should be described in the documentation on standard test methods.

2.2 Specifications and standard test methods in pharmacopoeias ("pharmacopoeial methods"), or suitably developed specifications or test methods ("non-pharmacopoeial methods") as approved by the national drug regulatory authority may be used.

2.3 Well-characterized reference materials, with documented purity, should be used in the validation study.

2.4 The most common analytical procedures include identification tests, assay of drug substances and pharmaceutical products, quantitative tests for content of impurities and limit tests for impurities. Other analytical procedures include dissolution testing and determination of particle size.

2.5 The results of analytical procedures should be reliable, accurate and reproducible. The characteristics that should be considered during validation of analytical methods are discussed in paragraph 6.

2.6 Verification or revalidation should be performed when relevant, for example, when there are changes in the process for synthesis of the drug substance; changes in the composition of the finished product; changes in the analytical procedure; when analytical methods are transferred from one laboratory to another; or when major pieces of equipment instruments change.

2.7 The verification or degree of revalidation depend on the nature of the change(s).

2.8 There should be evidence that the analysts, who are responsible for certain tests, are appropriately qualified to perform those analyses ("analyst proficiency").

3. Pharmacopoeial methods

3.1 When pharmacopoeial methods are used, evidence should be available to prove that such methods are suitable for routine use in the laboratory (verification).

3.2 Pharmacopoeial methods used for determination of content or impurities in pharmaceutical products should also have been demonstrated to be specific with respect to the substance under consideration (no placebo interference).

4. Non-pharmacopoeial methods

4.1 Non-pharmacopoeial methods should be appropriately validated.

5. Method validation

5.1 Validation should be performed in accordance with the validation protocol. The protocol should include procedures and acceptance criteria for all characteristics. The results should be documented in the validation report.

5.2 Justification should be provided when non-pharmacopoeial methods are used if pharmacopoeial methods are available. Justification should include data such as comparisons with the pharmacopoeial or other methods.

5.3 Standard test methods should be described in detail and should provide sufficient information to allow properly trained analysts to perform the analysis in a reliable manner. As a minimum, the description should include the chromatographic conditions (in the case of chromatographic tests), reagents needed, reference standards, the formulae for the calculation of results and system suitability tests.

6. Characteristics of analytical procedures

6.1 Characteristics that should be considered during validation of analytical methods include:

— specificity
— linearity
— range
— accuracy
— precision
— detection limit
— quantitation limit
— robustness.

6.1.1 *Accuracy* is the degree of agreement of test results with the true value, or the closeness of the results obtained by the procedure to the true value. It is normally established on samples of the material to be examined that have been prepared to quantitative accuracy. Accuracy should be established across the specified range of the analytical procedure.

Note: it is acceptable to use a "spiked" placebo where a known quantity or concentration of a reference material is used.

6.1.2 *Precision* is the degree of agreement among individual results. The complete procedure should be applied repeatedly to separate, identical samples drawn from the same homogeneous batch of material. It should be measured by the scatter of individual results from the mean (good grouping) and expressed as the relative standard deviation (RSD).

6.1.2.1 *Repeatability* should be assessed using a minimum of nine determinations covering the specified range for the procedure e.g. three concentrations/three replicates each, or a minimum of six determinations at 100% of the test concentration.

6.1.2.2 *Intermediate precision* expresses within-laboratory variations (usually on different days, different analysts and different equipment). If reproducibility is assessed, a measure of intermediate precision is not required.

6.1.2.3 *Reproducibility* expresses *precision* between laboratories.

6.1.3 *Robustness* (or *ruggedness*) is the ability of the procedure to provide analytical results of acceptable accuracy and precision under a variety of conditions. The results from separate samples are influenced by changes in the operational or environmental conditions. Robustness should be considered during the development phase, and should show the reliability of an analysis when deliberate variations are made in method parameters.

6.1.3.1 Factors that can have an effect on robustness when performing chromatographic analysis include:

— stability of test and standard samples and solutions;
— reagents (e.g. different suppliers);
— different columns (e.g. different lots and/or suppliers);
— extraction time;
— variations of pH of a mobile phase;
— variations in mobile phase composition;
— temperature; and
— flow rate.

6.1.4 *Linearity* indicates the ability to produce results that are directly proportional to the concentration of the analyte in samples. A series of samples should be prepared in which the analyte concentrations span the claimed range of the procedure. If there is a linear relationship, test results should be evaluated by appropriate statistical methods. A minimum of five concentrations should be used.

6.1.5 *Range* is an expression of the lowest and highest levels of analyte that have been demonstrated to be determinable for the product. The specified range is normally derived from linearity studies.

6.1.6 *Specificity* (*selectivity*) is the ability to measure unequivocally the desired analyte in the presence of components such as excipients and impurities that may also be expected to be present. An investigation of specificity should be conducted during the validation of identification tests, the determination of impurities and assay.

6.1.7 *Detection limit* (*limit of detection*) is the smallest quantity of an analyte that can be detected, and not necessarily determined, in a quantitative fashion. Approaches may include instrumental or non-instrumental procedures and could include those based on:

— visual evaluation;
— signal to noise ratio;
— standard deviation of the response and the slope;
— standard deviation of the blank; and
— calibration curve.

6.1.8 *Quantitation limit* (*limit of quantitation*) is the lowest concentration of an analyte in a sample that may be determined with acceptable accuracy and precision. Approaches may include instrumental or non-instrumental procedures and could include those based on:

— visual evaluation;
— signal to noise ratio;
— standard deviation of the response and the slope;

— standard deviation of the blank; and
— calibration curve.

6.2 Characteristics (including tests) that should be considered when using different types of analytical procedures are summarized in Table 1.

Table 1
Characteristics to consider during analytical validation

Type of analytical procedure	Identification	Testing for impurities	Testing for impurities	Assay — dissolution (measurement only) — content/potency
Characteristics		Quantitative tests	Limit tests	
Accuracy	–	+	–	+
Precision				
Repeatability	–	+	–	+
Intermediate precision[a]	–	+	–	+
Specificity	+	+	+	+
Detection limit	–	–[b]	+	–
Quantitation limit	–	+	–	–
Linearity	–	+	–	+
Range	–	+	–	+

– Characteristic is normally not evaluated;
+ Characteristic should normally be evaluated.
[a] In cases where a reproducibility study has been performed, intermediate precision is not needed.
[b] May be needed in some cases.

6.3 System suitability testing

System suitability testing is an integral part of many analytical procedures. The tests are based on the concept that the equipment, electronics, analytical operations and samples to be analysed constitute an integral system that can be evaluated as such. System suitability test parameters that need to be established for a particular procedure depend on the type of procedure being evaluated, for instance, a resolution test for an HPLC procedure.

Appendix 5

Validation of computerized systems

1. General

1.1 Computer systems should be validated at the level appropriate for their use and application. This is of importance in production as well as in quality control.

1.2 The use of a computer system includes different stages. These are planning, specification, programming, testing, commissioning, document operation, monitoring and modifying.

1.3 The purpose of validation of a computer system is to ensure an acceptable degree of evidence (documented, raw data), confidence (dependability and thorough, rigorous achievement of predetermined specifications), intended use, accuracy, consistency and reliability.

1.4 Both the system specifications and functional specifications should be validated.

1.5 Periodic (or continuous) evaluation should be performed after the initial validation.

1.6 There should be written procedures for performance monitoring, change control, programme and data security, calibration and maintenance, personnel training, emergency recovery and periodic re-evaluation.

1.7 Aspects of computerized operations that should be considered during validation include:

— networks
— manual back-ups
— input/output checks
— process documentation
— monitoring
— alarms
— shutdown recovery.

2. System specification

2.1 There should be a control document or system specification. The control document should state the objectives of a proposed computer system, the data to be entered and stored, the flow of data, how it interacts with other systems and procedures, the information to be produced, the limits of any variable and the operating programme and test programme. (Examples of each document produced by the programme should be included.)

2.2 System elements that need to be considered in computer validation include hardware (equipment), software (procedures) and people (users).

3. Functional specification

3.1 A functional or performance specification should provide instructions for testing, operating, and maintaining the system, as well as names of the person(s) responsible for its development and operation.

3.2 The following general aspects should be kept in mind when using computer systems:

— location
— power supply
— temperature, and
— magnetic disturbances.

Fluctuations in the electrical supply can influence computer systems and power supply failure can result in loss of memory.

3.3 The following general good manufacturing practice (GMP) requirements are applicable to computer systems.

- *Verification and revalidation.* After a suitable period of running a new system it should be independently reviewed and compared with the system specification and functional specification.
- *Change control.* Alterations should only be made in accordance with a defined procedure which should include provision for checking, approving and implementing the change.
- *Checks.* Data should be checked periodically to confirm that they have been accurately and reliably transferred.

4. Security

4.1 This is of importance in production as well as in quality control.

4.2 Data should be entered or amended only by persons authorized to do so. Suitable security systems should be in place to prevent unauthorized entry or manipulation of data. The activity of entering data, changing or

amending incorrect entries and creating back-ups should all be done in accordance with written, approved standard operating procedures (SOPs).

4.3 The security procedures should be in writing. Security should also extend to devices used to store programmes, such as tapes, disks and magnetic strip cards. Access to these devices should be controlled.

4.4 Traceability is of particular importance and it should be able to identify the persons who made entries/changes, released material, or performed other critical steps in manufacture or control.

4.5 The entry of critical data into a computer by an authorized person (e.g. entry of a master processing formula) requires an independent verification and release for use by a second authorized person.

4.6 SOPs should be validated for certain systems or processes, e.g. the procedures to be followed if the system fails or breaks down should be defined and tested. Alternative arrangements should be made by the validation team, and a disaster recovery procedure should be available for the systems that need to be operated in the event of a breakdown.

5. Back-ups

5.1 Regular back-ups of all files and data should be made and stored in a secure location to prevent intentional or accidental damage.

6. Validation

6.1 Planning, which should include the validation policy, project plan and SOPs, is one of the steps in the validation process.

6.2 The computer-related systems and vendors should be defined and the vendor and product should be evaluated. The system should be designed and constructed, taking into consideration the types, testing and quality assurance of the software.

6.3 After installation of the system it should be qualified. The extent of the qualification should depend on the complexity of the system. The system should be evaluated and performance qualification, change control, maintenance and calibration, security, contingency planning, SOPs, training, performance monitoring and periodic re-evaluation should be addressed.

7. Validation of hardware and software

Table 1 indicates aspects of computer systems that should be subjected to validation.

Table 1
Summary of validation requirements for computer systems

Hardware	Software
1. Types 1.1 Input device 1.2 Output device 1.3 Signal converter 1.4 Central processing unit (CPU) 1.5 Distribution system 1.6 Peripheral devices	1. Level 1.1 Machine language 1.2 Assembly language 1.3 High-level language 1.4 Application language
2. Key aspects 2.1 Location environment distance input devices 2.2 Signal conversion 2.3 I/O operation 2.4 Command overrides 2.5 Maintenance	2. Software identification 2.1 Language 2.2 Name 2.3 Function 2.4 Input 2.5 Output 2.6 Fixed set point 2.7 Variable set point 2.8 Edits 2.9 Input manipulation 2.10 Programme overrides
3. Validation 3.1 Function 3.2 Limits 3.3 Worst case 3.4 Reproducibility/consistency 3.5 Documentation 3.6 Revalidation	3. Key aspects 3.1 Software development 3.2 Software security
	4. Validation 4.1 Function 4.2 Worst case 4.3 Repeats 4.4 Documentation 4.5 Revalidation

I/O, Input/output.

7.1 Hardware

7.1.1 As part of the validation process appropriate tests and challenges to the hardware should be performed.

7.1.2 Static, dust, power-feed voltage fluctuations and electromagnetic interference could influence the system. The extent of validation should depend on the complexity of the system. Hardware is considered to be equipment, and the focus should be on location, maintenance and calibration of hardware, as well as on validation/qualification.

7.1.3 The validation/qualification of the hardware should prove:

- that the capacity of the hardware matches its assigned function (e.g. foreign language);

- that it operates within the operational limits (e.g. memory, connector ports, input ports);
- that it performs acceptably under worst-case conditions (e.g. long hours, temperature extremes); and
- reproducibility/consistency (e.g. by performing at least three runs under different conditions).

7.1.4 The validation should be done in accordance with written qualification protocols and the results should be recorded in the qualification reports.

7.1.5 Revalidation should be performed when significant changes are made.

7.1.6 Much of the hardware validation may be performed by the computer vendor. However, the ultimate responsibility for the suitability of equipment used remains with the company.

7.1.7 Hardware validation data and protocols should be kept by the company. When validation information is produced by an outside firm, e.g. computer vendor, the records maintained by the company need not include all of the voluminous test data; however, such records should be sufficiently complete (including general results and protocols) to allow the company to assess the adequacy of the validation. A mere certification of suitability from the vendor, for example, will be inadequate.

7.2 Software

7.2.1 Software is the term used to describe the complete set of programmes used by a computer, and which should be listed in a menu.

7.2.2 Records are considered as software; focus is placed on accuracy, security, access, retention of records, review, double checks, documentation and accuracy of reproduction.

Identification

7.2.3 The company should identify the following key computer programmes: language, name, function (purpose of the programme), input (determine inputs), output (determine outputs), fixed set point (process variable that cannot be changed by the operator), variable set point (entered by the operator), edits (reject input/output that does not conform to limits and minimize errors, e.g. four- or five-character number entry), input manipulation (and equations) and programme overrides (e.g. to stop a mixer before time).

7.2.4 The personnel who have the ability and/or are authorized to write, alter or have access to programmes should be identified.

7.2.5 Software validation should provide assurance that computer programmes (especially those that control manufacturing and processing) will consistently perform as they are supposed to, within pre-established limits.

When planning the validation, the following points should be considered.

- Function: does the programme match the assigned operational function (e.g. generate batch documentation, different batches of material used in a batch listed)?
- Worst case: perform validation under different conditions (e.g. speed, data volume, frequency).
- Repeats: sufficient number of times (replicate data entries).
- Documentation: protocols and reports.
- Revalidation: needed when significant changes are made.

Appendix 6

Qualification of systems and equipment

1. Principle

1.1 Systems and equipment should be appropriately designed, located, installed, operated and maintained to suit their intended purpose.

1.2 Critical systems, i.e. those whose consistent performance may have an impact on the quality of products, should be qualified. These may include, where appropriate, water purification systems, air-handling systems, compressed air systems and steam systems.

1.3 The continued suitable performance of equipment is important to ensure batch-to-batch consistency. Critical equipment should therefore be qualified.

2. Scope

2.1 These guidelines describe the general aspects of qualification for systems and equipment.

2.2 Normally qualification would be applicable to critical systems and equipment whose performance may have an impact on the quality of the product.

3. General

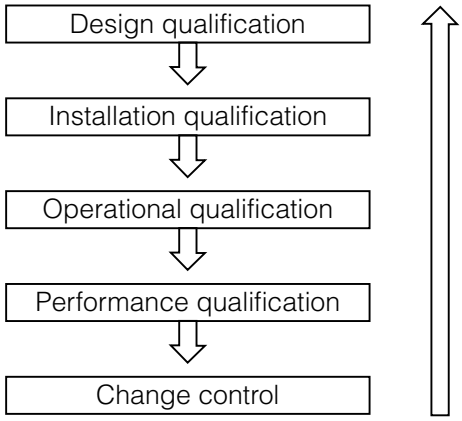
3.1 The manufacturer should have a qualification policy for systems and equipment.

3.2 Equipment (including instruments) used in production and quality control should be included in the qualification policy and programme.

3.3 New systems and equipment should pass through all stages of qualification including design qualification (DQ), installation qualification (IQ),

operational qualification (OQ) and performance qualification (PQ) as appropriate (Fig. 1).

Figure 1
Stages of qualification



3.4 In some cases, not all stages of qualification may be required. See also the guidelines on the qualification of water purification systems in Appendix 2 and heating, ventilation and air-conditioning (HVAC) in Appendix 1.

3.5 Systems should be qualified before equipment.

3.6 Equipment should be qualified prior to being brought into routine use to provide documented evidence that the equipment is fit for its intended purpose.

3.7 Systems and equipment should undergo periodic requalification, as well as requalification after change.

3.8 Certain stages of the equipment qualification may be done by the supplier or a third party.

3.9 The relevant documentation associated with qualification including standard operating procedures (SOPs), specifications and acceptance criteria, certificates and manuals should be maintained.

3.10 Qualification should be done in accordance with predetermined and approved qualification protocols. The results of the qualification should be recorded and reflected in qualification reports.

3.11 The extent of the qualification should be based on the criticality of a system or equipment (e.g. blenders, autoclaves or computerized systems).

4. Design qualification

Note: see also "Supplementary guidelines on good manufacturing practices (GMP): validation".

4.1 User requirements should be considered when deciding on the specific design of a system or equipment.

4.2 A suitable supplier should be selected for the appropriate system or equipment (approved vendor).

5. Installation qualification

Note: see also "Supplementary guidelines on good manufacturing practices (GMP): validation".

5.1 Systems and equipment should be correctly installed in accordance with an installation plan and installation qualification protocol.

5.2 Requirements for calibration, maintenance and cleaning should be drawn up during installation.

5.3 Installation qualification should include identification and verification of all system elements, parts, services, controls, gauges and other components.

5.4 Measuring, control and indicating devices should be calibrated against appropriate national or international standards, which are traceable.

5.5 There should be documented records for the installation (installation qualification report) to indicate the satisfactoriness of the installation, which should include the details of the supplier and manufacturer, system or equipment name, model and serial number, date of installation, spare parts, relevant procedures and certificates.

Format for an installation qualification protocol and report[a]

Validation protocol _____ Installation Qualification _____ Page _____ of _____

Title: _____ Name and address of site: _____

_____

Validation Protocol # _____ IQ Protocol number: _____

Title: _____

Protocol written by: _____

Protocol approved by: _____ Date: _____

QA Approval: _____ Date: _____

Objective

To ensure that _____ (system/equipment) installed conforms to the purchase specifications and the manufacturer details and literature, and to document the information that _____ (system/equipment) meets its specifications.

Equipment inventory number: _____

Scope

To perform installation qualification as described in this IQ protocol at the time of installation, modification and relocation.

Responsibility

_____ (post/person) overseeing the installation will perform the qualification and records results.

_____ (post/person) will verify results and write the report.

Quality Assurance will review and approve the IQ protocol and report.

[a] This format is used for training purposes and reflects some of the possible contents for an installation qualification protocol.

Format for an installation qualification protocol and report (continued)[a]

Validation protocol _____ Installation Qualification _____ Page _____ of _____

Title: _____ Name and address of site: _____

_____

System/Equipment _____ Code no.: _____

a. Description of the system/equipment being installed: general description of the function and the main components.

_____

_____

_____

b. List of the main components:

1. _____ Code no.: _____
2. _____ Code no.: _____
3. _____ Code no.: _____
4. _____ Code no.: _____

c. Description of supporting utilities (e.g. piping, connections, water supply)

1. _____ Code no.: _____
2. _____ Code no.: _____
3. _____ Code no.: _____
4. _____ Code no.: _____

Procedure

1. Prepare a checklist of all components and parts, including spare parts according to the purchase order and manufacturer's specifications.
2. Record the information for each actual part, component, item of auxiliary equipment, supporting facilities, and compare with the manufacturer's specifications.
3. Record any deviations to the system/equipment.
4. Prepare a deviation report including justification of acceptance and impact on the function.
5. Prepare an IQ report.[b]
6. Submit the report to QA for review and approval.

[a] This format is used for training purposes and reflects some of the possible contents for an installation qualification protocol.

[a] As a minimum, the IQ report should include the date of initiation of the study, date completed, observations made, problems encountered, completeness of information collected, summary of deviation report, results of any tests, sample data (if appropriate), location of original data, other information relevant to the study, and the conclusion on the validity of the installation.

Format for an installation qualification protocol and report (continued)[a]

Validation protocol _____ **Installation Qualification** _____ **Page** _____ **of** _____

Title: _____ **Name and address of site:** _____

_____

Checklist for component no. _____

Name: _____ Code no.: _____

Component function: _____

		Require/order	**Actual**	**Deviations**
1	Model/serial no.			
2	Specification			
3	Manual			
4	Drawing			
5	Wiring/cabling			
6	Power, fusing			
7	SOP (operation) SOP (maintenance) SOP (calibration)			
8	Input/output control			
9	Environment			
10	Test equipment or instruments			
11	Utilities and service			
12	Spare parts list, part number and supplier			
13	Other			

Performed by: _____ **Date:** _____

Deviations: _____ **Date:** _____

Verified by: _____ **Date:** _____

[a] This format is used for training purposes and reflects some of the possible contents for an installation qualification protocol.

Format for an installation qualification protocol and report (continued)[a]

Validation protocol _____ Installation Qualification _____ Page _____ of _____

Title: _____ Name and address of site: _____

_____

Deviation report

Deviations: _____

_____

_____

_____

_____

_____

_____

Justification for acceptance

_____

_____

_____

_____

_____

_____

_____

_____

Impact on operation:

_____

_____

_____

_____

_____

_____

_____

_____

Report written by: _____ Date: _____

[a] This format is used for training purposes and reflects some of the possible contents for an installation qualification protocol.

Format for an installation qualification protocol and report (continued)[a]

Validation protocol _____ **Installation Qualification** _____ **Page** _____ **of** _____ **Title:** _____ **Name and address of site:** _____ _____
Installation qualification report Results: _____ _____ _____ _____ _____ **Conclusions:** _____ _____ _____ _____ _____ _____ _____ _____ _____
Report written by: _____ **Date:** _____ **QA approved by:** _____ **Date:** _____

[a] This format is used for training purposes and reflects some of the possible contents for an installation qualification protocol.

6. Operational qualification

Note: see also "Supplementary guidelines on good manufacturing practices (GMP): validation".

6.1 Systems and equipment should operate correctly and their operation should be verified in accordance with an operational qualification protocol.

6.2 Critical operating parameters should be identified. Studies on the critical variables should include conditions encompassing upper and lower operating limits and circumstances (also referred to as "worst case conditions").

6.3 Operational qualification should include verification of operation of all system elements, parts, services, controls, gauges and other components.

Format for an operational qualification protocol[a]

Validation protocol _____ **Operational Qualification** _____ **Page** _____ **of** _____

Title: _____ **Name of Facility:** _____

_____

Validation Protocol # _____ Operational Qualification _____

Title _____

_____

Protocol written by _____

Departmental Approval by _____ Date _____

QA Approval by _____ Date _____

Objective

To determine that the system/equipment operates according to specifications, and to record all relevant information and data to demonstrate that the system/equipment functions as expected.

Scope

To be performed after installation, modification or relocation, after the Installation Qualification has been completed.

Responsibility

Person responsible for operating the system/equipment will perform the qualification and record the information.

The supervisor will supervise the study, verify the completion of the records, write the deviation report and the Operational Qualification (OQ) Report.

Qualify Assurance will review and approve the OQ protocol and report.

[a] This format is used for training purposes and reflects some of the possible contents for an operational qualification protocol.

6.4 There should be documented records for the verification of operation (operational qualification report) to indicate the satisfactory operation.

6.5 Standard operating procedures for the operation should be finalized and approved.

6.6 Training of operators for the systems and equipment should be provided, and training records maintained.

6.7 Systems and equipment should be released for routine use after completion of operational qualification, provided that all calibration, cleaning, maintenance, training and related tests and results were found to be acceptable.

Format for an operational qualification protocol (continued)[a]

Validation protocol _____ Operational Qualification _____ Page _____ of _____

Title: _____ Name of Facility: _____

_____

Materials, Equipment, Documents

List of calibration equipment required (Chart 1).

Materials or supplies needed to perform the Operational Qualification

1 _____ Code # _____

2 _____ Code # _____

3 _____ Code # _____

4 _____ Code # _____

5 _____ Code # _____

6 _____ Code # _____

SOPs and datasheets for normal operations of the system under test (Chart 2).

Training records documenting that operators have been trained (Chart 2).

Manuals for equipment (Chart 2).

Procedure

Test and record calibration data for calibrating apparatus and instruments (Chart 1).

Test and record operative condition of control points and alarms (Chart 3).

Test and record outputs (Chart 4).

List of calibration requirements for the system under test and records of the calibration of the system (Chart 5).

Measure and record the results of specific challenge to the system in normal and worst case situation where appropriate (Chart 6).

Record any deviations to the procedures performed.

Prepare a Deviation Report including the justification of acceptance and impact on the operation.

Prepare an Operational Qualification Report. This should include date study initiated; date completed; observations made; problems encountered; completeness of information collected; summary of deviation report; results of control/alarm tests; sample data if appropriate; location of original data; other information relevant to the study; and conclusions on the validity of the equipment/system operations.

Submit QA for review and approval.

[a] This format is used for training purposes and reflects some of the possible contents for an operational qualification protocol.

Format for an operational qualification protocol (continued)[a]

Validation protocol _____ Operational Qualification _____ Page _____ of _____

Title: _____ Name of Facility: _____

_____

Preparation

Chart 1: Calibrating apparatus and instruments.

Apparatus/Instrument	Calibration method	Calibration date
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____

Performed by: _____ Date _____

Deviations: _____

_____

_____

_____

Verified by: _____ Date _____

[a] This format is used for training purposes and reflects some of the possible contents for an operational qualification protocol.

Format for an operational qualification protocol (continued)[a]

Validation protocol _____ Operational Qualification _____ Page _____ of _____

Title: _____ Name of Facility: _____

_____

Preparation

Chart 2: Document check

SOP Title and number	File location	QA/QC approval date
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____

Training Records

Course on SOP #	Staff name	Date
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____

Equipment Make and Model	Manual Available
_____	Y [ ] N [ ]
_____	Y [ ] N [ ]
_____	Y [ ] N [ ]

Performed by: _____ Date _____

Deviations: _____

_____

_____

Verified by: _____ Date _____

[a] This format is used for training purposes and reflects some of the possible contents for an operational qualification protocol.

Format for an operational qualification protocol (continued)[a]

Validation protocol _____ Operational Qualification _____ Page _____ of _____

Title: _____ Name of Facility: _____

_____

Results

Chart 3: Control points and alarms.

Control point/Alarm	Results	Date
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____

Performed by: _____ Date _____

Deviations: _____

_____

_____

Verified by: _____ Date _____

[a] This format is used for training purposes and reflects some of the possible contents for an operational qualification protocol.

Format for an operational qualification protocol (continued)[a]

Validation protocol _____ Operational Qualification _____ Page _____ of _____

Title: _____ Name of Facility: _____

_____

Results

Chart 4: Outputs

Outputs	Results	Date

Performed by: _____ Date _____

Deviations: _____

_____

_____

Verified by: _____ Date _____

[a] This format is used for training purposes and reflects some of the possible contents for an operational qualification protocol.

Format for an operational qualification protocol (continued)[a]

Validation protocol _____ Operational Qualification _____ Page _____ of _____

Title: _____ Name of Facility: _____

_____

Chart 5: Calibration of Equipment/System

Calibration SOP (short title and #)	Result	Date

Performed by: _____ Date _____

Deviations: _____

_____

_____

Verified by: _____ Date _____

[a] This format is used for training purposes and reflects some of the possible contents for an operational qualification protocol.

Format for an operational qualification protocol (continued)[a]

Validation protocol _____ Operational Qualification _____ Page _____ of _____

Title: _____ Name of Facility: _____

_____

Chart 6: Specific challenge of the equipment or system

Test in normal conditions:

Test of worst case situation:
(e.g. start-up after shutdown, temperature recovery time, centrifuge imbalance)

Performed by: _____ Date _____

Deviations: _____

_____

_____

Verified by: _____ Date _____

[a] This format is used for training purposes and reflects some of the possible contents for an operational qualification protocol.

Format for an operational qualification protocol (continued)[a]

Validation protocol _____ Operational Qualification _____ Page _____ of _____

Title: _____ Name of Facility: _____

_____

Deviation Report

Deviation(s):

Justification for acceptance:

Impact on operation:

Written by: _____ Date _____

[a] This format is used for training purposes and reflects some of the possible contents for an operational qualification protocol.

Format for an operational qualification protocol (continued)[a]

Validation protocol _____ Operational Qualification _____ Page _____ of _____

Title: _____ Name of Facility: _____

_____

Operational Qualification Report

Results:

Conclusions:

Written by: _____ Date _____

QA approved by: _____ Date _____

[a] This format is used for training purposes and reflects some of the possible contents for an operational qualification protocol.

7. Performance qualification

Note: see also "Supplementary guidelines on good manufacturing practices (GMP): validation".

7.1 Systems and equipment should consistently perform in accordance with design specifications. The performance should be verified in accordance with a performance qualification protocol.

7.2 There should be documented records for the verification of performance (performance qualification report) to indicate the satisfactory performance over a period of time. Manufacturers should justify the selected period over which performance qualification is done.

Format for a performance qualification protocol[a]

Validation protocol _____ **Performance Qualification** _____ **Page** _____ **of** _____ **Title:** _____ **Name of facility:** _____ _____
Validation Protocol # _____ Performance Qualification Title _____ _____ Protocol written by _____ Departmental Approval by _____ Date _____ QA Approval by _____ Date _____
Objective To determine that the systems/equipment perform as intended by repeatedly running the system on its intended schedules and recording all relevant information and data. Results must demonstrate that performance consistently meets pre-determined specifications under normal conditions, and where appropriate for worst case situations.
Scope To be performed after the Installation and Operational Qualification have been completed and approved. To be performed after installation, modification or relocation and for re-validation at appropriate intervals. Each piece of equipment must be validated before it serves another piece of equipment/ system during validation of the latter (e.g. water system before steam generator; steam generator before autoclave).

[a] This format is used for training purposes and reflects some of the possible contents for a performance qualification protocol.

Format for a performance qualification protocol (continued)[a]

Validation protocol _____ Performance Qualification _____ Page _____ of _____

Title: _____ Name of facility: _____

_____

Responsibility

Person responsible for operating the system or equipment will perform the qualification and record the information.

The supervisor will supervise the study, verify the completion of the records and write the Deviation Report and the Performance Qualification Report.

Qualify Assurance will review and approve the Performance Qualification Protocol and Report.

Materials, Equipment, Documents

SOPs for normal operations of the equipment or system under test (including data record forms, charts, diagrams materials and equipment needed). Attach copies.

SOP list:

_____

_____

_____

_____

_____

_____

SOPs specific for performance tests (including data record forms, charts, diagrams, materials and equipment needed, calculations and statistical analyses to be performed, and pre-determined specifications and acceptance criteria). Attach copies.

SOP list:

_____

_____

_____

_____

_____

_____

[a] This format is used for training purposes and reflects some of the possible contents for a performance qualification protocol.

Format for a performance qualification protocol (continued)[a]

Validation protocol _____ Performance Qualification _____ Page _____ of _____

Title: _____ Name of facility: _____

_____

Procedure

Equipment: Run normal procedure three times for each use (configuration or load) and record all required data and any deviations to the procedure.

Systems: Run for 20 consecutive working days, recording all required data and any deviations to the procedure.

Prepare the Summary Data Record Form(Chart 1).

Evaluation

Attach all completed, signed data record forms.

Complete the Summary Data Record Form (Chart 1).

Perform all required calculations and statistical analyses (Chart 2).

Compare to acceptance criteria (Chart 3).

Prepare Deviation Report including the justification of acceptance and impact on the performance.

Prepare a Performance Qualification Report: This should include: date study initiated; date completed; observations made; problems encountered; completeness of information collected; summary of deviation report; results of any tests; do results meet acceptance criteria; location of original data; other information relevant to the study; and conclusions on the validity of the equipment/system.

Submit Performance Qualification Document to QA for review and approval.

[a] This format is used for training purposes and reflects some of the possible contents for a performance qualification protocol.

Format for a performance qualification protocol (continued)[a]

Validation protocol _____ Performance Qualification _____ Page _____ of _____ **Title: _____ Name of facility: _____** _____
Chart 1: Summary Data Record **(To be prepared for the specific procedure being tested)**
Performed by: _____ Date _____ **Verified by: _____ Date _____**

[a] This format is used for training purposes and reflects some of the possible contents for a performance qualification protocol.

Format for a performance qualification protocol (continued)[a]

Validation protocol _____ **Performance Qualification** _____ **Page** _____ **of** _____

Title: _____ **Name of facility:** _____

_____

Chart 2: Calculations and Statistical Analyses

Performed by: _____ **Date** _____

Verified by: _____ **Date** _____

[a] This format is used for training purposes and reflects some of the possible contents for a performance qualification protocol.

Format for a performance qualification protocol (continued)[a]

Validation protocol _____ **Performance Qualification** _____ **Page** _____ **of** _____

Title: _____ **Name of facility:** _____

_____

Chart 3: Acceptance Criteria vs. Performance Test Results

Criteria	Results	Pass/Fail

Performed by: _____ **Date** _____

Verified by: _____ **Date** _____

[a] This format is used for training purposes and reflects some of the possible contents for a performance qualification protocol.

Format for a performance qualification protocol (continued)[a]

Validation protocol _____ **Performance Qualification** _____ **Page** _____ **of** _____

Title: _____ **Name of facility:** _____

_____

Deviation Report

Deviation(s):

Justification for acceptance:

Impact on operation, function or process:

Written by: _____ **Date** _____

Verified by: _____ **Date** _____

[a] This format is used for training purposes and reflects some of the possible contents for a performance qualification protocol.

Format for a performance qualification protocol (continued)[a]

Validation protocol _____ Performance Qualification _____ Page _____ of _____

Title: _____ Name of facility: _____

_____

Performance Qualification Report

Results:

Conclusions:

Written: _____ Date _____

Verified by: _____ Date _____

[a] This format is used for training purposes and reflects some of the possible contents for a performance qualification protocol.

8. Requalification

Note: see also "Supplementary guidelines on good manufacturing practices (GMP): validation".

8.1 Requalification of systems and equipment should be done in accordance with a defined schedule. The frequency of requalification may be determined on the basis of factors such as the analysis of results relating to calibration, verification and maintenance.

8.2 There should be periodic requalification.

8.3 There should be requalification after changes. The extent of requalification after the change should be justified based on a risk-assessment of the change. Requalification after change should be considered as part of the change control procedure.

9. Qualification of "in-use" systems and equipment

9.1 There should be data to support and verify the suitable operation and performance of systems and equipment that have been "in use" for a period of time, and which had not been subjected to installation and or operational qualification.

9.2 These should include operating parameters and limits for critical variables, calibration, maintenance and preventive maintenance, standard operating procedures (SOPs) and records.

10. Reference

A WHO guide to good manufacturing practice (GMP) requirements. Part 2: Validation. Geneva, Global Programme for Vaccines and Immunization, Vaccine Supply and Quality, Global Training Network, World Health Organization, 1997 (WHO/VSQ/97.02).

Appendix 7

Non-sterile process validation

1. Principle

1.1 Process validation provides documented evidence that a process is capable of reliably and repeatedly rendering a product of the required quality.

1.2 The principles of planning, organizing and performing process validation are similar to those for qualification. It should be done in accordance with process validation protocols, data should be collected and reviewed against predetermined acceptance criteria, and reflected in process validation reports.

2. Scope

2.1 These guidelines describe the general aspects of process validation for the manufacture of non-sterile finished products.

2.2 Normally process validation should cover at least the critical steps and parameters (e.g. those that may have an impact on the quality of the product) in the process of manufacturing a pharmaceutical product.

3. General

3.1 The policy and approach to process validation should be documented, e.g. in a validation master plan, and should include the critical process steps and parameters.

3.2 Process validation should normally begin only once qualification of support systems and equipment is completed. In some cases process validation may be conducted concurrently with performance qualification.

3.3 Process validation should normally be completed prior to the manufacture of finished product that is intended for sale (*prospective validation*). Process validation during routine production may also be acceptable (*concurrent validation*).

4. Prospective validation

4.1 Critical factors or parameters that may affect the quality of the finished product should be identified during product development. To achieve this, the production process should be broken down into individual steps, and each step should be evaluated (e.g. on the basis of experience or theoretical considerations).

4.2 The criticality of these factors should be determined through a "worst-case" challenge where possible.

4.3 Prospective validation should be done in accordance with a validation protocol. The protocol should include:

— a description of the process;
— a description of the experiment;
— details of the equipment and/or facilities to be used (including measuring or recording equipment) together with its calibration status;
— the variables to be monitored;
— the samples to be taken — where, when, how, how many and how much (sample size);
— the product performance characteristics/attributes to be monitored, together with the test methods;
— the acceptable limits;
— time schedules;
— personnel responsibilities; and
— details of methods for recording and evaluating results, including statistical analysis.

4.4 All equipment, the production environment and analytical testing methods to be used should have been fully validated (e.g. during installation qualification and operational qualification).

4.5 Personnel participating in the validation work should have been appropriately trained.

4.6 Batch manufacturing documentation to be used should be prepared after these critical parameters of the process have been identified, and machine settings, component specifications and environmental conditions have been determined and specified.

4.7 A number of batches of the final product should then be produced. The number of batches produced in this validation exercise should be sufficient to allow the normal extent of variation and trends to be established and to provide sufficient data for evaluation.

4.8 Data within the finally agreed parameters, from at least three consecutive batches, giving product of the desired quality may be considered to constitute a proper validation of the process.

4.9 The batches should be of the same size, and should be the same as the batch size intended in full-scale production. Where this is not possible, the reduced batch size should be considered in the design of the protocol and when full-scale production starts, the validity of any assumptions made should be demonstrated.

4.10 Extensive testing should be performed on the product at various stages during the manufacturing process of the batches, including on the final product and its package.

4.11 The results should be documented in the validation report. As a minimum, the report should include:

- a description of the process: batch/packaging document, including details of critical steps;
- a detailed summary of the results obtained from in-process and final testing, including data from failed tests. When raw data are not included, reference should be made to the sources used and where it can be found;
- any work done in addition to that specified in the protocol, or any deviations from the protocol should be formally noted along with an explanation;
- a review and comparison of the results with those expected; and
- formal acceptance or rejection of the work by the team or persons designated as being responsible for the validation, after completion of any corrective action or repeated work.

4.12 A conclusion and recommendation should be made on the extent of monitoring and the in-process controls necessary for routine production, on the basis of the results obtained.

4.13 The conclusion and recommendation should be incorporated into the batch manufacturing and batch packaging documents and/or standard operating procedures (SOPs) for routine use. Limits and frequencies of testing and monitoring should be specified. Actions to be taken in the event of the limits being exceeded should be specified.

4.14 Batches manufactured as part of the validation exercise, and intended to be sold or supplied, should have been manufactured under conditions that comply fully with the requirements of good manufacturing practice and the marketing authorization (where applicable).

5. Concurrent validation

5.1 In certain cases, it may be appropriate to validate a process during routine production, e.g. where the product is a different strength of a previously validated product, a different tablet shape or where the process is well understood.

5.2 The decision to carry out concurrent validation should be made by appropriately authorized personnel.

5.3 It is essential that the premises and equipment to be used during concurrent validation have been previously qualified.

5.4 Prospective validation should be done in accordance with a validation protocol.

5.5 The results should be documented in the validation report.

6. Retrospective validation

6.1 Retrospective validation is based on a comprehensive review of historical data to provide the necessary documentary evidence that the process is doing what it is believed to do. This type of validation also requires the preparation of a protocol, the reporting of the results of the data review, a conclusion and a recommendation.

6.2 Retrospective validation is not the preferred method of validation and should be used in exceptional cases only. It is acceptable only for well-established processes and will be inappropriate where there have been changes in the composition of the product, operating procedures or equipment.

6.3 Sufficient data should be reviewed to provide a statistically significant conclusion.

6.4 When the results of retrospective validation are considered satisfactory, this should serve only as an indication that the process does not need to be subjected to validation in the immediate future.

7. Revalidation

Note: see main text on "Validation". The need for periodic revalidation of non-sterile processes is considered to be a lower priority than for sterile processes.

7.1 In the case of standard processes using conventional equipment, a data review similar to that which would be required for retrospective validation may provide an adequate assurance that the process continues to be under control. The following points should also be considered:

— the occurrence of any changes in the master formula, methods, starting material manufacturer, equipment and/or instruments;
— equipment calibrations and preventive maintenance carried out;
— standard operating procedures (SOPs); and
— cleaning and hygiene programme.

8. Change control

Note: see main text on "Validation".

8.1 Products manufactured by processes that have been subjected to changes should not be released for sale without full awareness and consideration of the change and its impact on the process validation.

8.2 Changes that are likely to require revalidation may include:

— changes in the manufacturing process (e.g. mixing times, drying temperatures);
— changes in the equipment (e.g. addition of automatic detection systems);
— production area and support system changes (e.g. rearrangement of areas or a new water treatment method);
— transfer of processes to another site; and
— unexpected changes (e.g. those observed during self-inspection or during routine analysis of process trend data).

WHO Technical Report Series, No. 937, 2006

Annex 5

Good distribution practices for pharmaceutical products

1. Introduction

Distribution is an important activity in the integrated supply-chain management of pharmaceutical products. Various people and entities are generally responsible for the handling, storage and distribution of such products. In some cases, however, a person or entity is only involved in and responsible for certain elements of the distribution process. This document sets out appropriate steps to assist in fulfilling the responsibilities involved in the different aspects of the distribution process. The guidelines are intended to apply to all steps in the distribution/supply chain. The relevant sections should be considered by various role players as applicable to their particular role in the distribution process. The document does not specifically cover

finished products in bulk, distribution of labels or packaging materials, as these aspects are considered to be covered by other guidelines, e.g. good manufacturing practices (GMP).

The practice of repacking, e.g. in pharmacies and other settings, needs to be carried out in accordance with good dispensing practices.

The storage, trade and distribution of pharmaceutical products are carried out by various companies, institutions and individuals. The nature of the risks involved, however, is likely to be the same as those in the manufacturing environment, e.g. mix-ups, contamination and cross-contamination. There are thus aspects of distribution to which the principles of GMP should be applied. These include, but are not limited to, storage, distribution, transportation, packaging, labelling, documentation and record-keeping practices.

The quality of pharmaceutical products can be affected by a lack of adequate control over the numerous activities which occur during the distribution process. Furthermore the need for establishment, development, maintenance and control over the activities involved in the distribution process has generally not been well emphasized. The objective of these guidelines is to assist in ensuring the quality and integrity of pharmaceutical products during all aspects of the distribution process.

To maintain the original quality of pharmaceutical products, every activity in the distribution thereof should be carried out according to the principles of GMP, good storage practice (GSP) and good distribution practice (GDP). Although these guidelines are intended to be a stand-alone text, they do not deal with all aspects of the standards for the storage of pharmaceuticals which are covered in the "WHO guide to good storage practices for pharmaceuticals" (*1*). These guidelines should also be read in conjunction with other guidelines such as "WHO good manufacturing practices: main principles" (*2*); "Guidelines for implementation of the WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce (*3*); "WHO pharmaceutical starting materials certification scheme (SMACS)" (*4*); and the "Guidelines on import procedures for pharmaceutical products" (*5*).

2. Scope of the document

This document lays down guidelines for the distribution of pharmaceutical products. Depending on the national and regional legislation on pharmaceuticals, this guide may also be applicable for veterinary products administered to food-producing animals.

This document does not cover the distribution of materials such as pharmaceutical starting materials (active pharmaceutical ingredients (API) and

excipients), reagents, solvents, process aids, intermediate products, packaging materials and labelling materials. The principles for the distribution of starting materials were laid down in the WHO guidance "Good trade and distribution practices for pharmaceutical starting materials" (*6*).

Different models for the distribution of pharmaceutical products are used in different countries and sometimes within the same country, for example, in the public and the private sector. These guidelines are intended to be applicable to all persons and companies involved in any aspect of the distribution of pharmaceutical products from the premises of manufacture to the point of supply to health establishments, e.g. private pharmacies, hospitals and clinics, for supply to patients. This includes all parties involved in trade and distribution, pharmaceutical manufacturers, including the manufacturers of finished products, brokers, suppliers, distributors, wholesalers, traders, transport companies and forwarding agents. The relevant sections of the guidelines should also be considered for implementation by, among others, governments, regulatory bodies, international organizations and donor agencies, certifying bodies, as well as all parties including health care workers involved in any aspect of the trade and distribution of pharmaceutical products. The guidelines can also be used as a tool in the prevention of the distribution of counterfeit and substandard medicines. It should, however, be noted that these are general guidelines which may be adapted to suit the prevailing situations and conditions in individual countries.

3. Glossary

The definitions provided below apply to the words and phrases used in these guidelines. Although an effort has been made to use standard definitions as far as possible, they may have different meanings in other contexts and documents.

agreement

Arrangement undertaken by and legally binding on parties.

auditing

An independent and objective activity designed to add value and improve an organization's operations by helping an organization to accomplish its objectives by using a systematic, disciplined approach to evaluate and improve the effectiveness of risk management, control and governance processes.

batch

A defined quantity of pharmaceutical products processed in a single process or series of processes so that it is expected to be homogeneous (*adapted from GMP*).

batch number

A distinctive combination of numbers and/or letters which uniquely identifies a batch, for example, on the labels, its batch records and corresponding certificates of analysis.

consignment (or delivery)

The quantity of pharmaceutical products supplied at one time in response to a particular request or order. A consignment may comprise one or more packages or containers and may include material belonging to more than one batch (*adapted from GMP*).

container

The material employed in the packaging of a pharmaceutical product. Containers include primary, secondary and transportation containers. Containers are referred to as primary if they are intended to be in direct contact with the product. Secondary containers are not intended to be in direct contact with the product.

contamination

The undesired introduction of impurities of a chemical or microbiological nature, or of foreign matter, into or on to a starting material, intermediate or pharmaceutical product during handling, production, sampling, packaging or repackaging, storage or transport.

contract

Business agreement for the supply of goods or performance of work at a specified price.

counterfeit

A counterfeit medicine is one which is deliberately and fraudulently mislabelled with respect to identity and/or source. Counterfeiting can apply to both branded and generic products and counterfeit products and may include products with the correct ingredients or with the wrong ingredients, without active ingredients, with insufficient active ingredients or with fake packaging.

cross-contamination

Contamination of a starting material, intermediate product or finished product with another starting material or product during production.

distribution

The division and movement of pharmaceutical products from the premises of the manufacturer of such products, or another central point, to the end user thereof, or to an intermediate point by means of various transport methods, via various storage and/or health establishments.

excipient

A substance or compound, other than the active pharmaceutical ingredient and packaging materials, that is intended or designated to be used in the manufacture of a pharmaceutical product.

expiry date

The date given on the individual container (usually on the label) of a product up to and including which the product is expected to remain within specifications, if stored correctly. It is established for each batch by adding the shelf-life to the date of manufacture.

first expiry/first out (FEFO)

A distribution procedure that ensures that the stock with the earliest expiry date is distributed and/or used before an identical stock item with a later expiry date is distributed and/or used; earliest expiry/first out (EEFO) has a similar meaning.

first in/first out (FIFO)

A distribution procedure to ensure that the oldest stock is distributed and/or used before a newer and identical stock item is distributed and/or used.

good distribution practices (GDP)

Good distribution practices are that part of quality assurance that ensures that the quality of a pharmaceutical product is maintained by means of adequate control of the numerous activities which occur throughout the distribution process.

good manufacturing practices (GMP)

That part of quality assurance which ensures that pharmaceutical products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization.

good storage practices (GSP)

Good storage practices are that part of quality assurance that ensures that the quality of pharmaceutical products is maintained by means of adequate control throughout the storage thereof.

good trade and distribution practices (GTDP)

Good trade and distribution practices are that part of quality assurance that ensures that the quality of pharmaceutical products is maintained by means of adequate control throughout the numerous activities which occur during the trade and the distribution process.

health establishment

A health establishment is the whole or part of a public or private facility, building or place, whether operated for profit or not, that is operated or de-

signed to provide health care services including the supply of pharmaceutical products to the end user.

importation

The act of bringing or causing any goods to be brought into a customs territory (national territory, excluding any free zone).

intermediate product

Partly processed product that must undergo further manufacturing steps before it becomes a bulk product.

labelling

Process of identifying a pharmaceutical product including the following information, as appropriate: name; active ingredient(s), type and amount; batch number; expiry date; special storage conditions or handling precautions; directions for use, warnings and precautions; names and addresses of the manufacturer and/or the supplier (*adapted from GMP*).

manufacture

All operations of purchase of materials and products, production, quality control, release, storage and distribution of pharmaceutical products, and the related controls.

material

A general term used to denote starting materials (active pharmaceutical ingredients and excipients), reagents, solvents, process aids, intermediates, packaging materials and labelling materials.

pharmaceutical product

Any medicine intended for human use or veterinary product administered to food-producing animals, presented in its finished dosage form, that is subject to control by pharmaceutical legislation in both the exporting state and the importing state (*adapted from GMP*).

product recall

Product recall is a process for withdrawing or removing a pharmaceutical product from the pharmaceutical distribution chain because of defects in the product or complaints of serious adverse reactions to the product. The recall might be initiated by the manufacturer, importer, distributor or a responsible agency.

quality assurance

Quality assurance is a wide-ranging concept covering all matters that individually or collectively influence the quality of a product. It is the totality of the arrangements made with the object of ensuring that

pharmaceutical products are of the quality required for their intended use.

quality control

Quality control covers all measures taken, including the setting of specifications, sampling, testing and analytical clearance, to ensure that starting materials, intermediates, packaging materials and finished pharmaceutical products conform with established specifications for identity, strength, purity and other characteristics.

quality system

An appropriate infrastructure, encompassing the organizational structure, procedures, processes and resources, and systematic actions necessary to ensure adequate confidence that a product (or services) will satisfy given requirements for quality.

quarantine

The status of pharmaceutical products isolated physically or by other effective means while a decision is awaited on their release, rejection or reprocessing (*adapted from GMP*).

sampling

Operations designed to obtain a representative portion of a pharmaceutical product, based on an appropriate statistical procedure, for a defined purpose, e.g. acceptance of consignments or batch release.

shelf-life

The period of time during which a pharmaceutical product, if stored correctly, is expected to comply with the specification as determined by stability studies on a number of batches of the product. The shelf-life is used to establish the expiry date of each batch.

standard operating procedure (SOP)

An authorized, written procedure giving instructions for performing operations not necessarily specific to a given product but of a more general nature (e.g. equipment operation, maintenance and cleaning, validation, cleaning of premises and environmental control, sampling and inspection). Certain SOPs may be used to supplement product-specific master and batch production documentation.

storage

The storing of pharmaceutical products up to the point of use.

supplier

Person or company providing pharmaceutical products on request. Suppliers include distributors, manufacturers or traders.

transit

The period during which pharmaceutical products are in the process of being carried, conveyed, or transported across, over or through a passage or route to reach the destination.

validation

Action of proving and documenting that any process, procedure or method actually and consistently leads to the expected results.

vehicle

Vehicle refers to trucks, vans, buses, minibuses, cars, trailers, aircraft, railway carriages, boats and other means which are used to convey pharmaceutical products.

4. Organization and management

4.1 The distributor or the organization to which the distributor belongs must be an entity that is appropriately authorized to perform the intended function in terms of the applicable legislation, and which can be held accountable for its activities.

4.2 There should be an adequate organizational structure defined with the aid of an organizational chart. The responsibility, authority and interrelationships of all personnel should be clearly indicated.

4.3 A designated person should be appointed at each distribution point who should have defined authority and responsibility for ensuring that a quality management system is implemented and maintained.

4.4 Managerial and technical personnel must have the authority and resources needed to carry out their duties and to set up and maintain a quality management system, as well as to identify and correct deviations from the established quality management system.

4.5 The responsibilities placed on any one individual should not be so extensive as to present any risk to product quality.

4.6 There should be arrangements in place to ensure that management and personnel are not subject to commercial, political, financial and other pressures or conflicts of interest that may have an adverse effect on the quality of service provided.

4.7 Individual responsibilities should be clearly defined and understood by the individuals concerned and recorded as written job descriptions. Certain activities may require special attention such as the supervision of performance of activities, in accordance with local legislation.

4.8 Some duties may be delegated or contracted out to suitably designated persons or entities as necessary. There should, however, be no gaps or

unexplained overlaps with regard to the application of GDP. These activities should be documented in quality agreements or contracts. There should be periodic audit of such activities with regards to application of GDP.

4.9 Safety procedures relating to all relevant aspects including, for example, the safety of personnel and property, environmental protection and product integrity, should be in place.

5. Personnel

5.1 All personnel involved in distribution activities should be trained in the requirements of GDP and be capable of meeting these requirements.

5.2 Key personnel involved in the distribution of pharmaceutical products should have the ability and experience appropriate to their responsibility for ensuring that pharmaceutical products are distributed properly.

5.3 There should be an adequate number of competent personnel involved in all stages of the distribution of pharmaceutical products in order to ensure that the quality of the product is maintained.

5.4 National regulations with regard to qualifications and experience of personnel should be complied with.

5.5 Personnel should receive initial and continuing training relevant to their tasks, and be assessed as applicable, in accordance with a written training programme.

5.6 Personnel dealing with hazardous pharmaceutical products (such as highly active, and radioactive materials, narcotics, and other hazardous, sensitive and/or dangerous pharmaceutical products, as well as products presenting special risks of abuse, fire or explosion) should be given specific training.

5.7 Records of all training should be kept.

5.8 Personnel involved in the distribution of pharmaceutical products should wear working or protective garments suitable for the activities that they perform. Personnel dealing with hazardous pharmaceutical products, including products containing materials that are highly active, toxic, infectious or sensitizing, should be provided with protective garments as necessary.

5.9 Appropriate procedures relating to personnel hygiene, relevant to the activities to be carried out, should be established and observed. Such procedures should cover health, hygiene and clothing of personnel.

5.11 Procedures and conditions of employment for employees, including contract and temporary staff, and other personnel having access to pharma-

ceutical products must be designed and administered to assist in minimizing the possibility of such products coming into unauthorized possession.

5.12 Codes of practice and disciplinary procedures should be in place to prevent and address situations where persons involved in the distribution of pharmaceutical products are suspected of, or found to be implicated in, the misappropriation and/or theft thereof.

6. Quality management

6.1 Within an organization, quality assurance serves as a management tool. In contractual situations quality assurance also serves to generate confidence in the supplier. There should be a documented quality policy describing the overall intentions and policies of the distributor regarding quality, as formally expressed and authorized by management.

6.2 Quality management should include:

— an appropriate infrastructure or "quality system", encompassing the organizational structure, procedures, processes and resources; and
— systematic actions necessary to ensure adequate confidence that a product (or service) and documentation will satisfy given requirements for quality. The totality of these actions is termed "quality assurance".

6.3 The system should at least cover the main principles of quality assurance as embodied in the WHO guidelines on GMP for pharmaceutical products.

6.4 All parties involved in the distribution of pharmaceutical products should share responsibility for the quality and safety of products to ensure that they are fit for their intended use.

6.5 Where electronic commerce (e-commerce) is used, defined procedures and adequate systems should be in place to ensure traceability and confidence in the quality of pharmaceutical products.

6.6 Authorized procurement and release procedures should be in place, to ensure that appropriate pharmaceutical products are sourced from approved suppliers and distributed by approved entities.

6.7 All entities in the supply chain should be traceable as applicable, depending on the type of product, and on the national policies and legislation. There should be written procedures and records to ensure traceability of the products distributed.

6.8 Inspection and certification of compliance with a quality system (such as the applicable International Standardization Organization (ISO) series, or national or international guidelines) by external bodies is recommended. Such certification should not, however, be seen as a substitute for

compliance with these guidelines and the applicable principles of GMP relating to pharmaceutical products.

6.9 Authorized SOPs for all administrative and technical operations performed should be in place.

7. Premises, warehousing and storage

7.1 Good storage practice (GSP) is applicable in all circumstances where pharmaceutical products are stored and throughout the distribution process. For additional guidance relating to the general principles of storage of pharmaceutical products, refer to the WHO guideline on good storage practices (*1*).

Storage areas

7.2 Precautions must be taken to prevent unauthorized persons from entering storage areas.

7.3 Storage areas should be of sufficient capacity to allow the orderly storage of the various categories of pharmaceutical products, namely bulk and finished products, products in quarantine, and released, rejected, returned or recalled products.

7.4 Storage areas should be designed or adapted to ensure good storage conditions. In particular, they should be clean and dry and maintained within acceptable temperature limits. Pharmaceutical products should be stored off the floor and suitably spaced to permit cleaning and inspection. Pallets should be kept in a good state of cleanliness and repair.

7.5 Storage areas should be clean, and free from accumulated waste and vermin. A written sanitation programme should be available indicating the frequency of cleaning and the methods to be used to clean the premises and storage areas. There should also be a written programme for pest control. The pest-control agents used should be safe, and there should be no risk of contamination of pharmaceutical products. There should be appropriate procedures for the clean up of any spillage to ensure complete removal of any risk of contamination.

7.6 If sampling is performed in the storage area, it should be conducted in such a way as to prevent contamination or cross-contamination. Adequate cleaning procedures should be in place for the sampling areas.

7.7 Receiving and dispatch bays should protect products from the weather. Reception areas should be designed and equipped to allow incoming containers of pharmaceutical products to be cleaned, if necessary, before storage.

7.8 Where quarantine status is ensured by storage in separate areas, these areas must be clearly marked and their access restricted to authorized

personnel. Any system replacing physical quarantine should provide equivalent security. For example, computerized systems can be used, provided that they are validated to demonstrate security of access.

7.9 Physical or other equivalent validated (e.g. electronic) segregation should be provided for the storage of rejected, expired, recalled or returned products. The products and areas concerned should be appropriately identified.

7.10 Radioactive materials, narcotics and other hazardous, sensitive and/or dangerous pharmaceutical products, as well as products presenting special risks of abuse, fire or explosion (e.g. combustible liquids and solids and pressurized gases) should be stored in a dedicated areas that are subject to appropriate additional safety and security measures.

7.11 Pharmaceutical products should be handled and stored in such a manner as to prevent contamination, mix-ups and cross-contamination.

7.12 A system should be in place to ensure that pharmaceutical products due to expire first are sold and/or distributed first (FEFO). Where no expiry dates exist for the products, the FIFO principle should be applied. Exceptions may be permitted as appropriate, provided that adequate controls are in place to prevent the distribution of expired products.

7.13 Rejected pharmaceutical products should be identified and controlled under a quarantine system designed to prevent their use until a final decision is taken on their fate.

7.14 Narcotic drugs should be stored in compliance with international conventions, and national laws and regulations on narcotics.

7.15 Broken or damaged items should be withdrawn from usable stock and stored separately.

7.16 Storage areas should be provided with adequate lighting to enable all operations to be carried out accurately and safely.

Storage conditions

7.17 Storage conditions for pharmaceutical products should be in compliance with the instructions on the label, which are based on the results of stability testing.

Monitoring of storage conditions

7.18 Recorded temperature monitoring data should be available for review. The equipment used for monitoring should be checked at suitable predetermined intervals and the results of such checks should be recorded and retained. All monitoring records should be kept for at least the shelf-

life of the stored pharmaceutical product plus one year, or as required by national legislation. Temperature mapping should show uniformity of the temperature across the storage facility. It is recommended that temperature monitors be located in areas that are most likely to show fluctuations.

7.19 Equipment used for monitoring of storage conditions should also be calibrated at defined intervals.

Stock rotation and control

7.20 Periodic stock reconciliation should be performed by comparing the actual and recorded stocks.

7.21 All significant stock discrepancies should be investigated to check that there have been no inadvertent mix-ups, incorrect issue and/or misappropriation of pharmaceutical products.

8. Vehicles and equipment

8.1 Vehicles and equipment used to distribute, store or handle pharmaceutical products should be suitable for their use and appropriately equipped to prevent exposure of the products to conditions that could affect their stability and packaging integrity, and prevent contamination of any kind.

8.2 The design and use of vehicles and equipment must aim to minimize the risk of errors and permit effective cleaning and/or maintenance to avoid contamination, build-up of dust or dirt and/or any adverse effect on the quality of pharmaceutical products being distributed.

8.3 Dedicated vehicles and equipment should be used, where possible, when handling pharmaceutical products.

8.4 Where non-dedicated vehicles and equipment are used, procedures must be in place to ensure that the quality of the pharmaceutical product will not be compromised. Appropriate cleaning should be performed, checked and recorded.

8.5 Defective vehicles and equipment should not be used, and should either be labelled as such or removed from service.

8.6 There should be procedures in place for the operation and maintenance of all vehicles and equipment involved in the distribution process, including cleaning and safety precautions.

8.7 Vehicles, containers and equipment should be kept clean and dry and free from accumulated waste. A written cleaning programme should be available, indicating the frequency of cleaning and the methods to be used.

8.8 Vehicles, containers and equipment should be kept free from rodents, vermin, birds and other pests. There should also be written programmes for such pest control. Cleaning and fumigation agents should not have an adverse effect on product quality.

8.9 Equipment used for the cleaning of vehicles should be chosen and used so as not to constitute a source of contamination.

8.10 Special attention should be given to the design, use, cleaning and maintenance of all equipment used for the handling of pharmaceutical products which are not in a protective shipping carton or case.

8.11 Where special storage conditions (e.g. temperature and/or relative humidity), different from, or limiting, the expected environmental conditions, are required during transit these should be provided, checked, monitored and recorded. All monitoring records should be kept for a minimum of the shelf-life of the product distributed plus one year, or as required by national legislation. Recorded monitoring data should be reviewed on receipt of pharmaceutical products to assess whether the required storage conditions have been met.

8.12 Equipment used for monitoring conditions within vehicles and containers, e.g. temperature and humidity, should be calibrated.

8.13 Vehicles and containers should be of sufficient capacity to allow orderly storage of the various categories of pharmaceutical products during transportation.

8.14 Where possible mechanisms should be available to allow for the segregation during transit of rejected, recalled and returned pharmaceutical products as well as those suspected to be counterfeits. Such goods must be securely packaged, clearly labelled, and be accompanied by appropriate supporting documentation.

8.15 Measures should be in place to prevent unauthorized persons from entering and/or tampering with vehicles and/or equipment, as well as to prevent the theft or misappropriation thereof.

9. Shipment containers and container labelling

9.1 All pharmaceutical products should be stored and distributed in shipment containers which do not have an adverse effect on the quality of the products, and which offer adequate protection from external influences, including contamination.

9.2 Shipping containers may not need to bear labels with full description of the identity of the container's content (in order to deter thieves), but should nonetheless provide sufficient information on handling and storage conditions and precautions to ensure the product is properly handled at all times.

9.3 The need for any special transport and/or storage conditions should be stated on the label. If a pharmaceutical product is intended for transfer outside the control of the manufacturer's products management system, the name and address of the manufacturer, special transport conditions and any special legal requirements including safety symbols should also be included on the label.

9.4 Only internationally and/or nationally accepted abbreviations, names or codes should be used in the labelling of containers.

9.5 Special care should be used when using dry ice in containers. In addition to safety issues it must be ensured that the pharmaceutical product does not come into contact with the dry ice, as it may have an adverse effect on the quality of the product.

9.6 Written procedures should be available for the handling of damaged and/or broken containers. Particular attention should be paid to those containing potentially toxic and hazardous products.

10. Dispatch

10.1 Pharmaceutical products should only be sold and/or distributed to persons or entities who are entitled to acquire such products as demonstrated by the applicable national, regional and international legislation. Written proof of such authority must be obtained prior to the dispatch of products to such persons or entities.

10.2 The supplier of pharmaceutical products should, prior to the dispatch of such products, ensure that the person or entity, e.g. the contract acceptor for transportation of the pharmaceutical products, is aware of and complies with the appropriate storage and transport conditions.

10.3 The dispatch and transportation of pharmaceutical products should be commenced only after the receipt of a valid delivery order or material replenishment plan which should be documented.

10.4 Written procedures for the dispatch of pharmaceutical products should be established. Such procedures should take into account the nature of the product, as well as any special precautions to be observed.

10.5 Records for the dispatch of pharmaceutical products should be prepared and should include at least the following information:

— date of dispatch;
— name and address of the entity responsible for the transportation;
— name, address and status of the addressee (e.g. retail pharmacy, hospital, community clinic);
— a description of the products including, e.g. name, dosage form and strength (if applicable);

— quantity of the products, i.e. number of containers and quantity per container;
— assigned batch number and expiry date;
— applicable transport and storage conditions; and
— a unique number to allow identification of the delivery order.

10.6 Records of dispatch should contain enough information to enable traceability of the pharmaceutical product. Such records should facilitate the recall of a batch of a product if necessary. Each party involved in the distribution chain has a responsibility to ensure traceability.

10.7 Methods of transportation, including vehicles to be used, should be selected with care, and local conditions should be considered, including the climate and any seasonal variations experienced. Delivery of products requiring controlled temperatures should be in accordance with the applicable storage and transport conditions.

10.8 Delivery schedules should be established and routes planned, taking local needs and conditions into account. Such schedules and plans should be realistic and systematic. Care should be taken to ensure that the volume of pharmaceutical products ordered does not exceed the capacity of storage facilities at the destination.

10.9 Vehicles and containers should be loaded carefully and systematically, where applicable on a first-out/last-in basis, to save time when unloading and to prevent physical damage. Extra care should be taken during loading and unloading of cartons to avoid breakage.

10.10 Pharmaceutical products should not be supplied or received after their expiry date, or so close to the expiry date that this date is likely to occur before the products are used by the consumer.

11. Transportation and products in transit

11.1 The transportation process should not compromise the integrity and quality of pharmaceutical products.

11.2 The manufacturer should communicate all relevant conditions for storage and transportation to those responsible for the transportation of pharmaceutical products. Such an entity(-ies) should ensure adherence to these requirements throughout transportation and at any intermediate storage stages.

11.3 Pharmaceutical products should be stored and transported in accordance with procedures such that:

- the identity of the product is not lost;
- the product does not contaminate and is not contaminated by other products;

- adequate precautions are taken against spillage, breakage, misappropriation and theft; and
- appropriate temperature and relative humidity conditions are maintained in the case of pharmaceutical products, e.g. using cold chain for thermolabile products.

11.4 A batch tracking system should be used to enable specific batches to be traced during the distribution process.

11.5 The required storage conditions for pharmaceutical products should be maintained within acceptable limits during transportation. There should be no gross deviation from the specific storage conditions for the product, or deviation for an unacceptable period of time, during the transit period. Any deviations from storage conditions which are considered to be acceptable should be determined in consultation with the marketing authorization holder and/or the manufacturer.

11.6 Where special conditions are required during transportation which are different from or limit the given environmental conditions (e.g. temperature, humidity) these should be provided, monitored and recorded.

11.7 Written procedures should be in place for investigating and dealing with any violations of storage requirements, e.g. temperature violations.

11.8 Products comprising highly active and radioactive materials, other dangerous medicines and substances presenting special risks of abuse, fire or explosion (e.g. combustible liquids, solids and pressurized gases) should be stored in safe, dedicated and secure areas, and transported in safe, dedicated and secure containers and vehicles. In addition, applicable international agreements and national legislation should be complied with.

11.9 Products containing narcotics and other dependence-producing substances should be stored in safe and secure areas, and transported in safe and secure containers and vehicles. In addition, applicable international agreements and national legislation should be complied with.

11.10 Spillages should be cleaned as soon as possible to prevent possible contamination, cross-contamination and hazards. Written procedures should be in place for the handling of such occurrences.

11.11 Physical or other equivalent (e.g. electronic) segregation should be provided for the storage and distribution during transit of rejected, expired, recalled or returned pharmaceutical products and suspected counterfeits. The products should be appropriately identified, securely packaged, clearly labelled and be accompanied by appropriate supporting documentation.

11.12 Products containing toxic and/or flammable substances should be stored and transported in suitably designed, separate and closed containers, in accordance with national legislation and international agreements.

11.13 The interiors of vehicles and containers should remain clean and dry while pharmaceutical products are in transit.

11.14 Packaging materials and transportation containers should be of suitable design to prevent damage of pharmaceutical products during transport.

11.15 Sufficient security should be provided to prevent theft and other misappropriation of products. Steps should be taken to prevent unauthorized access to pharmaceutical products during transport.

11.16 Damage to containers and any other event or problem which occurs during transit must be recorded and reported to the relevant department, entity or authority, and investigated.

11.17 Pharmaceutical products in transit must be accompanied by the appropriate documentation.

12. Documentation

12.1 Written instructions and records should be available which document all activities relating to the distribution of pharmaceutical products, including all applicable receipts and issues. The name of the applicable entity should appear on all relevant documents.

12.2 Procedures should be established and maintained for the preparation, review, approval, use of and control of changes to all documents relating to the distribution process. Procedures must be in place for both internally generated documents and documents from external sources.

12.3 Documents, and in particular instructions and procedures relating to any activity that could have an impact on the quality of pharmaceutical products, should be designed, completed, reviewed and distributed with care.

12.4 The title, nature and purpose of each document should be clearly stated. The contents of documents should be clear and unambiguous. Documents should be laid out in an orderly fashion and be easy to check.

12.5 All documents should be completed, approved, signed (as required) and dated by an appropriate authorized person(s) and should not be changed without the necessary authorization.

12.6 The nature, content and retention of documentation relating to the distribution of pharmaceutical products should comply with national legislative requirements. Where such requirements are not in place the docu-

ments should be retained for a period equal to the shelf-life of the products where applicable, plus one year.

12.7 The distributor must establish and maintain procedures for the identification, collection, indexing, retrieval, storage, maintenance, disposal of and access to all applicable documentation.

12.8 All records must be readily retrievable, and be stored and retained using facilities that are safeguarded against unauthorized modification, damage, deterioration and/or loss of documentation.

12.9 Documents should be reviewed regularly and kept up to date. When a document has been revised, a system should exist to prevent inadvertent use of the superseded version.

12.10 Mechanisms should exist to allow for transfer of information, including quality or regulatory information, between a manufacturer and a customer, as well as the transfer of information to the relevant regulatory authority as required.

12.11 Records relating to storage of pharmaceutical products should be kept and be readily available upon request in accordance with the WHO guidelines on good storage practice (*1*).

12.12 Permanent records, written or electronic, should exist for each stored product indicating recommended storage conditions, any precautions to be observed and retest dates. Pharmacopoeial requirements and current national regulations concerning labels and containers should be respected at all times.

12.13 Procedures should be in place for temperature mapping, security services to prevent theft or tampering with goods at the storage facilities, destruction of unsaleable stocks and on retention of the records.

12.14 In the case of temperature-sensitive pharmaceutical products, records of investigations and actions should be retained for at least one year after the expiry date of the product.

12.15 Where the records are generated and kept in electronic form, backups should be maintained to prevent any accidental data loss.

13. Repackaging and relabelling

13.1 Repackaging (including relabelling) of pharmaceutical products should only be performed by distributors appropriately authorized and/or licensed to do so, and in accordance with GMP principles. Where these functions are performed they should comply with the applicable national, regional and international guidelines relating to repackaging and relabelling of pharmaceutical products.

14. Complaints

14.1 There should be a written procedure in place for the handling of complaints. A distinction should be made between complaints about a product or its packaging and those relating to distribution. In the case of a complaint about the quality of a product or its packaging the original manufacturer and/or marketing authorization holder should be informed as soon as possible.

14.2 All complaints and other information concerning potentially defective and potentially counterfeit pharmaceutical products should be reviewed carefully according to written procedures describing the action to be taken, including the need to consider a recall where appropriate.

14.3 Any complaint concerning a material defect should be recorded and thoroughly investigated to identify the origin or reason for the complaint (e.g. repackaging procedure or original manufacturing process).

14.4 If a defect relating to a pharmaceutical product is discovered or suspected, consideration should be given to whether other batches of the product should also be checked.

14.5 Where necessary, appropriate follow-up action should be taken after investigation and evaluation of the complaint.

15. Recalls

15.1 There should be a system which includes a written procedure, to recall promptly and effectively pharmaceutical products known or suspected to be defective, with a designated person(s) responsible for recalls.

15.2 Such procedures should be checked regularly and updated as necessary.

15.3 The original manufacturer and/or marketing authorization holder should be informed in the event of a recall. Where a recall is instituted by an entity other than the original manufacturer and/or marketing authorization holder, consultation with the original manufacturer and/or marketing authorization holder should, where possible, take place before the recall is instituted.

15.4 The effectiveness of the arrangements for recalls should be evaluated at regular intervals. All recalled pharmaceutical products should be stored in a secure, segregated area pending appropriate action.

15.6 Recalled pharmaceutical products should be segregated during transit and clearly labelled as recalled products. Where segregation in transit is not possible, such goods must be securely packaged, clearly labelled, and be accompanied by appropriate documentation.

15.7 The storage conditions applicable to a pharmaceutical product which is subject to recall should be maintained during storage and transit until such time as a decision has been made regarding the fate of the product in question.

15.8 All customers and competent authorities of all countries to which a given pharmaceutical product may have been distributed should be informed promptly of any intention to recall the product because it is, or is suspected to be, defective.

15.9 All records should be readily available to the designated person(s) responsible for recalls. These records should contain sufficient information on pharmaceutical products supplied to customers (including exported products).

15.10 The progress of a recall process should be recorded and a final report issued, which includes a reconciliation between delivered and recovered quantities of products.

16. Rejected and returned products

16.1 Rejected pharmaceutical products and those returned to a distributor should be appropriately identified and handled in accordance with a procedure which involves at least the physical segregation of such pharmaceutical products in quarantine in a dedicated area, or other equivalent (e.g. electronic) segregation, to avoid confusion and prevent distribution until a decision has been taken with regard to their disposition. The storage conditions applicable to a pharmaceutical product which is rejected or returned should be maintained during storage and transit until such time as a decision has been made regarding the product in question.

16.2 The necessary assessment and decision regarding the disposition of such products must be taken by a suitably authorized person. The nature of the product returned to the distributor, any special storage conditions required, its condition and history and the time elapsed since it was issued, should all be taken into account in this assessment. Where any doubt arises over the quality of a pharmaceutical product it should not be considered suitable for reissue or reuse.

16.3 Provision should be made for the appropriate and safe transport of returned products in accordance with the relevant storage and other requirements.

16.4 Provision should be made for the appropriate and safe transport of rejected and waste materials prior to their disposal.

16.5 When pharmaceutical products are destroyed this should be done in accordance with international, national and local requirements regarding

disposal of such products, and with due consideration to protection of the environment.

16.6 Records of all returned, rejected and/or destroyed pharmaceutical products should be kept.

17. Counterfeit pharmaceutical products

17.1 Any counterfeit or suspected counterfeit medicines found in the pharmaceutical supply chain should be segregated immediately from other pharmaceutical products and recorded.

17.2 The holder of the marketing authorization, the appropriate national and/or international regulatory bodies, as well as other relevant competent authorities, should be informed immediately.

17.3 Such products should be clearly labelled to prevent further distribution or sale.

17.4 Upon confirmation of the product being counterfeit a formal decision should be taken on its disposal and the decision recorded.

18. Importation

18.1 Consideration should be given to the WHO guidelines on import procedures for pharmaceutical products (*5*). The following aspects should be given particular attention.

18.2 The number of ports of entry in a country for the handling of imports of pharmaceutical products should be limited by appropriate legislation.

18.3 The most appropriately located and best equipped to handle imports of pharmaceutical products should be chosen as the port(s) of entry for the import of such products into a country.

18.4 At the port of entry, consignments of pharmaceutical products should be stored under suitable conditions for as short a time as possible.

18.5 All reasonable steps should be taken by importers to ensure that products are not mishandled or exposed to adverse storage conditions at wharves or airports.

18.6 Where necessary, people with pharmaceutical training should be involved with the customs procedures or should be readily contactable.

18.7 The WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce should be used to provide data regarding quality assessment of imported pharmaceutical products.

19. Contract activities

19.1 Any activity relating to the distribution of a pharmaceutical product which is delegated to another person or entity should be performed according to the terms of a written contract which is agreed upon by the contract giver and the contract accepter.

19.2 The contract should define the responsibilities of each party including observance of the principles of GDP.

19.3 All contract accepters should comply with the requirements in these guidelines.

19.4 Subcontracting may be permissible under certain conditions subject to the written approval of the contract giver.

19.5 Any contract accepter should be audited periodically.

20. Self-inspection

20.1 The system of quality assurance should include self-inspections. These should be conducted to monitor implementation and compliance with the principles of GDP and if necessary, to trigger corrective and preventive measures.

20.2 Self-inspections should be conducted in an independent and detailed way by a designated, competent person.

20.3 The results of all self-inspections should be recorded. Reports should contain all observations made during the inspection and, where applicable, proposals for corrective measures. There should be an effective follow-up programme. Management should evaluate the inspection report, and the records of any corrective actions taken.

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Annex 6

A model quality assurance system for procurement agencies (Recommendations for quality assurance systems focusing on prequalification of products and manufacturers, purchasing, storage and distribution of pharmaceutical products)

Introduction

The World Health Organization (WHO), the United Nations Children's Fund (UNICEF) and many other organizations are involved in the procurement of pharmaceutical products. In particular, the supply of pharmaceutical products used in the treatment of human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS), malaria and tuberculosis has become a major concern at both the international and country levels. Commitments by the European Commission and G8 countries, among others, offer the potential for significant increases in funding for efforts to combat communicable diseases. Low-cost pharmaceutical products of assured quality have the greatest potential for maximizing the impact of these efforts.

The need for a model quality assurance system

Efforts to accelerate access to pharmaceutical products used in the treatment of HIV/AIDS through negotiation and generic competition have highlighted the importance of quality assurance for procurement of pharmaceutical products and diagnostics. Considerable sums of money are invested in procuring pharmaceutical products from various manufacturers in different countries. However, evaluation of product-specific data and information on quality is often lacking, and inspections at manufacturing sites are not routinely performed to a consistent standard. At present, some organizations involved in procurement of pharmaceutical products do have quality systems for the different activities in place. However, these systems vary greatly between organizations. Some procurement agencies request manufacturers to submit a checklist or questionnaire containing product information for assessment. In some cases, these checklists fail to address important aspects that should be evaluated as part of prequalification. Others use detailed questionnaires or request product dossiers for evaluation. Some procurement agencies contract inspectors to perform inspections at the place of manufacture, but the extent and quality of these inspections may vary according to the resources available. Moreover, mutual recognition and coordination of such inspections is an exception rather than the rule.

Without a quality assurance system, organizations risk sourcing substandard, counterfeit or contaminated pharmaceutical products, leading to complaints about products and product recalls, wastage of money and serious health risks to patients. Such problems affect the credibility of procurement agencies, cause financial losses and put patients' safety in danger.

Background

A preparatory study carried out by a team of experts emphasized the substantial differences between prequalification of vaccines and pharmaceuticals. A pilot project to study the feasibility of prequalifying manufacturers of essential pharmaceutical products for treating priority diseases was recommended.

The accumulated experience of experts from UNICEF, the United Nations Population Fund (UNFPA), WHO and the World Bank has identified the necessary elements to ensure appropriate procedures for procurement.

WHO therefore undertook a project with the above-mentioned United Nations partners, which was supported in principle by the World Bank. The project focused on the prequalification of products and manufacturers of HIV/AIDS-related products, and the drafting of a model quality assurance system (hereafter referred to as the Model). This Model is intended to assist organizations purchasing pharmaceutical products, vaccines, or other health sector goods or which are otherwise involved in the prequalification, purchasing, storage and distribution of such products, hereafter referred to as procurement agencies, to procure safe, effective pharmaceuticals of suitable quality.

Goal and objectives

The long-term goal of these recommendations is the design and implementation of a uniform and harmonized system that will ensure procurement of pharmaceutical products of defined quality for supply to patients, based on a mutually recognized process of prequalification of products and manufacturers by means of product dossier evaluation and inspection of manufacturing sites. Such a process, as defined in the Glossary and described in Module II, will hereafter be referred to as prequalification.

Establishing, harmonizing and implementing a quality assurance system for prequalification, purchasing, storage and distribution of pharmaceuticals is a task of considerable magnitude, which should be undertaken in stages. The following objectives were identified:

- creation of a model quality assurance system (MQAS) to be adopted and implemented by procurement agencies;
- creation of guidelines to harmonize the evaluation of data and information on products as part of the prequalification procedure; and
- creation of unified standards for inspection of manufacturers and suppliers to assess compliance with good manufacturing practices (GMP).

Quality assurance in procurement

Quality assurance is a wide-ranging concept which covers all matters that individually or collectively influence the quality of a product. It is the totality of the arrangements made to ensure that pharmaceutical products are of the quality required for their intended use. Quality assurance therefore incorporates several factors and it is an integral part of all key activities in procurement.

The implementation of a quality assurance system in procurement, including systems for prequalification, storage and distribution, may affect costs. However, the benefits of ensuring quality outweigh the cost investment because they reduce the possible losses caused by the purchase and supply of substandard products.

Prequalification of products and manufacturers, purchasing, storage and distribution are complex processes that may involve many offices, procurement agencies, sections or departments and several stages of administration, finance and technical decisions. Pharmaceutical products are not ordinary commodities of trade and require special attention. Support from the offices responsible for quality assurance is crucial. The efficiency of the procedures depends in great part on the use of a proven method in a consistent manner. The use of a standard approach will ensure consistency in all activities involved in procurement of pharmaceutical products of defined acceptable quality.

This Model focuses on the following four key activities of procurement agencies:

- prequalification of pharmaceutical products and manufacturers;
- purchase of pharmaceutical products;
- storage of pharmaceutical products; and
- distribution of pharmaceutical products.

Procurement agencies are ultimately responsible for the outcomes of all four key activities. In some cases, one or more of the activities may be contracted out. Where this occurs, a written contract which describes the responsibilities of both parties should be agreed upon between the two parties. The contract-giver remains responsible for ensuring that the contract-acceptor meets the norms and standards reflected in this Model.

Recommendations

It is recommended that procurement agencies involved in any of the key activities of procurement develop and implement their own internal quality assurance systems on the basis of the Model, including the elements described and technical details specified. It is important to ensure that the system is adapted to reflect the activities of each specific procurement agency. The system should cover all aspects of the agency's activities and should be comprehensive enough to ensure that interrelated activities which impact on the quality of pharmaceutical products are linked.

This document provides guidelines for United Nations procurement agencies, but they may also be used by other procurement agencies to establish quality assurance systems for their own activities.

These guidelines are designed for procurement of pharmaceutical products. They may also be applicable to the procurement of diagnostic kits or medical devices.

Overview

This document is divided into six modules. Module I addresses the general requirements for the quality assurance system that should be in place

at all procurement agencies, irrespective of the number of key activities performed. Module II sets out recommendations that procurement agencies should implement when evaluating their product needs, assessing the products offered and the manufacturing and supply arrangements provided by the manufacturers. Module III describes principles of purchasing pharmaceutical products. Module IV contains recommendations on how to receive and store purchased products. In Module V, good distribution practices are described and Module VI deals with monitoring and reassessment of products and contracted-out activities. This document also includes documentation examples of elements of this Model as well as relevant existing WHO guidelines.

Throughout this document, reference will be made to existing WHO norms, standards, guidelines and texts. An effort has been made to avoid duplication wherever possible. Where relevant, reference is made to related documents.

The standard text *Managing drug supply (1)* provides a complete and detailed overview of technical aspects of pharmaceuticals management, including all the key activities of procurement.

Glossary

accountability

The obligation to account for one's conduct and actions, usually to an individual or group, but ultimately to the public. Both individuals and organizations may be accountable. There is some overlap between accountability and *transparency* (see below).

active pharmaceutical ingredient (API)

A substance or compound intended to be used in the manufacture of a pharmaceutical product as a therapeutically active compound (ingredient).

affordability

The extent to which pharmaceutical products are available to the people who need them at a price they can pay.

authorized person

A person (among key personnel of a manufacturing establishment) responsible for the release of batches of finished products for sale. In some *good manufacturing practice* (GMP) guides and legal texts, the term *qualified person* is used to describe analogous functions.

bioequivalence

Two pharmaceutical products are bioequivalent if they are pharmaceutically equivalent or pharmaceutical alternatives and their bioavailabilities, in terms of peak (C_{max} and T_{max}) and total exposure (area under the curve (AUC)), after administration in the same molar dose under the same conditions, are similar to such a degree that their effects can be expected to be essentially the same.

bioavailability

The rate and extent at which the active pharmaceutical ingredient or active moiety is absorbed from a pharmaceutical dosage form and becomes available at the site(s) of action.

competitive tender

A procedure for procuring pharmaceutical products which puts a number of suppliers into competition. Purchasing is done on the basis of quotations submitted by the suppliers in response to a public notice.

drug

Any substance or pharmaceutical product for human or veterinary use that is intended to modify or explore physiological systems or pathological states for the benefit of the recipient. In this document, the terms *drug, medicine* and *pharmaceutical product* (see below) are used interchangeably.

drug legislation

The legal conditions under which pharmaceutical activities should be organized. (See also *legislation* below.)

drug regulatory authority

A national body that administers the full spectrum of drug regulatory activities, including at least all of the following functions in conformity with national drug legislation:

- marketing authorization of new products and variations of existing products;
- quality control laboratory testing;
- monitoring of adverse drug reactions;
- provision of drug information and promotion of rational drug use;
- *good manufacturing practice* (GMP) inspections and licensing of manufacturers, wholesalers and distribution channels;
- enforcement operations;
- monitoring of drug utilization.

effectiveness

An expression of the degree to which activities have produced the effects planned.

efficiency

The relationship between the results of activities and the corresponding effort expended in terms of money, resources and time.

essential pharmaceutical products

Those pharmaceutical products that satisfy the health care needs of the majority of the population. WHO's Expert Committee on the Selection and Use of Essential Medicines updates the *WHO Model List of Essential Medicines* at two-year intervals. Each country may use this model to generate its own list of essential pharmaceutical products.

generic products

The term *generic product* has somewhat different meanings in different jurisdictions. The use of this term is therefore avoided as far as possible, and the term *multisource pharmaceutical product* (see below) is used instead. Generic products may be marketed either under the approved nonproprietary name or under a brand (proprietary) name. They may be marketed in dosage forms and/or strengths different from those of the *innovator products* (see below). Where the term *generic product* is used, it means a pharmaceutical product, usually intended to be interchangeable with the innovator product, which is usually manufactured without a licence from the innovator company and marketed after expiry of the patent or other exclusivity rights. The term should not be confused with generic names for APIs.

generic substitution

Practice of substituting a product, whether marketed under a trade name or generic name, with an equivalent product, usually a cheaper one, containing the same active ingredient(s).

good manufacturing practice (GMP)

That part of quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization.

indicator

Criterion used to measure changes, directly or indicrectly, and to assess the extent to which the targets or objectives of a programme or project are being attained. Indicators should meet the criteria of clarity, usefulness, measurability, *reliability*, *validity* (see below) and acceptance by key stakeholders.

innovator pharmaceutical product

Generally the pharmaceutical product which was first authorized for marketing (normally as a patented product) on the basis of documentation of efficacy, safety and quality according to requirements at the time of the authorization. When a substance has been available for many years, it may not be possible to identify an innovator pharmaceutical product.

interchangeability

An interchangeable pharmaceutical product is one that is therapeutically equivalent to a comparator (reference) product.

International Nonproprietary Name

The shortened scientific name based on the active ingredient. WHO is responsible for assigning INNs to pharmaceutical substances.

legislation

The first state of the legislative process, in which laws are passed by the legislative body of government with regard to a subject matter, e.g. control of pharmaceuticals. Laws define the roles, rights and obligations of all parties involved in the subject matter in general terms (see also *regulations* below).

licensing system

National legal provisions on who should manufacture, import or supply pharmaceutical products, what qualifications people in the supplying agency should have, and who should dispense and sell pharmaceutical products.

manufacture (manufacturing)

All or any operations of purchase of materials and products, production, quality control, release, storage and distribution of finished products and the related controls.

marketing authorization

A legal document issued by the competent drug regulatory authority for the purpose of marketing or free distribution of a product after evaluation for safety, efficacy and quality. It must set out, inter alia, the name of the product, the pharmaceutical dosage form, the quantitative formula (including excipients) per unit dose (using INNs or national generic names where they exist), the shelf-life and storage conditions, and packaging characteristics. It specifies the information on which authorization is based (e.g. "The product(s) must conform to all the details provided in your application and as modified in subsequent correspondence."). It also contains the product information approved for health professionals and the public, the sales category, the name and address of the holder of the authorization, and the period of validity of the authorization.

Once a product has been given marketing authorization, it is included on a list of authorized products – the register – and is often said to be "registered" or to "have registration". Market authorization may occasionally also be referred to as a "licence" or "product licence".

medicine

See *drug*.

multisource (generic) pharmaceutical product

Pharmaceutically equivalent or pharmaceutically alternative products that may or may not be therapeutically equivalent. Multisource pharmaceutical products that are therapeutically equivalent are interchangeable.

national list of essential pharmaceutical products

The list of *essential pharmaceutical products* (see above) that has been defined, adopted and published at country level. It is normally used by all health facilities, including the main hospitals.

pharmaceutical product

See *drug*.

prequalification

The activities undertaken in defining a product or service need, seeking expressions of interest from enterprises to supply the product or service, and examining the product or service offered against the specification and the facility where the product or service is prepared against common standards of *good manufacturing practice* (GMP). The examination of the product or service and of the facility where it is manufactured is performed by trained and qualified inspectors against common standards. Once the product is approved, and the facility is approved for the delivery of the specified product or service, other procurement agencies are informed of the decision. Prequalification is required for all pharmaceutical products regardless of their composition and place of manufacture/registration, but the amount and type of information requested from the supplier for assessment by the procurement agency may differ.

procurement

The process of purchasing or otherwise acquiring any pharmaceutical product, vaccine, or nutraceuticals for human use. For the purpose of this document, *procurement* means the pre-selection of products and manufacturers through a procedure of qualification, including *prequalification* (see above) and continuous monitoring thereafter, purchase of the prequalified products from prequalified manufacturers (linked to the specific product) through defined purchasing mechanisms, storage and distribution.

procurement agency

Any organization purchasing or otherwise acquiring any pharmaceutical product, vaccine or nutraceutical for human use. In the context of these guidelines it will normally be a not-for-profit organization, a nongovernmental organization (NGO) or a United Nations organization. A *procurement agency* in the context of this document is defined as any organization purchasing pharmaceutical products, vaccines, or other health sector goods or otherwise involved in their *prequalification* (see above), purchasing, storage and distribution.

product information

In the context of this document, product information means information on pharmaceutical products submitted by manufacturers or suppliers in any of the formats specified in the procurement agency's guidelines (including product dossiers, product questionnaires or other formats) to obtain prequalification for the products.

qualification

Action of proving and documenting that any premises, systems and equipment are properly installed and/or work correctly and lead to the expected results. Qualification is often apart (the initial stage) of validation, but the individual qualification steps alone do not constitute process validation. In the context of this document it is the work done to prove that the supply system will deliver products of the quality required and specified on a routine basis, meeting all the applicable quality requirements.

quality assurance

Quality assurance is a wide-ranging concept covering all matters that individually or collectively influence the quality of a product. It is the totality of the arrangements made with the object of ensuring that pharmaceutical products are of the quality required for their intended use.

quality control

Quality control is concerned with sampling, specifications and testing, and with the procurement agency's documentation and acceptance/rejection procedures which ensure that the necessary and relevant tests are actually carried out and

that starting materials, intermediates and finished products are not accepted for use, sale or supply until their quality has been judged to be satisfactory.

regulations

The second stage of the legislative process (the first stage being *legislation*, see above). Regulations are specifically designed to provide the legal machinery to achieve the administrative and technical goals of legislation.

reliability

An expression of the degree to which a measurement performed by different people at different times and under different circumstances produces the same results (see also *validity*).

reliable quantification of drug needs

A careful evaluation of the quantities needed of each drug, based on either adjusted past consumption or anticipated pattern of diseases and standard treatment, which can be expected to match actual needs reasonably well.

transparency

The term transparency means:

— defining policies and procedures in writing and publishing the written documentation; and
— giving reasons for decisions to the public (see also *accountability* above).

validation

Action of proving and documenting, in accordance with the principles of good manufacturing practice, that any procedure, process, or method actually and consistently leads to the expected results (see also *qualification* above).

validity

An expression of the degree to which a measurement performed actually measures the characteristic which the investigator wishes to measure (see also *reliability* above).

WHO-type certificate

A certificate of pharmaceutical product of the type defined in the WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce.[1]

[1] World Health Organization. *WHO Certification Scheme on the quality of pharmaceuticals products moving in international commerce*. Geneva, World Health Organization, 2000. WHO/EDM/QSM/2000.2 (http://www.who.int/medicines/organization/qsm/activities/drugregul/certification/certifschemes.html).

Module I

General requirements for procurement agencies

Introduction

Procurement agencies often have to purchase and supply pharmaceutical products using scarce resources. In many cases, product quality is compromised when products are obtained from unqualified sources. Procurement agencies will deal with various types of suppliers and customers, including drug regulatory authorities, manufacturers, quality control laboratories, contract manufacturers, contract laboratories, traders, brokers, distributors and pharmacies. A quality assurance system will assist in ensuring that transactions with these partners ultimately result in procuring pharmaceutical products of the best possible quality.

This module addresses the general requirements for such a system, including physical resources such as premises, equipment and personnel, as well as the documented policies, standards and procedures required to ensure consistency in all the key activities of procurement. The general requirements described in this module are therefore applicable to all the activities covered in subsequent modules.

I.1 Physical resources

I.1.1 *Premises*

Offices

The procurement agency should have sufficient office space to accommodate the personnel required and the activities to be performed.

Storage

The procurement agency should have sufficient space for storage and retention of commodities, including product documentation, product samples, stock, reports, files and other records relating to all key activities of procurement.

Samples and products should be stored under suitable conditions which are specified, e.g. with regard to temperature, humidity or protection from light. Details of storage requirements are given in Module IV.

There should be sufficient space for storage of equipment, stationery and materials for proper distribution. Details of distribution requirements are given in Module V.

I.1.2 *Equipment*

Computers

The use of computers can facilitate, but not replace, efficient procedures in pharmaceutical procurement. When implemented appropriately, computerization will speed up complex tasks, increase accuracy and automate repetitive tasks. Staff must be trained adequately in the use of computerized systems.

Many aspects of procurement are suitable for computerization, including planning of requirements, budget management, financial analysis, preparation of documentation and reports and inventory control. Hard copies (printouts) should be produced as required to provide documented evidence of the activities.

Where computer systems are not used, manual systems should provide documented evidence of the activities performed.

Software

The software selected should be suitable for the intended use. The programmes used should be able to provide the required quality and management information reliably and accurately. They should be user-friendly and staff should be trained adequately in their use. Where possible, different programmes used should be compatible so that data can be transferred between them without having to be retyped.

Where information is exchanged between the procurement agency and the manufacturer(s) by electronic means, appropriate programmes should be in place.

Suitable security systems should be in place to prevent unauthorized access or changes to computer records and reports. Back-up systems must be in place to prevent loss of data. A good-quality virus protection programme and firewall must be installed, configured, used and updated regularly to prevent unauthorized access and loss of data.

Technical support should be available to ensure that software and security systems are kept functional and up to date.

Hardware

The hardware selected which should be able to handle the required software efficiently. The system should have sufficient capacity and memory for the intended use, as well as adequate input and output devices, including good quality printers. Access to the Internet and possibly to an internal network (LAN) should be provided to facilitate exchange of information.

A maintenance and upgrading plan must be in place to ensure that the system remains functional.

Telecommunications

There should be access to telephone and facsimile facilities to ensure instant communication. If at all possible, electronic mailing (e-mail) systems should be available.

Furniture

Suitable office furniture should be provided, including desks, chairs, shelves, cupboards, filing cabinets and other items as required.

Office equipment

Office equipment including copying machines, staplers and punches should be provided.

I.1.3 *Materials and consumables*

Stationery and consumables

The procurement agency should provide stationery to enable staff to perform the relevant tasks, including paper, letterheads, business cards and pre-printed forms as required. Computer consumables to be provided include removable storage devices (floppy disks, CDs and/or flash memory sticks), printer cartridges, printing paper, as well as any replacement parts not covered by a maintenance contract.

Vehicles and transport

Official transport or reimbursement of transport costs incurred should be provided for trips to meetings, visits, inspections and performance of other official duties.

In cases where the procurement agency is responsible for local transportation and distribution of products, appropriate transport should be provided to ensure that the quality of the products is maintained.

I.1.4 *Financial systems*

The procurement agency should be able to effect national and international financial transactions as required. Funds must be available to ensure continued operations, whether or not cost recovery mechanisms for key activities, e.g. prequalification, are in place.

Adequate banking facilities must be available. Signatories of bank accounts should be appointed to ensure control on one hand, and continuity of operations during the absence of key personnel on the other hand.

An accounting system should be in place. Regular financial audits should be performed.

If the procurement agency is part of a larger organization, it should have sufficient autonomy and/or sufficiently good communication with the mother organization's financial department to enable it to conduct all its financial transactions without delay.

I.1.5 *Human resources*

Personnel

There should be a sufficient number of appropriately trained, educated and experienced personnel to perform the key activities. The number of members of staff required in the department responsible for the key activities will depend on the volume and value of products sourced and to be supplied. Sufficient support staff for secretarial, organizational and accounting duties as well as legal support should also be available.

Key personnel should include those responsible for prequalification, purchasing, storage and distribution. The person responsible for prequalification could also be responsible for quality assurance. National legislation should be complied with, e.g. requirements for a responsible person for purchasing, storage and distribution of pharmaceutical products.

The person responsible for prequalification and the person responsible for purchasing should be independent of one another. One should not report to the other.

The responsibilities of the staff in charge of the different key activities are described in Modules II to V.

Qualifications and experience

Personnel responsible for prequalification, purchasing, storage and distribution should have sufficient qualifications, knowledge and experience of their respective fields (see Modules II to V).

Code of conduct

All staff members should comply with a code of conduct which should guide all their professional activities. More detail on codes of conduct is given in section I.2.4. An example of a code of conduct is shown in Appendix 1.

Confidentiality

It is essential that all information obtained by any person working for the procurement agency is treated as confidential. Most of the information obtained from companies and manufacturers is product-specific, may be patented and will be commercially sensitive. The evaluators and inspectors must treat all information submitted and observed during the assessment

of product dossiers and inspections at manufacturing sites, and otherwise in connection with the discharge of their responsibilities in regard of the above-mentioned project, as strictly confidential and proprietary to the party collaborating with the procurement agency.

Confidentiality agreements should be signed by assessors and inspectors. An example of such an agreement is attached in Appendix 2. Additional information may be found in Appendix 3 (example of a guideline on conflict of interest).

Conflict of interest

Before undertaking any work, assessors and inspectors (including contracted personnel) should sign a declaration of interest. If, based on their declaration of interest, it is deemed appropriate for them to undertake the work specified, they agree to carry out their functions exclusively for the agency. They should confirm that the information disclosed by them in the declaration of interest is correct, that no situation of real, potential or apparent conflict of interest is known to them and that they have no financial or other interest in, and/or relationship with a party which:

- may have vested commercial interest in obtaining access to any confidential information disclosed to them in the course of the evaluation activities described in the declaration; and/or
- may have a vested interest in the outcome of the evaluation activities including, but not limited to, parties such as the manufacturers whose products are subject to evaluation or manufacturers of competing products.

Personnel should undertake to advise the procurement agency promptly of any change in the above circumstances, for instance if an issue arises leading to a conflict of interest during the course of their work for the procurement agency.

Job descriptions

There should be written job descriptions, with definitions of responsibilities, for all personnel.

Organizational structure

The procurement agency should have an organization chart indicating the positions, names of responsible persons and reporting lines.

The organization chart should reflect the responsibilities and reporting lines in accordance with the job descriptions.

I.2 Documentation of policies and standards

Documentation is a critical part of a quality assurance system. The procurement agency should have a comprehensive documentation infrastructure,

which should include policies, guidelines, norms, standards, manuals, procedures, records and related documents.

All activities of each section or department should be performed and documented in a standardized manner, following approved written procedures.

The main elements of the documentation system of this Model are described below.

I.2.1 *Quality manual*

The procurement agency should have a quality manual. The purpose of such a manual is to document the quality policy as defined by management in relation to the various activities undertaken by the procurement agency. There should be policy statements and a quality policy in terms of the agency's activities and objectives, as well as documents describing the policy of each section or department with regard to all activities in prequalification and subsequent purchasing, storage and distribution.

Once this quality policy is defined, it should be implemented, maintained, reviewed and amended as necessary at regular intervals by the procurement agency.

I.2.2 *Standard operating procedures*

The procurement agency should have written, clear and detailed standard operating procedures (SOPs) for all the activities to be performed in the procurement agency. The content of each SOP, particularly the step-by-step descriptions of activities and approved recording or reporting formats attached as addenda (see below), should reflect the operations of the particular procurement agency.

SOPs should be drafted by the person responsible for the procedure. An SOP for writing an SOP should be followed to ensure consistency of design, format and layout. An SOP on how to write an SOP is attached as Appendix 4.

Style and layout

SOPs should be written in the procurement agency's approved format, and be formally approved (signed and dated) by the authorized person(s).

SOPs should be written in clear, unambiguous language.

The name and/or logo of the procurement agency should be included on the front page of each SOP.

Elements of standard operating procedures

The SOP should contain at least the following elements.

Title and number

Each SOP should have a title. The title should give a clear indication of the activity which it describes. A numbering system is useful to identify to which activity or department the SOP refers.

Objective

This section should describe what is to be accomplished and/or achieved with the SOP.

Scope

This section should describe to what level or depth, or how widely, the SOP is applicable.

Policy

This section should reflect the procurement agency's policy regarding this particular activity.

Responsibility

This section should list the person(s) responsible for performing the activities listed in the procedure. It may be useful to refer to the position rather than the name of the person.

Action

This section should describe the sequence of action steps to be followed, from the beginning to the end of the process, to perform the activity.

The action steps should be written in the imperative and should be numbered. It is advisable to indicate who is responsible for each step. This could be done by putting the position (job title) of the responsible person in brackets next to each step, or by indicating the numbers of the relevant steps next to the positions listed under the heading "Responsibility".

Where a step leads to another procedure to be followed, the applicable SOP should be referred to in that particular step.

Distribution and retrieval

Documentation should be distributed with care. No superseded or obsolete SOPs should be available at user points. The sections and/or responsible persons (positions) to whom the SOP was distributed should be listed. Each time the SOP is reviewed and amended, superseded versions of the SOPs should be removed from all the user points listed and replaced with the updated version; the retrieval should be documented.

Revisions

In a section which could be headed "History", the date of each change to the SOP, the person responsible for the review, the change itself and the reason

for the change should be recorded. This section will provide the procurement agency with the history of the amendments to the SOP.

Addenda

Any records to be completed or maintained as part of the activity should have a standardized format. It is useful to define and approve these formats in advance. The approved standard format should be part of the SOP and can be attached as an addendum to the SOP.

Activities to be covered by standard operating procedures

The following list gives examples of activities which could be covered by SOPs:

— how to write a standard operating procedure (see Appendix 4);
— drafting a contract or agreement;
— amendments to contract or agreement;
— identifying and reporting counterfeit products;
— reporting of deviations;
— appointing evaluators of product information;
— appointing contract inspectors;
— maintaining a master documentation list;
— receiving and screening of an offer received;
— evaluating offers received;
— ordering product(s) from supplier or manufacturer;
— publishing specifications of products for procurement;
— sending out, receiving and evaluating supplier questionnaires;
— handling recalls;
— policy for regular re-inspection;
— routine follow-up of inspections;
— inspection fault correction; and
— standard formats for inspection reporting.

I.2.3 *Change control policy*

The procurement agency should have a policy for change control. This policy should be designed to manage changes in the agency's own procedures and documentation, as well as changes in data and information on the pharmaceuticals to be prequalified.

A procedure for controlling changes that affect APIs, formulation, manufacturing processes, analytical testing methods or packaging of prequalified products is essential. The procedure should ensure that these changes are reported to the procurement agency before new batches are manufactured or before they are delivered and released for distribution. Details of managing changes in product information are given in Module VI.

I.2.4 *Code of conduct*

The procurement agency should design, authorize and implement a written code of conduct.

The code of conduct should describe the policy of the procurement agency regarding the conduct of staff in respect to their activities. It should be followed by all personnel.

The code of conduct should give guidance to staff members on appropriate conduct in various situations. The following topics could be covered in the code:

— introduction and objectives;
— key responsibilities;
— personal responsibilities;
— safety;
— professional competence;
— qualifications and experience;
— conduct;
— integrity and attitude;
— attire, health and hygiene;
— management relationship;
— SOPs;
— travel and accommodation;
— confidentiality and conflict of interest;
— documentation and records;
— contracts and terms of reference (TOR);
— product files, evaluation and inspection;
— samples;
— evaluation and inspection reports; and
— provision of information and advice.

I.2.5 *Guidelines on conflict of interest*

The procurement agency should have a policy on conflict of interest which all personnel should observe. An example of a guideline on conflict of interest is shown in Appendix 3.

The document should address at least the following points:

— introduction and objectives;
— definitions and principles;
— responsibilities;
— confidentiality; and
— impartiality.

I.2.6 *List of prequalified products and manufacturers*

The procurement agency should have a procedure for drafting and maintaining a list of prequalified products and manufacturers, based on the outcome

of the evaluation of product data and information and manufacturing site inspections. The list should be product- and manufacturing site-specific, i.e. sites are prequalified for one or more specified products, and products are prequalified as manufactured at specified sites.

The key person responsible for prequalification should be responsible for addition to and/or deletions from the list.

Once the evaluation of a product dossier is complete, and the inspection has been performed to assess compliance with good manufacturing practices, good storage practices and good distribution practices as appropriate, the procurement agency should prepare a list reflecting the status of the prequalified products and manufacturers.

The list should contain at least the following information:

— name of the procurement agency;
— authorization signatures;
— reference number and version of the list;
— date of preparation of the list;
— name and physical address of manufacturer, including the approved site(s) of manufacture linked to each product;
— contact details, including postal address, telephone, fax number and e-mail address of the manufacturer and supplier;
— product details, including the brand name, INN, dosage form, strength per dose and pack size;
— date of original prequalification;
— date of expiry of the prequalification; and
— date until which the list is valid.

I.2.7 *Maintenance of records*

Records of all operations should be maintained and kept in a suitably organized manner.

Sufficient areas for the storage of records, including product information, manufacturers' information and inspection reports, should be available.

Access to these areas should be restricted to authorized personnel only, as confidential information may be filed (including records of manufacture, testing and/or storage).

Records should be maintained for a defined period of time, in accordance with national legislation. Generally they should be retained for at least one year beyond the expiry date of the finished product.

Module II.Further guidance on record-keeping in quality assurance systems is provided in the WHO publication *Quality assurance of pharmaceuticals (2, 3)*.

Module II

Prequalification

Introduction

Prequalification is one of the key elements in ensuring purchase and supply of pharmaceutical products of acceptable quality. The prequalification process can be subdivided into two major parts, i.e. product-related assessment and manufacturer-related assessment.

- *Product-related assessment* should ensure that the correct product is specified by the procurement agency. The procurement agency should then assess whether the manufacturer is offering a product that meets the predetermined norms and standards in terms of safety, quality and efficacy.
- *Manufacturer-related assessment* should ensure that the manufacturer is able to manufacture the product as specified in the product information package and in accordance with good manufacturing practices (GMP) as recommended by WHO. The manufacturer must be capable of routinely carrying out the activities to the specified standards to ensure batch-to-batch consistency of the product.

Assessment of contracted-out services, e.g. by storage and distribution agents, contract research organizations (CROs) and quality control laboratories for compliance with GMP, good clinical practices (GCP) and good laboratory practices (GLP), are further elements that may supplement the prequalification process.

The procurement agency is responsible for ensuring that all steps in the prequalification process are carried out in accordance with this Model. This should ensure that the manufacturers will be providing products as specified that meet all predetermined norms and standards are met. It will assist procurement agencies in maximizing the use of resources and will avoid duplication of prequalification by different procurement agencies. It should also minimize the risk of procurement agencies purchasing and supplying substandard products.

This module sets out recommendations which procurement agencies should implement when evaluating their product needs and when assessing the products and the manufacturing and supply arrangements offered by the manufacturers.

II.1 Principles for prequalification

Prequalification procedures should be based on the following principles:

- reliance on the information supplied by the national drug regulatory authority;
- evaluation of product data and information submitted by manufacturers, including product formulation, manufacture and test data and results;

- a general understanding of the production and quality control activities of the manufacturers and suppliers and of their commitment to the principles of GMP;
- assessment of consistency in production and quality control through compliance with GMP as described in the WHO publication *Quality assurance of pharmaceuticals*, Volumes 1 and 2 (*2, 3*) and supplementary WHO GMP guidelines;
- availability of appropriate quality systems and SOPs;
- random sampling and testing of pharmaceutical products supplied;
- adequate purchasing mechanisms (see Module III);
- good storage practices (see Module IV);
- good distribution practices (see Module V);
- monitoring of complaints from procurement agencies and countries;
- adequate handling of complaints and recalls; and
- continuous monitoring and requalification.

The procurement agency should have a document describing the policy and procedures for prequalification, including the assessment of product information and of manufacturers for compliance with standards.

II.1.1 *WHO Model List of Essential Medicines*

Procurement agencies may find that many of the products they require are on WHO's *Model List of Essential Medicines*, which contains medicines of proven safety and efficacy and is updated periodically (*4*). Procurement agencies should focus on procurement of medicines reflected in the Model List. They will find this list a useful reference for establishing specifications for the medicines needed for their purposes.

II.2 Standards for prequalification

The prequalification procedure should be based on the *Procedure for assessing the acceptability, in principle, of pharmaceutical products for purchase by United Nations Agencies* (*5*).

In principle, products should meet at least the recommendations made by WHO in *Marketing authorization of pharmaceutical products with special reference to multisource (generic) products – a manual for drug regulatory authorities* (*6*). Manufacturing sites should comply with at least WHO GMP (*3*).

II.3 Key persons and responsibilities

II.3.1 *Staff responsible for prequalification*

The person responsible for prequalification should be independent from the person responsible for purchasing.

The key responsibilities of the person responsible for prequalification activities should include the following:

— establishing specifications for products;
— publication of invitations for expressions of interest (EOI);
— preparation of a questionnaire for collecting product data and information and/or guidelines for the — compilation of product information;
— assessment of product data and information for compliance with norms and standards;
— assessment of manufacturing sites, through inspection, for compliance with WHO GMP; and
— preparation of the list of prequalified products and manufacturers.

II.3.2 *Staff responsible for evaluation of product information*

The person responsible for evaluation of product information should be independent from the person evaluating the manufacturing site. Neither should report to the other in terms of decision-making.

The key responsibilities of the person responsible for evaluating product information should include:

— preparing and implementing SOPs and guidelines for evaluation of product information;
— receipt of product information;
— screening of product information;
— evaluation of product information;
— informing manufacturers of the outcome of the evaluation of the product information; and
— communicating with the person responsible for inspections of manufacturing sites.

The person responsible for the evaluation of product information may be a member of the existing staff or appointed for this task.

The people assigned to evaluate product information should have relevant qualifications and experience, including a background in pharmaceuticals, pharmaceutical chemistry and pharmacology. Ideally they should be from a regulatory background, or have regulatory experience.

II.3.3 *Staff responsible for inspection of manufacturing sites*

The key responsibilities of the person responsible for inspection of manufacturing sites should include the following:

— preparation and implementation of guidelines and SOPs;
— coordination of inspections to be performed;
— recruiting or appointing inspectors with appropriate qualifications and experience when necessary;

— training of inspectors;
— organization of inspections;
— finalizing inspection reports; and
— informing manufacturers of the outcome of the inspection.

As a minimum, the personnel responsible for inspecting manufacturing sites should have relevant qualifications and experience in pharmaceutical manufacturing, quality assurance, GMP, performing inspections and audits, chemistry and quality control. Ideally they should have an inspection background from working with a regulatory authority.

Although decision-making should be independent, there should be communication between the person responsible for evaluation of product information and the person responsible for inspection of manufacturing sites, as some information on the product may have to be verified during the site inspection.

II.4 Key steps in prequalification

The key steps in prequalification are summarized in Fig. 1. Detailed descriptions of the different steps are given below. The preparatory steps of drafting a documentation system, including confidentiality agreements, declaration of conflict of interest, SOPs and guidelines, are described in Module I.

II.4.1 *Step 1: solicit and receive expressions of interest*

Draft product specifications for prequalification

Specifications for the product(s) to be prequalified should be drafted with input from the person responsible for purchasing, so that the product meets the requirements for the intended purpose.

The specifications should be detailed, clear and unambiguous to avoid unnecessary submission and processing of documentation not relevant to the product to be sourced.

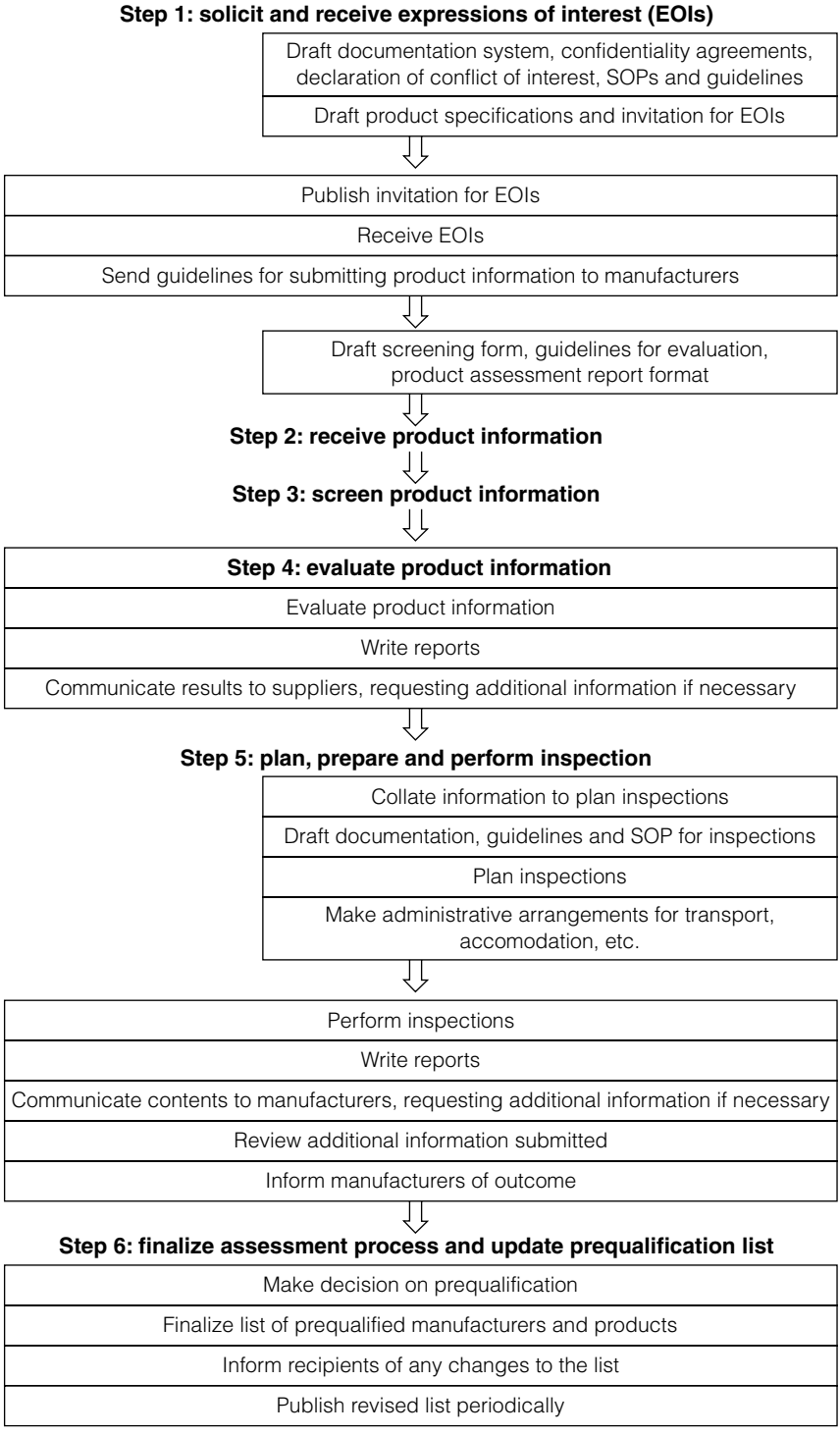
The specification should state at least:

— the name of the active pharmaceutical ingredient(s);
— pharmacopoeia reference (if any), e.g. European Pharmacopoeia, Japanese Pharmacopoeia, United States Pharmacopeia and International Pharmacopoeia;
— strength per dose and dosage form;
— dosage form (route of administration);
— pack size;
— packing material; and
— labelling requirements.

The specification could be published as part of the invitation for EOIs.

Figure 1

Key steps in prequalification



Draft and publish invitation for expressions of interest

Once the specification is finalized, an invitation for EOIs should be published widely to reach any manufacturers that may be interested in supplying the product(s). The process of inviting all interested manufacturers to submit their EOI for the pharmaceutical products listed should be open and transparent. Invitations for EOIs may be published for groups of products, and may be repeated as necessary.

The invitation for EOIs should be detailed and should state at least:

— the purpose of the invitation for EOIs;
— the objective of the invitation for EOIs;
— the list of products, including specifications for each product;
— information on quantities required (if available);
— details of the information to be submitted;
— guidelines for submission, including information on details to be submitted as part of the EOI, on the focal point for the submission and on the format for the submission;
— contact details (name, address, telephone number, fax, e-mail and postal address) for submission of the EOI; and
— the closing date for receipt of the EOI by the procurement agency.

An example of an invitation for EOIs is shown in Appendix 5.

Manufacturers should submit their EOI with the requested information about the product(s) and manufacturer(s), before the date specified by the procurement agency.

Receive expressions of interest

The procurement agency should ensure that the relevant infrastructure exists for the receipt and processing of the EOIs through the subsequent prequalification steps.

The procurement agency should have a clear policy regarding the acceptance of EOIs after the specified closing date. Processing of late submissions should not normally be allowed. Only in exceptional instances should late EOIs be considered, e.g. when a manufacturer is the only one to express an interest in supplying a specific product.

It would be appropriate to express concern at the late arrival of the EOI, and manufacturers should give reasons for late submission.

A record of all the EOIs received from each manufacturer should be maintained.

Send guidelines for submitting product information to manufacturers

Manufacturers who have submitted an EOI before the closing date specified in the invitation should be given guidelines for the compilation and submis-

sion of information on products and manufacturers. The guidelines should be publicly available and accessible. In cases where this is not done, reasons for the decision should be given and documented.

The guidelines should be written in clear, unambiguous language. Guidelines should contain information including at least:

- the content and format of submission, including the type and format of information required (e.g. the procedure for submission of information for a product registered in a country recognized as having an effective drug regulatory agency, and instructions for cross-referencing an existing dossier with the prescribed submission format); and
- the process of submission, including the address to which the documentation should be sent and a statement of any fees payable for cost recovery.

Content and format of submission

For each product to be prequalified, interested manufacturers should be asked to submit product information, together with a sample of sufficient quantity to allow analyses of the product against its finished product specification as stated in the product information, a covering letter (as recommended on the EOI) and a checklist for the product information.

Depending on the active ingredients, country of manufacture and registration of products to be prequalified, different formats for submission will be required. Detailed information should be submitted for products for which bioavailability may be altered by chirality, isomerism, controlled release formulation, polymorphism or other properties which may affect the therapeutic outcome.

In this document, the term "product information" refers to any of the following four formats, in which submissions should be made:

1. A product dossier, which should be submitted for multisource (generic) products, for innovator products which have been on the market for less than five years, and for products containing substances that have specific properties that may have explicit impact on the safety, efficacy or quality of the product. The *"Model application form for new marketing authorizations, periodic reviews and variations, with notes to the applicant"* (*7*) may also provide a helpful example of guidelines for this type of submission.
2. A standard product dossier as prepared for a national drug regulatory authority can be submitted, provided it contains the appropriate information as required in these guidelines. In such cases, the supplier should provide a covering letter which indicates where the required information can be found in the standard product dossier.
3. For products manufactured and registered in countries where regulatory requirements are in line with international regulations for assessment of safety, efficacy and quality, the following information should be submitted:

- a WHO-type certificate of a pharmaceutical product (CPP) (*8*) issued by one of the regulatory authorities of an International Conference on Harmonisation (ICH) region (European Union, Japan or the USA), together with a summary of product characteristics (SmPC);
- an assessment report issued by the regulatory authority;
- a WHO-type batch certificate from the manufacturer;

  If the packaging of the product is different from that approved by a regulatory authority of an ICH region, stability testing data should be submitted.

  If the formulation, strength or other specifications are different from the product for which the WHO-type product certificate (CPP) was issued, arguments and/or data to support the applicability of the certificate despite the differences should be submitted.

4. A completed questionnaire with limited information on the product should be submitted for products containing only substances that do not have specific properties that may have explicit impact on the safety, efficacy or quality of the product. An example of a pharmaceutical product questionnaire is shown in Appendix 6.

Information about the site(s) where each product is manufactured will also be required at a later stage. For guidelines on submission of information on manufacturing sites, see "Planning and preparation of inspections".

The same process as outlined above should be followed for suppliers who perform only part of the supply process. This is particularly relevant where a product from a prequalified manufacturer is to be supplied through a new distribution channel. For example, a procurement agency might wish to ship an already prequalified product to a new country using new traders, brokers or distributors. The organizations involved in the new distribution channel will need to be appropriately prequalified. Depending upon the nature of the supply arrangement, the requirements for product information and the GMP inspection process may be modified.

Process of submission

Suppliers should be allowed at least 60 days for the compilation and submission of product information.

Suppliers should be requested to submit a covering letter, containing a clear statement by the responsible person that the information submitted is true and correct.

The procurement agency should reserve the right to terminate the prequalification procedure of a product and manufacturer if the manufacturer fails to provide the required information in a specified time period, or if the information supplied is inadequate to complete the prequalification effectively.

II.4.2 *Step 2: receive product information*

The procurement agency should have the necessary infrastructure to receive and process the product information submitted by manufacturers. It will require personnel for processing the documentation; written procedures for receiving, identification, marking files, containers and samples, and sufficient space for unpacking and storage.

Containers with product information should be received at the specified address before a specified date as determined by the procurement agency.

Containers should be opened in the presence of at least two people. A record should be kept of the names of the people who opened the containers and the contents of the containers.

Each product should be allocated a unique reference number to ensure traceability of the product information.

II.4.3 *Step 3: screen product information*

Each product information package submitted by the manufacturer should be screened for completeness. The screening should be done in accordance with a written procedure. If the product information submitted fails to meet the requirements, it should be excluded from the evaluation procedure and inspection process.

A screening form should be used to ensure consistency of screening. There should be a written record of the screening of each product information package.

Information to be recorded should include:

— date of receipt;
— name of the interested manufacturer(s);
— address of the manufacturer;
— name of the product;
— country of manufacture;
— product number; and
— outcome of the screening.

An example of an SOP for screening and assessing product information, including a sample screening form, is shown in Appendix 7.

Incomplete information should not be kept for evaluation purposes. The manufacturer should be informed that an incomplete information package was received, and be requested to supply the missing information within a specified period. If this request is not complied with, the application should be rejected on grounds of incompleteness.

Product information packages which meet the requirements of the screening procedure should be retained for full evaluation.

A summary should be made of each product information package received, stating any reference number allocated to the product by the procurement agency, the INN, strength, dosage form and pack size of the product, the name of the supplier, the name and address of the manufacturing site(s), whether a sample has been submitted, and if so, the sample size.

II.4.4 *Step 4: evaluate product information*

Evaluators

Evaluators with suitable qualifications and experience in the evaluation of product data and information should be available to conduct the assessment.

Suitably qualified external evaluators may be appointed. Appointment of external evaluators should be subject to compliance with the policy of the procurement agency, regarding aspects such as confidentiality, conflicts of interest and financial resources. Examination of potential conflicts of interest and confidentiality must go beyond the potential evaluator signing a declaration. Checks on references should also be made.

A formal agreement for the performance of work and terms of reference for contracted evaluators should be in place before commencement of work.

A summary list of names, addresses, dates of appointment, qualifications and experience of evaluators should be maintained. Copies of signed agreements should be kept in a central file.

Evaluation

Time frames should be set for evaluation of product information. Product information should be evaluated within 21 days after the closing date for submission. A written procedure for evaluation should be followed. An example of an SOP for screening and assessing product information is attached as Appendix 7.

The person responsible for evaluation should monitor the process to ensure that each product information package is evaluated in compliance with these requirements. Information on the product's patent status should be considered to avoid infringement of intellectual property rights (see also Section III.10).

Contract research organizations should be inspected as part of the assessment process to ensure that bioequivalence studies have been done in accordance with GCP and GLP, and that tabulated data submitted to prove bioequivalence accurately reflect the generated raw data.

Evaluation reports

Each evaluator should prepare a formal evaluation report for each product, including a recommendation for acceptance or rejection. The evaluation report should be communicated to the manufacturer within 14 days of the evaluation.

A response should be invited from the manufacturer in cases where data and information are found to be incomplete or do not meet the guidelines. A period of at least 60 days should be allowed for submission of additional data and information.

This additional information should be assessed and the final outcome of the evaluation should be communicated to the manufacturer.

The evaluation report should be filed with the product evaluation documentation for reference purposes and follow-up where relevant.

Analysis of samples

Samples submitted together with product information packages should be analysed in accordance with the finished product specification. Certificates of analysis of final products released by the manufacturer should be made available to the procurement agency on request.

The procurement agency should have access to a quality control laboratory to perform the analyses. The WHO *Guide for a quality systems manual in a control laboratory* (*9*) seeks to establish a practical basis for the quality systems manual of a control laboratory which each country can adopt and adapt to prepare its own more detailed manual to meet the required level of specificity and complexity.

A laboratory may be contracted to perform the analyses. In that case, the procurement agency should ensure that the laboratory complies with GMP and good practices for control laboratories (*10*). The use of an accredited laboratory is therefore recommended. The procurement agency should verify the accreditation. There should be a written contract or agreement between the procurement agency and the contract laboratory. The wording of the contract should be clear and it should specify the responsibilities of the contract-giver and the contract-acceptor.

The procurement agency is responsible for ensuring access to raw data.

The procurement agency should have a procedure for investigating, handling and reporting out-of-specification results when these are obtained from laboratories. If a sample fails to meet the specifications, the procurement agency should investigate the problem and communicate the outcome to the manufacturer.

II.4.5 *Step 5: plan, prepare and perform inspections*

Each batch of every product procured by a procurement agency should be manufactured in compliance with GMP to ensure batch-to-batch consistency. The actual site of manufacture of the product should be known and specified. In some cases, a contract manufacturer may manufacture the product on be-

half of the supplier or agent. Each manufacturing site specified in the product information should be inspected to assess compliance with WHO GMP.

Manufacturers of the active pharmaceutical ingredients (APIs) used should be inspected as part of the assessment procedure to ensure that the APIs were manufactured in accordance with GMP.

Existing certificates

ISO certification is not an assurance of compliance with GMP and is not a replacement or substitute for verification of compliance with GMP.

Similarly, a CPP is not a guarantee of compliance with GMP. Participation in the WHO Certification scheme (*8*) is a voluntary process, and there is no formal assessment or evaluation of drug regulatory authorities entering the scheme. In some cases, reliance on the CPP alone is therefore not recommended. The certification scheme is an administrative tool and is reliable only where the relevant national drug regulatory authority has an established system which is known to comply with acceptable standards for evaluation and registration/licensing of products and manufacturers, including products for export markets. Information in addition to the CPP, e.g. a copy of the inspection report and corrective action plan from the manufacturer, may be requested. These documents, in addition to other documentation, may be considered useful in the prequalification process and in follow-up assessment or evaluation at a later stage.

The procurement agency should still verify compliance with WHO GMP as part of the prequalification procedure, and an inspection of the manufacturing site must be considered in every case.

Inspectors

Inspections should be performed by a suitably qualified, experienced inspector or team of inspectors with relevant qualifications, training and experience in performing inspections in foreign countries. Inspectors should have sound knowledge of quality assurance and GMP in pharmaceutical product production and quality control. A sufficient number of inspectors should be appointed to carry out inspections within predetermined time frames.

Where possible, a representative from the procurement agency (the person responsible for prequalification with a knowledge of GMP) should be part of the inspection team.

In exceptional cases, consultants from the private sector may be appointed to perform inspections, provided that there is no conflict of interests and that all confidentiality undertakings are agreed upon and maintained. For these reasons, persons working in a manufacturing company may not be considered suitable. Interested external inspectors should submit their letters of

interest and curriculum vitae to the procurement agency. The agency should review the documentation before deciding to appoint any inspectors. A formal agreement for the performance of work and terms of reference should be in place before commencement of work by contracted inspectors.

A summary list of names, addresses, dates of appointment, qualifications and experience of inspectors should be maintained.

Planning and preparation of inspections

In preparation for the inspection, the procurement agency should ensure that the manufacturers who have submitted EOIs to supply products are listed in a recording system for inspection planning purposes.

To facilitate planning and to save costs, manufacturers should be grouped together by country. In some countries, one manufacturer may have different manufacturing sites in addition to the submitted address of the headquarters.

Manufacturers should be informed of tentative inspection dates, and should be requested to submit information about each manufacturing site to be inspected. This information should normally be provided in a site master file (SMF). An example of a technical questionnaire for pharmaceutical manufacturers is attached as Appendix 8. This information will be used during the preparation for the inspection and during the inspection itself to verify information supplied by the manufacturer to the procurement agency.

An example of a standard operating procedure for planning an inspection is shown in Appendix 9.

As the manufacturer will be inspected as part of the prequalification process for specific products to the procurement agency, inspectors should prepare for inspections by studying the product information submitted by the manufacturer. Appendix 10 contains an example of an SOP for preparing for an inspection.

A site visit before deciding whether a GMP inspection should be performed may in some cases be appropriate. This visit is optional and does not lead to the requirement for the performance of the inspection being waived.

Performing inspections

Inspections should be performed in accordance with a written procedure. The inspection should cover all aspects of GMP. An example of an SOP for performing an inspection is shown in Appendix 11.

Information submitted in relation to the supply of the API, formulation of the product, manufacturing method and stability data should also be verified during the inspection.

The inspection should cover the evaluation and assessment of the documentation, premises, equipment, utilities and materials. It should also cover verification of data and documentation such as results, batch records, compliance with SOP and information submitted on the manufacturing method, equipment and aspects including (but not limited to) validation of the manufacturing process, validation of utilities and support systems, and validation of equipment.

If checklists are used, these should be drawn up and agreed upon for use by collaborating procurement agencies implementing this Model. An example of a GMP checklist is shown in Appendix 12.

Waiving of inspections

The need for an inspection may be waived where an inspection report is available from inspectors representing national drug regulatory authorities for the manufacturing site under consideration, covering activities for the product(s) being prequalified, provided that the report satisfies the agency that:

- all aspects of GMP for the relative product(s) have been covered;
- the inspection report is not older than 24 months;
- there is a statement from the manufacturer that no major changes have been made to premises, equipment and key personnel since the inspection by the medicines regulatory authority;
- the reports of the national drug regulatory authority demonstrate that the manufacturer has a history of compliance with GMP; and
- the inspection report has a favourable outcome.

Inspection report

Each inspector or inspection team (where inspection teams are performing inspections) should prepare a formal inspection report for each manufacturing site inspected.

The inspector or inspection team should make a recommendation on the status of the manufacturer in relation to compliance with GMP. According to the findings, the recommendation following the inspection may for example be one of the following.

- The manufacturer is considered to be operating at a reasonable level of compliance with WHO GMP and a follow-up inspection is recommended to verify implementation and acceptability of corrective actions prior to participation in any tender.
- The manufacturer is considered to be operating at an acceptable level of compliance with WHO GMP.
- The manufacturer is considered not to be operating at an acceptable level of compliance with WHO GMP.

The inspector or inspection team(s) will finalize a report according to the recommended format. The WHO *Guidance on Good Manufacturing Practices (GMP): inspection report* (*11*) (see Appendix 13) provides information on how to write an inspection report.

A copy of the inspection report should be filed in a central manufacturer's file that is unique to that manufacturer.

The inspection report should be communicated to the manufacturer. Where non-compliance was observed, corrective actions and time lines for completing them should be suggested. A response with supportive documentation should be invited from the manufacturer.

If any additional information is required, or if corrective action has to be taken, a final recommendation as to the acceptability of the product and manufacturer should be made only after such information has been evaluated, or the corrective action has been verified.

In the event of any dispute, a standard procedure should be followed for discussing and resolving the issue.

The ownership of the report should be with the procurement agency, as it is responsible for the prequalification.

II.4.6 *Step 6: finalize assessment process and update prequalification list*

Decision-making process for acceptance or rejection of a manufacturer

The procurement agency should follow a written procedure to collate the outcomes of the evaluation of product information, laboratory results for samples analysed and inspection reports.

The SOP should also identify the people responsible for taking the decision to accept or reject a product and/or manufacturer, including the grounds for the decision. It may be helpful to refer to the person by position, rather than by name.

The procurement agency should inform the manufacturer in writing of the outcome of the prequalification of each product manufactured at each specified site.

Recording of outcomes

The person responsible for prequalification should record the outcome of the prequalification process in a list of prequalified products and manufacturers. The list should include only those products evaluated as indicated by the manufacturer and listed in the EOI. It should be product- and manufacturing site-specific.

The list should be published in the public domain and should include at least the following information.

General information

— Norms and standards used;
— reference to the general procedure for prequalification;
— a statement to indicate that the list is not comprehensive for any disease category, but includes only those products submitted by possible suppliers and prequalified by the procurement agency;
— a statement to indicate that the purchaser of products from the list should ensure that only prequalified products (i.e. the same formula, manufacturing methods, manufacturing site, etc. as in the product information submitted) will be supplied by the supplier through contractual agreement between the buyer and the supplier;
— a statement that being on the list does not guarantee contracts or sales to the suppliers;
— a statement that the list should not be used by suppliers as a marketing tool to generate business;
— date of publication; and
— period of validity.

Product information

- Products and their manufacturing sites where products and manufacturers meet the standards set for the prequalification, including the following specifications:

  — INN of active ingredient(s)
  — strength
  — dosage form
  — pack size
  — shelf-life
  — storage conditions
  — name of supplier
  — name of manufacturer and manufacturing site(s).

The procurement agency should have a mechanism for sharing information with other procurement agencies.

The procurement agency should have an agreement with the supplier to ensure compliance with the prequalification principles and that the products supplied are the same products as were prequalified (e.g. they are manufactured at the same site and the same processes are adhered to).

The list should be reviewed and updated at regular intervals, at least every year. Newly prequalified manufacturers should be added to the list as they

become qualified, and non-compliant manufacturers should be removed from the list as soon as they are recognized as such.

Where possible, more than one supplier of a product should be included on the list to ensure open and transparent procurement through competitive procurement procedures (see Module III).

II.5 Requalification and monitoring

Requalification should occur at regular intervals. Routine reinspection of manufacturers should take place at least once every three years. Routine re-evaluation of product information or questionnaires should be done every three years. Non-routine re-evaluation and/or inspection should be done when necessary, e.g. when the manufacturer implements any change to the formula, manufacturing method or manufacturing site; if any product supplied is considered not to be in compliance with the agreed specification of the product; or if a serious complaint has been received. For more details on reassessment see Module VI.

Random samples of batches of pharmaceutical product(s) supplied by prequalified manufacturers should be taken for independent testing for compliance with final product specifications as part of the continuous monitoring programme.

II.6 Monitoring of complaints

Complaints should be handled in accordance with a written procedure.

A written report of the complaint, investigation, recommendations for action where relevant, and outcome should be available to the procurement agency.

Any complaint concerning a pharmaceutical product or batch of products supplied by the manufacturer should be thoroughly investigated. The nature of the complaint should be communicated to the manufacturer.

II.7 Cost recovery

It is recommended that the costs of prequalification should be covered by the procurement agency.

If costs are to be recovered, defined transparent procedures should be established and manufacturers should be notified of these procedures in advance. Cost recovery should be based on a fee-for-services structure.

Module III

Purchasing

Introduction

Pharmaceutical products should be purchased with the aim of procuring effective, good-quality medicines at the lowest possible cost. Prequalification of products and manufacturers as described in Module II contributes to ensuring in advance that manufacturers and suppliers can deliver quality products on a sustained basis.

This module gives an overview of the strategies and methods used in pharmaceutical procurement. The term *procurement* in this module relates specifically to the purchase of health sector goods from manufacturers or suppliers. The module goes on to describe the key activities in purchasing pharmaceutical products, as well as the recommended organizational structure of the procurement agencies who carry out these key activities.

III.1 Strategies for health systems

Although many health systems are decentralizing, some aspects of the health system are often handled more efficiently at a central level. Approval for a list of essential pharmaceutical products and registration or licensing of pharmaceutical products are normally the responsibility of the competent authority at the national level. Centralized procurement of pharmaceutical products increases the quantity obtained under each purchase contract and usually reduces the cost of the products. Programme officials should therefore consider consolidating quality assurance procedures at the national level and pooling demands for pharmaceutical products under a common contract.

Four strategic objectives for good pharmaceutical procurement are relevant to any public sector drug supply system, whether it is managed using public or private services or a combination of both. These are as follows (*12*):

- selection of reliable suppliers of quality products;
- procurement of the most cost-effective pharmaceutical products in the right quantities;
- timely delivery; and
- achievement of the lowest possible *total* cost.

These objectives should be achieved through efficient and transparent management reflected in an adequate division of the different activities and responsibilities; appropriate standardization, selection, specification and quantification of pharmaceutical products; the use of good financial management procedures and competitive procurement methods; and a quality

system that involves the selection and monitoring of qualified suppliers and their products.

It is recommended that a standard procedure be prepared to assist in the calculation of the lowest possible total cost. This approach aims to ensure that costs are calculated in a consistent manner, with a consistent weight given to each of the factors taken into account.

To be effective, a procurement office should ensure that the following principles are applied.

- Prequalified products are purchased from approved manufacturers whenever possible.
- Procurement and purchasing procedures are transparent.
- Activities follow formal written procedures throughout the process, including explicit criteria for awarding contracts.
- Purchasing is based on competitive procurement methods, except for very small or emergency orders.
- Members of the purchasing groups purchase all contracted items from the suppliers who hold the contract.
- Purchasing and tender documents list all pharmaceutical products by their INN or national generic names.
- Suppliers are selected and monitored through a process that takes into account product quality, service reliability, delivery time and financial viability.
- Intellectual property rights are respected in accordance with best practice and international law.

Considerable effort has been put into the development of appropriate policies and procedures for the procurement of health sector goods (pharmaceuticals, vaccines and condoms) by the World Bank. The reference documents are the standard bidding documents (*13*) and the accompanying technical note (*14*).Although these documents are designed to meet the World Bank's specific requirements, they include much sound guidance for use by all involved in the processes of procuring health sector goods.

III.2 Procurement methods

Although there are different methods of procurement, they all involve a number of common activities that must take place beforehand. These activities are the establishment of technical specifications, quantification of requirements, issuing of some form of tender, and selection of product(s) and manufacturer(s) preferably based on prequalification.

Responses to tenders should be examined to ensure that offers have been received from invited suppliers and that the offers are substantially responsive to the terms and conditions of the tender. Awards should be made to

the maker of the lowest acceptable bid that meets the terms and conditions of the tender. Disqualification of low bidders should be documented and form part of the tender record. Following a review of the adjudication by an independent panel, the companies should be informed of the outcome of the tender, and a contract should be awarded to the successful company. The contract must substantially reflect the terms and conditions detailed in the tender.

A brief description of different procurement methods is given below.

III.2.1 *Restricted tender*

In a restricted tender, also called a "closed bid" or "selective tender", interested suppliers are approved in advance through a prequalification process. This type of procurement is often referred to as "limited international bidding" (LIB) which is an "invitation to competitive bids" (ICB) conducted by direct invitation to all prequalified suppliers.

Procurement agencies should use restricted tenders to invite bids from prequalified suppliers for all health sector goods and services whenever possible.

III.2.2 *Competitive negotiation*

This method is also referred to as "international/national shopping". The basis of this method is the comparison of price quotations obtained from several local or foreign suppliers. Usually, quotations are solicited from a minimum of three suppliers to ensure competitive prices.

This method is appropriate for procuring small amounts of readily available products. However, its use should be explicitly justified, and approval should be obtained from senior management. Only prequalified suppliers should be used.

III.2.3 *Direct procurement*

In direct procurement, products are obtained directly from a single source without applying the requirements of a tender process or comparing price quotations.

Normally direct procurement is not recommended, but it may be used when there is only one prequalified source for the product to be procured. A history of "reasonable" prices for the product in question should be assessed to negotiate the price with the supplier.

III.2.4 *Open tender*

Open tender is the formal procedure by which all manufacturers, national and international, are invited to bid for the sale of general goods. The term

"international competitive bidding" (ICB), which is an open tender to all manufacturers, is often used.

Open tendering is not appropriate for health sector goods, because it may be difficult to establish, before a contract is awarded, whether unknown bidders will be able to supply products of the required quality in the required quantities on a sustained basis.

III.3 Quality assurance in purchasing

The procurement agency should have a documented infrastructure for purchase and procurement of health sector goods and services, which should aim to ensure that pharmaceutical products are of the quality required for their intended use. Quality assurance therefore incorporates GMP and other factors, some of which are outside the scope of these guidelines, such as product design and development.

III.4 Key activities in purchasing

III.4.1 *Product selection and specification*

The selection of pharmaceutical products based on a national formulary or on the essential medicines list is recommended. WHO's *Model Formulary* (*15*) and *Model Essential Medicines List* (*4*) identify the most cost-effective and affordable pharmaceutical products to treat prevailing health problems. They are updated regularly and are made freely available for adaptation by countries. The health systems of many industrialized and developing countries have used the essential medicines concept for decades to use existing resources effectively. Because the use of a national formulary reduces the number of products used, supply management activities and inventory-carrying costs are minimized.

Mechanisms for procurement of non-essential pharmaceutical products by public and private health systems should be available. Procurement of such products should be explicitly justified and subject to approval by authorized officials.

Procurement and tender documents should list pharmaceutical products by their INN or national generic names.

Each product selected should be available in a dosage form which offers acceptable safety, efficacy and quality, including acceptable stability and shelf-life under the recommended storage conditions.

If two or more pharmaceutical products appear to be similar according to these criteria, the choice between them should be made after a careful evaluation of their relative efficacy, safety, quality, cost, lead time and availability from prequalified manufacturing sites. When comparing costs of pharmaceu-

tical products, the cost of the whole course of treatment, not only the unit cost, should be taken into consideration. The choice may also be influenced by other factors such as transportation charges, storage requirements and shelf-life.

III.4.2 *Product quantification*

All requests for products should include quantities and required delivery dates. Accurate quantification of needs is essential to avoid shortages or excess stocks. Shortages could lead to patients not being treated or being improperly treated. Excess stocks could lead to additional storage costs and expiry of products before they are used.

The possible methods of product quantification include the consumption method, the morbidity method, and the adjusted or extrapolated consumption method.

The consumption method uses records of past consumption of individual pharmaceutical products.

The morbidity method estimates the need for specific pharmaceutical products according to the incidence of common diseases, the number of patients attending health care facilities and treatment patterns for the diseases treated. Adherence to standard treatment guidelines will make treatment patterns more predictable.

The adjusted or extrapolated consumption method uses data on disease incidence and drug consumption from a standard supply system and extrapolates the utilization rate to the supply system under consideration.

The consumption method is the most reliable method provided that the consumption records are accurate, the supply pipeline has been consistently full and no major changes are anticipated in the near future. Otherwise, one of the other methods should be used to enable a more accurate quantification of procurement requirements to be made.

If sufficient data are available, the morbidity method of quantifying drug requirements can be used to detect discrepancies in past consumption patterns, which could be indicative of irrational drug use or theft of pharmaceutical products.

III.4.3 *Selection of suppliers*

Prequalification is the procedure by which the products, manufacturers and suppliers are assessed before bids are solicited for specific products. The prequalification process for pharmaceutical products developed by WHO is based on the principles stated in Modules I and II.

Prequalification requires time. However, once a list of prequalified products and manufacturers has been prepared, adjudication and awarding of contracts can be expedited.

Postqualification is the process by which products and manufacturers are assessed after bids have been received. This process may cause delays because, if there are several offers from unknown suppliers, it will be necessary to validate the ability of these suppliers to supply products of the required quality in the required quantities before any contracts are awarded. Postqualification is therefore not recommended for pharmaceutical product procurement.

Procurement agencies should restrict tenders to prequalified products and manufacturers, soliciting bids from those manufacturers and suppliers that have been prequalified as described in Module II, or by contracting the services of a procurement agency which meets the recommended norms and standards for carrying out prequalification.

III.4.4 *Adjudication of tenders*

The adjudication of tenders is an important step in procurement. The procedure, including the decision-making process, should be transparent and documented. Decisions taken should ensure both appropriate quality and lowest cost to the procurement agency.

Following a bid the award should be made to the supplier making the lowest offer responding fully to the bid. When considering information submitted on aspects of quality assurance, the procurement agency should seek expert advice to determine if the offer is fully responsive.

When adjudicating tenders, the attention given to the financial stability of the manufacturer should not outweigh the consideration of measures taken to ensure quality of products.

III.5 Organization and responsibilities

The key activities of purchasing pharmaceutical products (product selection and specification, quantification, prequalification and adjudication of tenders) should be performed by different people, sections or departments with the appropriate expertise and resources for performing the specific functions.

III.5.1 *Procurement agency structure*

The section or department responsible for purchasing pharmaceutical products in the procurement agency should have an organizational chart indicating the positions and names of the personnel responsible for the key activities, as well as the reporting lines.

Purchasing office

The purchasing office should be appropriately staffed to prepare and issue tenders, and to award, administer and monitor contracts. In addition, it should be able to ensure that information concerning product selection,

specification, quantification, supplier preselection and funding is handled appropriately. This office should follow transparent, written procedures throughout the process of purchasing and should use explicit criteria for deciding to whom to award contracts.

All staff in the purchasing group must sign confidentiality agreements and declarations of conflict of interest.

Product selection office

A committee should be responsible for identifying products to be purchased from the essential medicines list or the national formulary. If such a committee does not exist, an ad hoc committee may be set up for this purpose.

Each selected product should have standard specifications, including the dosage form, pack size, acceptable shelf-life and any other information necessary (e.g. storage conditions).

Quantification office

This office should be responsible for ensuring the following.

- The quantities ordered are based on a reliable estimate of actual need.
- Procurement takes into consideration long-term contracts to achieve economies of scale and reduce work in prequalification. This approach applies to both centralized and decentralized systems.
- Procurement takes into account the potential benefits of joining with other procurement agencies and pooling requirements.
- Products are delivered according to requested delivery dates.

Finance office

There should be mechanisms in place to ensure reliable financing for procurement. Good financial management procedures should be followed to ensure that financial resources are used with maximum efficiency.

Funds should be allocated before the tender is issued, and should be released in accordance with the purchase contract.

Quality office

Prequalification procedures should provide assurance that the pharmaceutical products purchased are of acceptable quality and meet applicable international standards as described in Module II.

Adequate laboratory services should be available to test pharmaceutical products independently according to specifications and standards. Random sampling and testing should be carried out before and after purchase.

The procurement agency (contract-giver) may decide to contract the services of an agency (contract-acceptor) with expertise in technical assessment of product data and information and/or inspection of manufacturing facilities. However, the contract-giver remains responsible for the implementation and monitoring of these activities.

Management oversight

Procurement should be planned properly, and procurement performance should be monitored regularly.

An independent committee should review adjudicated tenders. Committee members should have financial, legal and programme planning expertise and experience.

III.5.2 *Responsibilities*

Each staff member who undertakes procurement or provides support to procurement should have a job description which clearly describes his or her tasks and responsibilities. All staff must have signed confidentiality agreements and declarations of conflict of interest before they carry out any tasks related to purchasing of pharmaceutical products.

The responsibility placed upon any individual should not be more than that person can handle. There should not be any gaps or overlaps in the areas of responsibility.

III.6 Monitoring of performance of prequalified manufacturers

There should be a procedure for continuous monitoring of prequalified products and manufacturers, whether or not the manufacturer is supplying product(s).

If a decision is taken to remove a product or manufacturer form the prequalification list, the manufacturer should be notified. All recipients of the list should be informed accordingly.

Performance of manufacturers and product compliance should be monitored. Monitoring should include at least the following aspects:

- sampling and testing of samples for quality control;
- verification that the product batches supplied have been manufactured in compliance with standards and specifications accepted in the product information;
- pharmacovigilance;
- monitoring of complaints;
- reinspection of manufacturing sites;
- reassessment of product information;

- monitoring of direct and indirect product costs; and
- monitoring of adherence to delivery schedules.

The monitoring process should include continuous commercial monitoring that includes tracking of lead-time and monitoring for compliance with all of the contract terms and conditions.

In addition, the quality of the pharmaceutical products supplied should be monitored. This includes sampling and independent testing of ordered and delivered products. Tests should include at least visual examination; shelf-life; compliance with labelling, packaging and shipping instructions; and laboratory analysis when appropriate (e.g. identification or assay).

There should be an information system that keeps track of the value of contracts awarded, the value of total purchases from each supplier per year and the performance for each tender (e.g. speed of delivery and compliance with specifications).

The section or department of the procurement agency responsible for prequalification of products and manufacturers should schedule routine requalification at predetermined intervals as described in Module VI.

III.7 Patents

In evaluating product information during prequalification and during tendering, information regarding the patent status should be requested. No infringement of patents by any United Nations or other procurement agency should occur.

A person within the procurement agency should be identified as having responsibility for checking the patent status of a particular product or formulation and to recommend actions to be taken regarding the protection of intellectual property rights for the product. This person will often be a member of the legal department of the organization.

Countries requesting products from procurement agencies should be responsible for ensuring that the products supplied comply with the destination country's legislation on registration/licensing status and patent registration or restrictions.

III.8 Donations

Any procurement agency receiving donations should handle donated drugs in accordance with a written procedure to ensure that patients receive products of known, appropriate quality.

The WHO's *Guidelines for drug donations* (*16*) outline the key issues. The principles established in these guidelines should be followed.

Module IV

Receipt and storage of purchased products

Introduction

The procurement agency should ensure that the pharmaceutical products purchased are received and stored correctly and in compliance with applicable legislation and regulations. Products should be received and stored in in such a way that their quality and integrity is preserved, batch traceability is maintained and stock can be rotated. This module focuses on quality assurance and quality control during receipt and storage of products.

Quality control is concerned with sampling, specifications and testing as well as with the organization, documentation and release procedures which ensure that the necessary and relevant tests are carried out, and that materials or products are not released for use until their quality has been judged satisfactory for their intended purpose.

Each procurement agency should have access to a quality control department, which should meet the general requirements for facilities, policies and procedures, staff expertise, experience and training as specified in Module I, as well as the requirements outlined in Module II under "Analysis of samples". The quality control department must be capable of undertaking the full range of tests required, or of managing any subcontracting of such work to third parties correctly while retaining responsibility for the quality of the work done.

The principles established in the WHO *guidelines for good storage practice* (*17*) (see Appendix 14) should be followed throughout the steps described in this module.

IV.1 Pre-shipment quality control

Each batch of finished product should be tested in a laboratory to determine that it conforms satisfactorily to its finished product specification, prior to supply.

In lieu of testing by the procurement agency, a certificate of analysis may be accepted from the supplier, provided that the agency establishes the reliability of the supplier's analysis through appropriate periodic validation of the supplier's test results and through on-site audits of the supplier's capabilities.

Products failing to meet the established specifications or any other relevant quality criteria should be rejected.

IV.2 Receipt of stock

Receiving and dispatch bays should protect materials and products from the weather. Receiving areas should be designed and equipped to allow containers of incoming materials to be cleaned if necessary before storage.

All incoming materials and finished products should be quarantined immediately after receipt until they are released for use or distribution. Imported pharmaceutical products should be quarantined until test results confirm that the products meet all of the requirements, specifications, terms and conditions of the purchase order. A review of certificates of analysis should be made to confirm that what has been delivered is what was ordered and is certified by the manufacturer to meet specifications.

Upon receipt, each incoming delivery should be checked for correspondence between the order, the delivery note and the supplier's labels. The consignment should be examined for integrity of packages and seals, and for uniformity of the containers. Should the delivery comprise more than one batch, it should be subdivided according to the supplier's batch number. Containers should be cleaned where necessary and labelled, if required, with the prescribed data, e.g. label description, batch number, type and quantity. Each container should be carefully inspected for possible contamination, tampering and damage, and any suspect containers or the entire delivery should be quarantined. Damage to containers and any other problem that might adversely affect the quality of the material should be recorded and investigated.

The person responsible for receiving the goods should be independent of the person responsible for purchasing the goods.

IV.3 Postprocurement quality control

IV.3.1 *Sampling*

The procedures for receipt of supplies should include random sampling for independent laboratory analysis to ensure that pharmaceutical products meet the required standards. Sampling should be performed in accordance with a written procedure. Products may also be randomly sampled at the end of the distribution chain and sent for independent analysis. Representative samples should be taken from containers in the consignment. The samples should be analysed for compliance with the product specification.

Samples should be taken only by appropriately trained and qualified personnel and strictly in accordance with written sampling instructions. Containers from which samples have been taken should be labelled accordingly.

Following sampling goods should be quarantined. Batch segregation should be maintained during quarantine and all subsequent storage. Materials and

pharmaceutical products should remain in quarantine until an authorized release or rejection is obtained.

IV.3.2 *Rejected materials*

Stringent precautions should be taken to ensure that rejected materials and pharmaceutical products cannot be used. Rejected goods should be clearly marked as such and stored separately from other materials and pharmaceutical products in a locked compound accessible only to authorized and trained responsible personnel, while the materials await destruction or return to the supplier. Whatever action is taken should be approved by authorized personnel and recorded. Rejected materials should be handled in accordance with a written procedure.

IV.4 Storage of materials and products

IV.4.1 *Staff*

All members of staff should be trained to observe high levels of personal hygiene and sanitation. The duties and responsibilities of all members of staff should be available in the form of a written job description.

Personnel employed in storage areas should wear protective or working garments appropriate for the activities they perform.

IV.4.2 *Storage areas*

Storage areas should be of sufficient capacity to allow orderly storage of the various categories of materials and products, including segregation of rejected, expired, recalled or returned stock.

Adequate ventilation should be in place to control temperature and relative humidity. Where special storage conditions are required (e.g. temperature and humidity) these should be provided, checked and monitored.

Precautions should be taken to prevent unauthorized entry into the storage areas.

A written procedure for fire control measures should be in place, including prevention of fire, fire detection measures and fire drills. Fire detection and fire-fighting equipment should be serviced regularly. Smoking should not be permitted in the storage areas.

IV.4.3 *Storage conditions*

All materials and products should be stored under the appropriate conditions established by the manufacturer and in an orderly fashion to permit batch segregation and stock rotation according to the first-in, first-out rule.

Stock should be stored off the floor and suitably spaced to permit cleaning and inspection. Pallets should be kept in a good state of cleanliness and repair.

Storage areas should be kept clean and free of vermin and accumulated waste. A written sanitation programme should be available indicating the cleaning and pest-control methods used, and their frequency of use. Safe pest-control agents should be used which will not contaminate materials and pharmaceutical products. There should be appropriate procedures for the cleaning up of any spillage to eliminate any risk of contamination.

Storage conditions used for pharmaceutical products and materials should comply with the instructions on the label which are based on the results of stability testing.

In general, the instructions on the label have the meanings given in Table 1.

Table 1
Meaning of storage instructions given on the labels of pharmaceutical products

On the label	Means:
Do not store over 30 °C	From +2 °C to +30 °C
Do not store over 25 °C	From +2 °C to +25 °C
Do not store over 15 °C	From +2 °C to +15 °C
Do not store over 8 °C	From +2 °C to + 8 °C
Do not store below 8 °C	From +8 °C to +25 °C
Protect from moisture	No more than 60% relative humidity under normal storage conditions; to be provided to the patient in a moisture-resistant container
Protect from light	To be kept in a light-resistant container

In certain cases, e.g. with freeze-sensitive vaccines, products that have been stored below the temperature specified on the label should be destroyed. Freeze-sensitive products should be equipped with a "freeze-watch" monitoring device.

Monitoring of storage conditions

The equipment used for monitoring should be calibrated at suitable predetermined intervals and the results should be recorded and retained. All monitoring records should be kept for at least one year after the end of the shelf-life of the stored material or product, or as long as required by national legislation. Temperature mapping of the facility should be well designed to support assurance of uniformity of the temperature across the storage facility. It is recommended that temperature monitors should be placed in the worst-case areas of the facility. Recorded temperature monitoring data should be available for review.

Equipment used for monitoring should be calibrated at defined intervals.

IV.4.4 *Labelling and containers*

All materials and pharmaceutical products should be stored in containers which do not adversely affect the quality of the material or products, and which offer adequate protection from external influences, including bacterial contamination in some circumstances.

All containers should be clearly labelled with at least the name of the material or product, the batch number, the expiry date or retest date, the specified storage conditions and reference to the relevant pharmacopoeia where applicable. Only authorized abbreviations, names or codes should be used.

IV.4.5 *Miscellaneous and hazardous materials*

Materials which may affect other materials stored in their vicinity should be handled in accordance with a written procedure. Rodenticides, insecticides, fumigating agents and sanitizing materials should not be permitted to contaminate equipment, starting materials, packaging materials, in-process materials or finished products. Toxic substances and flammable materials should be clearly marked as such and should be stored in suitably designed, separate, enclosed areas as required by national legislation. Flammable substances should be kept away from corrosive or oxidant substances at all times.

IV.4.6 *Stock control*

Stock rotation and control is best maintained by the use of a proprietary stock control system. Care must be taken to select a system that can manage the rigid requirements for batch number control and expiry dating which are essential for handling pharmaceutical products. Many commercial systems lack these features. In case of doubt advice should be sought from competent experienced personnel.

Periodic stock reconciliation should be performed comparing actual and recorded stock levels.

All significant stock discrepancies should be subjected to investigation as a check against inadvertent mix-ups and/or incorrect issue.

In manufacturing facilities, partly used containers of materials and pharmaceutical products should be securely reclosed and resealed to prevent spoilage and/or contamination during subsequent storage. Materials and pharmaceutical products from containers which are open or partly used should be used up before a new container is opened.

Damaged containers should not be issued unless it is certain that the quality of the material inside is unaffected. Where possible, damaged containers should be brought to the attention of the person responsible for quality control. Any action taken should be documented.

Control of obsolete and outdated materials and products

All stock should be checked regularly for obsolete and outdated materials and pharmaceutical products. All due precautions should be observed to prevent issue of outdated materials and pharmaceutical products. The handling of such materials should be subject to a written procedure.

Recalled materials

Recalled materials should be handled in accordance with a written procedure. Written records of all major actions with the signatures of the person responsible for carrying out each action should be maintained.

Recalled products should be identified and stored separately in a secure area until a decision has been taken on their fate. The decision should be made as soon as possible. An assessment may be made only by an appropriately qualified and experienced member of staff.

Returned goods

Returned goods should be handled in accordance with a written procedure. They should be placed in quarantine until a decision has been taken on their fate. Products returned from the market should be destroyed unless it is certain that their quality is satisfactory. In that case, they may be considered for resale. The nature of the product, any special storage requirements, its condition and history, and the time elapsed since it was issued should all be taken into account in this assessment. Where any doubt arises over the quality of the product, it should not be considered suitable for reissue or reuse, although basic chemical reprocessing to recover the active ingredient may be possible. Any action taken should be recorded.

Waste materials

Waste materials should be handled in accordance with a written procedure. Provision should be made for the proper and safe storage of waste materials awaiting disposal. Toxic substances and flammable materials should be stored in suitably designed, separate, enclosed cupboards, as required by national legislation.

Waste material should not be allowed to accumulate. It should be collected in suitable receptacles for removal to collection points outside the buildings and disposed of safely and in a sanitary manner at regular and frequent intervals.

IV.4.7 *Documentation: written instructions and records*

Written instructions and records should be kept which describe the storage procedures and define the routes of materials, pharmaceutical products and information through the procurement agency, including handling of expired stock. Batch traceability is essential in the event of a product recall.

Permanent information, written or electronic, should exist for each stored material or product to indicate recommended storage conditions, any precautions to be observed and retest dates. Pharmacopoeial requirements and other current national regulations concerning labels and containers should be respected at all times.

Records should be retained for each delivery. They should include the description of the goods, quality, quantity, supplier, supplier's batch number, the date of receipt, assigned batch number and the expiry date. National regulations which state a period for retention of records must be observed. Where no such regulations exist, records should be retained for one year after the end of the shelf-life of incoming products.

Comprehensive records should be maintained of all receipts and issues of materials and pharmaceutical products according to a specified system, e.g. by batch number.

Module V

Distribution

Introduction

A well-managed distribution system should achieve the following objectives (*1*).

- Maintain a constant supply of drugs.
- Keep drugs in good condition throughout the distribution process.
- Minimize drug losses due to spoilage and expiry.
- Maintain accurate inventory records.
- Rationalize drug storage points.
- Use available transportation resources as efficiently as possible.
- Reduce theft and fraud.
- Provide information for forecasting drug needs.

This module focuses on measures to be taken to ensure product integrity and quality during distribution, and outlines the main points. The principles established in the WHO *guidelines for good trade and distribution practice* (*18*) (see Appendix 15) should be followed.

V.1 Transport conditions

Materials and pharmaceutical products should be transported in such a way that the integrity of the material or pharmaceutical product is not adversely affected and that appropriate storage conditions are maintained.

Every precaution should be taken to minimize the risk of theft and fraud.

V.2 Cold chain

Special care should be exercised when using dry ice in cold chains. In addition to addressing safety concerns, it is necessary to ensure that the material or product does not come in contact with the dry ice, as this may adversely affect the quality of the product, e.g. as a result of freezing.

V.3 Temperature monitoring and records

Where appropriate, the use of devices to monitor conditions such as temperature during transportation is recommended. Records should be available for review.

V.4 Delivery order

The dispatch and transport of materials and pharmaceutical products should be carried out only after receipt of a delivery order, which has to be docu-

mented. There should be a procedure to ensure that products are supplied to authorized recipients only.

V.5 Dispatch procedures and policies

Rules for dispatch procedures should be established according to the nature of the materials and pharmaceutical products being dispatched and after taking into account any special precautions to be observed. Any special packaging requirements for movement of goods must be met. Some goods may require special protection before they can be shipped by boat or by air. All legislation that may affect these requirements must be fulfilled.

V.6 Dispatch containers

The outside container should offer adequate protection from all external influences and should be indelibly and clearly labelled.

Products should be packed in such a way as to minimize the risk of theft, e.g. by using locked containers or by shrink-wrapping entire pallets in plastic.

V.7 Dispatch records

Records for dispatch should be retained, stating at least the following:

— date of dispatch;
— customer's name and address;
— product description, e.g. name, dosage form and strength (if appropriate), batch number and quantity; and
— transport and storage conditions.

V.8 Traceability

Records of distribution should contain sufficient information to enable traceability of the product from the point of supply to the end user.

Traceability of goods is crucial in case of the need for product recalls. It will also help to detect theft and fraud. Any discrepancies should be investigated and followed up by appropriate measures to tackle possible security breaches.

V.9 Port of entry

All conditions required for storage should be achievable at the port of entry of goods. This is particularly important for all temperature-sensitive products shipped to ports where temperatures may be less well controlled. Specific arrangements may need to be made with local handling agents and customs to ensure speedy handling and clearance.

Security measures to prevent theft, fraud and bribery should be in place during storage at the port of entry.

V.10 Packaging of products and materials

If any packaging or repackaging is required because of breakages, all the policies and procedures described in WHO GMP guidelines (*3*) should be followed in their entirety.

Module VI

Reassessment

Introduction

The quality of all products and services procured in accordance with this Model should be continuously monitored. Reassessment will be required to ensure that the products procured continue to meet the norms and standards defined. This module briefly outlines the principles of routine and non-routine assessment of manufacturers, products and contracted-out services.

VI.1 Re-evaluation of manufacturers

Re-inspection of manufacturers should take place at regular intervals at least every three years.

Manufacturers should inform the procurement agency immediately of any changes to the manufacturing site or equipment that may have an impact on its prequalification.

Non-routine requalification may be required in the following situations:

- in case of any omission of information in the initial assessment;
- if false or misleading information is suspected during the follow-up assessment;
- if changes are implemented that may have an impact on the prequalification of the manufacturing site, such as changes to key personnel or organizational structure, changes to equipment, apparatus or the manufacturing process, or the renovation or addition of facilities that need validation, commissioning or re-inspection; or
- if a complaint considered to be serious in nature has been received.

The procurement agency should suspend or withdraw a prequalified facility from the prequalification list if there is evidence of non-compliance with the requirements for prequalification.

VI.2 Re-evaluation of products

Product information should be reviewed every three years, or sooner if major changes occur in the meantime.

Under routine circumstances there will be no requirement for the manufacturer to retest the product as part of the re-evaluation process. However, circumstances may arise in which retesting is necessary.

Manufacturers should inform the procurement agency of any contemplated changes to the product that may affect its safety, performance, efficacy or quality. With regard to the product, manufacturers should for instance report the following changes:

— change of manufacturing process, site or equipment relating to the product;
— change of contract manufacturers;
— change of pharmaceutical product release control laboratories;
— changed suppliers of starting materials or container or closure;
— changes to the formulation or composition of the product;
— new analytical method in the testing of starting material, intermediate or final product; or
— change of specifications.

Sufficient time must be allowed for the necessary testing, e.g. stability testing or bioequivalence testing. Based on the information submitted, the person responsible for prequalification should decide whether to approve the changes or whether to request additional data which demonstrate the equivalence of the product to the one that has been prequalified.

The section or department responsible for prequalification of products and manufacturers should inform the purchasing office about the changes and the result of the evaluation of such changes.

Non-routine re-evaluation of products should be done in the following cases.

- If any omission by the manufacturer in the initial evaluation procedure, or during the follow-up activities, is evident in relation to the requirements, including compliance with quality system standards and failure to notify complaints.
- If any batch or batches of supplied product(s) are documented by the procurement agency not to be in compliance with the agreed specifications of the product or to reveal failure(s) regarding safety, performance or quality of the device.
- If the investigation of a complaint considered leads to the conclusion that the quality and/or safety of the product is in question.
- If any fraud or misconduct by the manufacturer is evident.
- If any batch or batches of product(s) was supplied and is considered not to be in compliance with the agreed specification of the product.
- If a complaint considered to be serious in nature had been received by the organization.
- In cases of changes or variations to products, the WHO guidelines *Marketing authorization of pharmaceutical products with special reference to multisource (generic) products: a manual for drug regulatory authorities* (*6*) give guidance on when to proceed with which type of re-evaluation.

- If, in the opinion of the organization, changes made in the sourcing of the API, formulation, manufacturing method, facility or other production aspects require that a reassessment be made.
- If supply has been suspended for one year or longer.

VI.3 Monitoring of contracted-out services

VI.3.1 *Storage and distribution*

Monitoring of the performance of contractors and follow-up of non-compliance should be carried out according to a written procedure. It should include continuous monitoring, as well as periodic review and renewal of the contract.

Continuous monitoring should include tracking of cost, order and delivery status, lead-time and compliance with contract terms and conditions. A management information system should be in place for this purpose. There should be continuous quality control of pharmaceutical products supplied including random sampling and a procedure for dealing with complaints. The procurement agency should document any reported problems with quality control or service and inform the contractor of each problem. Continuous monitoring should also include compliance of the contract-giver with contract conditions, and correction of any factors that prevent the contract-acceptor from fulfilling the specified duties.

Periodic review of the contract should be based on an assessment of the contractor's overall performance. The criteria outlined for monitoring of prequalified products and manufacturers (see Section III.6) also apply to monitoring of contract-acceptors who store and distribute pharmaceutical products.

VI.3.2 *Quality control laboratories*

Contracted laboratories should comply with the principles of good laboratory practice (GLP) (*19*). The accreditation status alone does not guarantee compliance with GLP. The performance of contracted laboratories should be continuously monitored.

VI.3.3 *Contract research organizations*

Contract research organizations (CROs) should be inspected as part of the assessment process to verify that raw data correspond to submitted data, and to assess compliance with standards during the conduct of clinical and bioequivalence studies. Monitoring and requalification should ensure that the principles of good clinical practices (GCP) (*20*), good practices for quality control laboratories (*10*) and GLP (*19*) are adhered to.

Conclusion

A trend towards the introduction of quality systems principles in the internal operations of organizations concerned with pharmaceutical quality assurance has led to the publication of the WHO document *Quality systems requirements for national good manufacturing practice inspectorates* (*21*), which outlines principles for implementing a quality management system (see Appendix 16). The quality management principles described are valid for all key aspects of procurement and have been considered in designing and testing the model quality assurance system presented in this document. It is recommended that procurement agencies implement this Model to ensure a harmonized approach to quality assurance in all key activities of procurement.

The establishment and operation of a quality system is an essential element in the mutual recognition of the outcomes of prequalification activities. Once a harmonized system is in place, agencies will be able to exchange information on assessment of product information and inspection findings. Sharing this information will eliminate the need for duplication of prequalification procedures.

Reliance on a harmonized system for the procurement of products meeting predefined norms and standards will expedite procedures for obtaining quality products at competitive prices. The benefit will be greatest for those medicines for which demand is high, e.g. medicines for priority diseases affecting a large part of the world's population in areas where drug regulatory capacities and health budgets are limited.

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Appendix 1

Example of a Code of Conduct

1. Introduction

This Code of Conduct must be followed by appointed staff members as well as all other staff involved.

All members of staff including temporary advisers and experts appointed to carry out evaluations and inspection on behalf of WHO should keep in mind at all times the image of WHO.

(In the context of this Code of Conduct, staff and members of staff include contract appointments, short-term staff, advisers and experts appointed for the performance of work.)

2. Key responsibilities

Each member of staff, expert and temporary adviser has key responsibilities to fulfil. The overall objective is to perform these key responsibilities within the framework of this Code of Conduct.

An internal oversight framework has existed within WHO since the early days of the Organization. It is necessary periodically to ensure that all staff understand this function. The WHO summary statement on WHO's Office of Internal Audit and Oversight (IAO) which describes its purpose, authority and scope of work, should be read by each member of staff. This document summarizes the expectations for IAO and it furnishes direction for internal audit at WHO.

By accepting appointment, staff members pledge themselves to discharge their functions and to regulate their conduct to serve the best interests of WHO.

In the performance of their duties staff members shall neither seek nor accept instructions from any government or from any other authority external to the Organization.

No staff member shall accept, hold or engage in any office or occupation, which is incompatible with the proper discharge of his duties with WHO.

Staff members shall conduct themselves at all times in a manner compatible with their status as international civil servants.

Staff shall avoid any action and in particular any kind of public pronouncement which may adversely reflect on their status. While they are not ex-

pected to give up their national sentiments or their political and religious convictions, they shall at all times bear in mind the reserve and tact incumbent upon them by reason of their international status.

Staff members shall exercise the utmost discretion in regard to all matters of official business. They shall not communicate to any person any information known to them by reason of their official position, which has not been made public, except in the course of their duties or by authorization of the Director-General. At no time shall they in any way use to private advantage information known to them by reason of their official position. These obligations do not cease with separation from service.

Any staff member who becomes a candidate for a public office of a political character shall resign from the Secretariat.

The immunities and privileges attaching to WHO by virtue of Article 67 of the Constitution are conferred in the interests of the Organization. These privileges and immunities furnish no excuse to staff members for non-performance of their private obligations or failure to observe laws and police regulations. The decision whether to waive any privileges or immunities of the staff in any case that arises shall rest with the Director-General.

All staff members shall subscribe to the oath or declaration as set out in WHO Staff Regulations.

A staff member may not act as a delegate or observer for, or adviser to, his or her government.

A staff member may participate in international or national societies when such participation is not in conflict with the standards referred to in WHO Staff Rules and may represent such societies at an international meeting with the Director-General's authorization.

A staff member shall obtain the Director-General's permission before publishing articles whose contents reflect work performed for the Organization or information obtained arising out of such work.

All rights, including title, copyright and patent rights, in any work or invention produced or developed by a staff member as part of his official duties shall be vested in the Organization.

"Misconduct" means:

- any improper action by a staff member in his official capacity;
- any conduct by a staff member, unconnected with his official duties, tending to bring the Organization into public discredit; and
- any improper use or attempt to make use of his or her position as an official for his or her personal advantage.

Any conduct contrary to the terms of his oath or declaration.

2.1 Personal responsibilities

Staff members must be committed to a strong oversight environment and must give IAO their full cooperation.

Staff must observe, implement and maintain the responsibilities in relation to the position in which they have been appointed.

Staff must perform the work they have been allocated to the best of their ability and finalize tasks in accordance with the timeframes set by WHO.

2.2 Safety

Safety is the responsibility of WHO staff, supervisors and WHO management. It includes reporting of possible hazards and suspected hazards and taking the necessary precautions and implementing safeguards to minimize safety problems.

Staff involved in activities where safety problems may arise, e.g. the inspection of a manufacturing site, should observe safety rules and regulations as recommended by WHO, the manufacturer and national legislation.

Staff must wear protective devices such as protective clothing, shields, eye covers (glasses), earplugs, where relevant, to protect the body, organs and extremities from possible harm. Staff must use their professional knowledge to ensure that they take appropriate care of their own safety. This means that should a manufacturer not provide what is deemed to be adequate personal protection, then the inspectors should refuse to enter an area on the grounds of lack of safety.

Staff must observe national regulations when driving vehicles.

Staff must be aware of, and take, the necessary precautions when collecting samples.

Special attention to safety requirements is necessary when performing site inspections. These include aspects in relation to the dosage form and activities observed (e.g. radioactive pharmaceuticals, hazardous materials, laboratory reagents, equipment and apparatus, explosions, personnel lifts, ladders, glassware, freezers, steam, radiation, microbiological hazards, viral and biological products and waste, and other relevant possible hazards).

3. Professional competence

3.1 Qualifications and experience

The staff appointed must have the required qualifications and experience to perform the tasks required. Any person appointed to perform work for or on behalf of WHO must indicate if he/she is not suitably qualified to perform

the task, or does not have the relevant experience, before taking on the work or being appointed.

When people are approached to perform work on behalf of WHO, they must be truthful in providing evidence of their qualifications and experience.

Staff must not mislead WHO or procurement agencies in relation to their qualifications and/or experience. Any case of misrepresentation of qualifications or experience will be treated as fraud and may eventually lead to prosecution. No future employment in any capacity by any WHO or United Nations organization will be possible at any time.

4. Conduct

During daily activities, staff must maintain high standards of ethical conduct.

Staff must observe the WHO constitution and are responsible for complying with the WHO regulations and guidelines.

4.1 Integrity and attitude

To ensure that the business of WHO is conducted effectively, and without improper influence, all staff members must be persons of integrity and observe the highest standards of conduct.

- WHO must be able to rely upon staff to do the right things.
- Staff must be honest and dependable.
- Staff must be devoted to accuracy, truthfulness, objectiveness and fairness.
- Staff must not use restricted information not available to the general public for gain or to advance private interests.
- Staff must report findings such as presentation of false, misleading and fraudulent information provided to WHO.
- Staff should maintain a positive attitude towards WHO and its policies and projects.
- Staff must be dignified, diplomatic, tactful and courteous. Strong-arm tactics must be avoided.
- Staff must not act with an air of superiority or special authority.
- Staff must use a firm approach when requesting necessary and authorized information.
- Staff members are the contact persons of WHO and their action will be the basis upon which the public will judge the organization. Staff must exhibit exemplary behaviour at all times.

A staff member who has any financial interest in any business concern with which he may be required, directly or indirectly, to have official dealings on behalf of the procurement agency shall report such interests to the Director-General, who shall decide on the applicability of Staff Regulations. Staff

may not have financial interests in companies to be evaluated or inspected. Shareholdings through pension schemes and other such "arm's length" arrangements will not normally be taken as a financial interest in this context. Any doubts on this matter should be referred to the WHO Internal Audit Office for clarification.

4.2 Attire, health and hygiene

Good public relations require that all members of staff dress appropriately for the activities to be performed. Staff should observe WHO guidelines regarding appropriate dress code.

Staff should normally wear protective clothing for inspections. Inspectors must wear protective clothing at least equivalent to that worn by employees of manufacturing sites (e.g. head covering or masks, when appropriate). Staff should conform to company procedures at all times. However, if company procedures are considered inappropriate then this fact should be recorded.

Staff involved in inspections must inform supervisors or managers of their health status when this could have impact on inspections, as persons with communicable diseases, wounds and open lesions may not be allowed in areas where products and material are exposed.

Staffs are responsible for taking the necessary precautions when travelling (e.g. having the appropriate inoculations).

Staff must practice good hygiene at all times.

4.3 Gifts, meals and favours

No staff member shall accept any honour, decoration, favour, gift or remuneration from any government, or from any other source external to the Organization, if such acceptance is incompatible with his status as an international civil servant.

A staff member who is offered any honour, decoration or gift from sources external to the Organization shall report this offer to the Director-General who shall decide on the applicability of Staff Regulations.

No member of staff shall receive or accept anything of value from any manufacturer for or because of any official act that has been performed or is to be performed.

Staff will not solicit or accept directly or indirectly any gift, gratuity, favour, entertainment loan or any other item of monetary value from members of the public with whom staff members have official relationships.

When performing inspections, staff must pay for their own meals whenever possible and must make an effort to pay for their own meals even when

invited by the manufacturer, unless the situation is such that it will provoke a scene or create an embarrassment to WHO.

4.4 Management relationship

Staff must promote a positive relationship with supervisors and managers.

4.5 Standard operating procedures

Staff must follow authorized standard operating procedures (SOPs) for the performance of tasks.

4.6 Travel and accommodation

Staff must observe WHO regulations, guidelines and SOPs when travelling. The relevant procedures shall be followed for planning of visits, meetings, inspections and other activities such as making reservations and paying for accommodation.

4.7 Confidentiality and conflict of interest

Staff must observe the WHO policy, country rules and regulations, and company policy with respect to confidentiality.

Staff must sign and abide by the conflict of interest and confidentiality undertaking.

4.8 Documentation and records

Staff shall follow SOPs and maintain appropriate records as required in the procedures.

All information provided by staff members must be truthful and correct, including reports and related documentation.

4.9 Contracts and terms of reference

Staff shall perform activities as stipulated in the contract or agreement for performance of work (APW) and terms of reference (TOR).

4.10 Product files, evaluation and inspection

Staff shall handle product files with care and treat all information as confidential relating to the task to be performed.

All data submitted initially and as a result of the evaluation, shall be dealt with in accordance with SOPs and be considered as confidential information between WHO and the manufacturer.

All aspects relating to the inspection performed shall be considered as confidential between WHO and the manufacturer.

Staff members shall observe the requirements and undertaking with regard to confidentiality and conflict of interest.

4.11 Samples

Samples taken during inspections shall be in accordance with a WHO SOP, with the approval of the manufacturer.

4.12 Evaluation and inspection reports

There shall be written evaluation and inspection reports for every product evaluated, and every manufacturing site inspected.

The reports shall be a true reflection of the findings of the evaluation and inspection.

4.13 Provision of information and advice

Staff shall not act as consultants to individual companies or manufacturers when appointed for the purposes of evaluation or inspection for a particular project, where the company can in particular benefit from such advice, unless the information is in the public domain or given to all manufacturers.

Appendix 2
Example of a guideline on confidentiality

The evaluators and inspectors will treat all information submitted and observed during the inspections and otherwise in connection with the discharge of their responsibilities with regard to the above-mentioned project, as strictly confidential and proprietary to WHO or parties collaborating with WHO in accordance with the terms set forth below and those contained in the attached provisions for team members participating in site visits within the scope of the prequalification procedure of pharmaceutical products. An example of a confidentiality undertaking is shown at the end of Appendix 3.

Evaluators and inspectors will take all reasonable measures to ensure:

— that the confidential information is not used for any purpose other than the evaluation activities described in this document; and
— that confidential information is not disclosed or provided to any person who is not bound by similar obligations of confidentiality and non-use as contained herein.

Evaluators and inspectors will not, however, be bound by any obligations of confidentiality and non-use to the extent they are clearly able to demonstrate that any part of the confidential information:

— was known to them prior to any disclosure by or on behalf of WHO (including by manufacturers); or
— was in the public domain at the time of disclosure by or on behalf of WHO (including by manufacturers); or
— has become part of the public domain through no fault of theirs; or
— has become available to them from a third party not in breach of any legal obligations of confidentiality.

All personnel involved in prequalification and related matters, having access to confidential information regarding products and manufacturers, should treat all information submitted and observed during the inspections and otherwise in connection with the discharge of their responsibilities with regard to these activities, as strictly confidential and proprietary to the procurement agency or the parties collaborating with the procurement agency.

Appendix 3

Example of a guideline on conflict of interest

Introduction

This document presents policy on "conflict of interest" as it applies to external evaluators and members of advisory committees. These two categories are together referred to as "consultants" for the purposes of these guidelines. An example of a signed statement on conflict of interest is shown at the end of this Appendix.

Definitions and principles

The common meaning of "conflict of interest" is a conflict between an individual's private or personal interest and his or her duty. However, it may also refer to a situation where an individual has several duties which conflict without involvement of any private or personal interests.

A conflicting private or personal interest may be financial or non-financial as explained below.

When a decision-maker or consultant has a direct *financial* interest, however slight, in the matter to be decided, there is a conclusive presumption of bias and the decision-maker or consultant will thus be disqualified from acting.

Where a decision-maker or consultant has a *non-financial* interest, which gives rise to a reasonable presumption of bias, the decision-maker or consultant will be disqualified from acting. The test here is whether a reasonable observer would suspect that there is a possibility of bias, not whether that bias actually exists. A relevant non-financial interest may arise, for example, out of personal or family involvement between a decision-maker or consultant and a party whose interests are affected by the decision or recommendations. Such an interest may also arise where a decision-maker or consultant is seen to have prejudged the issues, either through preconceived opinions or prior involvement with the facts of a case on which he or she is required to make a decision on recommendations.

Conflict of interest in relation to consultants

There are a variety of situations in which consultants may find themselves in a situation of conflict of interest between their professional activities (e.g. preparation of objective and independent evaluations or membership of independent committees) and personal and private interest (e.g. private con-

sultancies, grants to cover travel and accommodation at company-sponsored conferences, share holdings, research grants or honoraria). It is recognized that almost all consultants have some *potential* conflict of interest because of their present or past association with the pharmaceutical industry.

Some situations of conflict of interest are clear-cut and some are more difficult to determine. If an individual is an employee of, or a retained consultant to, a pharmaceutical company, there is a clear possibility of conflict of interest. If an individual is an employee of a government organization, does no work on behalf of pharmaceutical companies, and is not in receipt of gratuities or funding, there is a minimal risk. Between these two situations is a spectrum of possibilities where the decision as to whether there is a conflict of interest may be less obvious.

Contracts are unlikely to be offered to consultants in any one of categories 1 to 6 listed below.

1. The consultant works in the pharmaceutical industry, either as an employee or as an owner or part owner (e.g. shareholder in the pharmaceutical company to be assessed).
2. The consultant receives a retainer (fee) from one or more of the pharmaceutical companies whose products she or he has to assess or which the new product is likely to replace.
3. The consultants have a *significant* direct current relationship with one or more companies. This may take the form of (a) financial support for a current research project or projects; (b) sponsorship of graduate or postgraduate students; or (c) company employees who are under the direct responsibility of the consultant.
4. He or she receives *substantial* financial assistance or *expensive* equipment to conduct research on behalf of the pharmaceutical company.
5. The consultant acts or has acted as a consultant for a pharmaceutical company *on the product she or he has agreed to assess*. Such a consultancy may include sponsorship as a speaker, or appointment as chairperson at professional meetings concerning the product, or attendance on behalf of the sponsoring company at national or international professional meetings concerning the product.
6. The consultant has provided significant input to the planning or conduct of a clinical trial of the product to be assessed, for example as a principal investigator, signatory to the study report, or author of any published or unpublished paper or other report of the study. Participation limited to the inclusion of patients in a large-scale multicentre study is *not* considered a significant conflict of interest.

A conflict of interest is less likely to be seen in situations 7 to 10 (see below).

7. The consultant has occasional contracts with one or more companies for particular projects, but does not have a significant relationship with

any one company. She or he has not been directly involved with the product in question.

8. The consultant owns or works for a consultancy, which does not provide advice to the pharmaceutical industry but may provide advice to other industries, such as the devices, food or paint industries. However it is unlikely that such consultants will have the technical knowledge or experience to qualify as a consultant in the pharmaceuticals field.
9. The consultant occasionally provides advice to one or more companies on the design of clinical trials to be conducted prior to submission of an application for marketing authorization, but does not have a significant current relationship with any one company (e.g. points 1 to 6 above).
10. The consultant has been invited to attend and contribute to national or international meetings organized by professional or academic associations.

The responsibility of consultants

A drug regulatory authority cannot be aware of all of the consultant's involvements and their ramifications when a contract is offered. The onus is therefore on the consultant to declare in writing any potential conflict or what may be seen as a potential conflict to the staff member of the drug regulatory authority who negotiated the contract or committee membership. If there is any doubt, the potential conflict must be declared. The consultant may only proceed with the evaluation of the data or take up committee membership after any potential conflict has been discussed with the drug regulatory authority and found not to be significant.

For this reason, each evaluation contract requires the evaluator to sign a statement to the effect that she or he has no current conflict of interest and that, if the risk of such a conflict arises during the evaluation, the drug regulatory authority will be notified immediately in writing.

The evaluator is expected to cease reading the application *immediately she or he becomes aware of a conflict of interest*, and return it promptly to the drug regulatory authority. This clause applies also to those involved in the inspection of facilities.

Confidentiality

Any data concerning a company's product which are supplied by the drug regulatory authority to a consultant for review are strictly confidential. As stated in the contract, all materials related to or referred to in the contract must be accepted in strict confidence and held in safe and secure custody at all times. An application may be discussed only with the staff members of the drug regulatory authority.

Consultants must be aware of and avoid the possibility of indirect breaches of confidence. There is clearly a potential, consciously or subconsciously, to misuse information gained from a consultancy in other papers or scientific presentations on the product in question. Such a case would also constitute a conflict of interest. The consultant must not use information gained in this way in future scientific papers or presentations without the agreement of the company or individual that submitted the data.

Impartiality

To protect impartiality, the company concerned is not informed by the drug regulatory authority of the identity of the consultant to whom applications, data or committee papers are forwarded. For this reason, the consultant should have no direct communication with the company concerning the product. The consultant may not disclose his or her role to the company, even after a decision on the application has been completed. This is clearly not possible in the case of an inspector of the manufacturing facility.

Subcontracting the evaluation

A consultant is not allowed to subcontract part or all of an evaluation to any second person without written permission from the drug regulatory authority. If the drug regulatory authority agrees to such an arrangement, the consultant must ensure that the subcontractor is fully aware of the provisions on conflict of interest, confidentiality and impartiality set out in these notes.

If any part of an evaluation is subcontracted, the person who actually undertakes the work must also sign all the reports to which she or he has contributed.

Example of a confidentiality undertaking and declaration of Conflict of Interest

World Health Organization  Organisation Mondiale de la Santé

PROVISIONS FOR EVALUATORS OF PRODUCT INFORMATION AND FOR INSPECTORS (TEAM MEMBER PARTICIPATING IN SITE VISITS) WITHIN THE SCOPE OF THE QUALITY ASSESSMENT PROCEDURE OF PHARMACEUTICAL PRODUCTS

In the course of discharging your functions as an expert adviser to WHO under the attached agreement for performance of work (APW), you will gain access to certain information, which is proprietary to WHO or entities collaborating with WHO, including the manufacturers of the product(s) which need to be assessed as part of the quality assessment procedure by WHO. You undertake to treat such information (hereinafter referred to as "the Information") as confidential and proprietary to WHO or the aforesaid parties collaborating with WHO. In this connection, you agree:

- *(a) not to use the Information for any other purpose than discharging your obligations under the above-mentioned APW; and*
- *(b) not to disclose or provide the Information to any person who is not bound by similar obligations of confidentiality and non-use as contained herein.*

However, you will not be bound by any obligations of confidentiality and non-use to the extent that you are clearly able to demonstrate that any part of the Information:

- *(i) was known to you prior to any disclosure by or on behalf of WHO (including by the manufacturer(s)); or*
- *(ii) was in the public domain at the time of disclosure by or on be half of WHO (including the manufacturer(s)); or*
- *(iii) becomes part of the public domain through no fault of your own; or*
- *(iv) becomes available to you from a third party not in breach of any legal obligations of confidentiality.*

You also undertake not to communicate your deliberations and findings and/or those of the team(s) of experts in which you will participate, as well as any resulting recommendations to, and/or decisions of, WHO to any third party, except as explicitly agreed by WHO.

You will discharge your responsibilities under the above-mentioned APW exclusively in your capacity as an expert adviser to WHO. In this connection, you confirm that the information disclosed by you in the declaration of interest is correct and that no situation of real, potential or apparent conflict of interest is known to you, including that you have no financial or other interest in, and/or other relationship with, a party, which:

(i) may have a vested commercial interest in obtaining access to any part of the Information referred to above; and/or

(ii) may have a vested interest in the outcome of the evaluation of the product(s), in which you will participate (such as the manufacturers of those products or of competing products).

You undertake to promptly advise WHO of any change in the above circumstances, including if an issue arises during the course of your work for WHO.

I hereby accept and agree with the conditions and provisions contained in this document.

Signed _____

Name (typewritten) _____

Organization _____

Place _____ Date _____

Appendix 4

Example of a standard operating procedure (SOP) for writing an SOP

1. Title

Standard procedure for writing a standard operating procedure (SOP)

	Signature	Date
Prepared by		9 May 2005
Authorized by		

2. Policy and objective

2.1 The procurement agency should have an SOP for each activity performed by the procurement agency. All SOPs should be in the required format and distributed with care to a predetermined list of personnel. SOPs should be authorized, implemented and kept up to date.

2.2 All SOPs should be written in English if any international use is expected, or in the local language if required only by local staff,

2.3 Documentation is a prime necessity in quality assurance. Its purpose is to define the system of control, to reduce the risk of error inherent in oral communication, to ensure that personnel are instructed in the details of, and follow the procedures concerned in a logical, reproducible manner.

2.4 There should be a written SOP for every critical or important activity in the procurement agency. SOPs should be written in the standardized format as attached.

2.5 A list should be kept of all SOPs required by the procurement agency.

2.6 Management should authorize SOPs prior to their distribution and implementation.

3. Responsibility

All members of staff should adhere to the SOP when drawing up the SOP. The project manager should supervise its implementation.

4. Action

4.1 Any person may initiate the first draft of an SOP. The headings (listed below) should conform to the attached format and should be used when writing the relevant sections of the SOP.

4.2 The SOP should include at least the following headings:

A. Title
B. Policy and objective
C. Responsibility
D. Action
E. Addenda
F. Distribution
G. Review date
H. Revision history

The following information should appear under each heading.

A. Title

Write in clear language the title of the procedure to ensure understanding of the process that the SOP will be describing. The procedure should also contain a clear indication of who was responsible for the preparation, review and approval of the procedure.

B. Policy and objective

Describe the WHO or procurement agency policy regarding the matter to be dealt with under the SOP. Describe the objective to be reached in following the SOP.

C. Responsibility

Describe and list the people responsible for performing the activities listed in the SOP. Wherever possible, it is preferable to use job descriptions or position names for these people rather than names of individuals. Use of the personal names of staff members means the SOP has to be changed every time personnel changes occur.

D. Action

4.1 Describe the sequence of actions needed to perform the task.

4.2 List the actions in the order in which they need to be performed and number them from 1 to the end.

4.3 Explain all the steps in detail in clear, unambiguous, language.

4.4 Put the initials of the responsible person in brackets next to the action step if a specific person is responsible for the action step.

4.5 Read the completed SOP to determine whether it describes all the action steps to be followed from the start of the process to the end.

4.6 If a step leads to another SOP, then refer to the relevant SOP in that step.

4.7 If the SOP requires any records to be kept, draft the required format of the document to be completed and attach it to the SOP as an addendum.

4.8 Forward the SOP to the supervisor or person responsible for documentation and quality assurance.

4.9 Read the SOP and assess its suitability and applicability.

4.10 If any changes are to be made, make amendments to the SOP in ink and return it to the person who wrote the SOP for their comments.

4.11 Return the SOP to the supervisor.

4.12 Sign and date the SOP if satisfied with its contents.

4.13 Forward the SOP to the second person who is responsible for approving documentation.

4.14 The SOP should be signed and dated by the second person who is responsible for approving the documentation if he or she is in agreement with the contents.

4.15 Return the SOP to the person responsible for maintaining the documentation infrastructure.

4.16 If applicable, proceed with the steps for distribution and retrieval of the previous version of the SOP.

4.17 File the original SOP in the SOP file.

E. Addenda

4.18 Draft each addendum in such a manner that it leads the person responsible for completing the addendum to document all the required information.

4.19 Each addendum shall form part of the authorized SOP and shall be reviewed when the SOP is reviewed, or when necessary.

F. Distribution

4.20 Records shall be maintained of the distribution and retrieval of SOPs to ensure that superseded SOPs are not still in use anywhere.

4.21 Complete the table (see Addendum A, point 6) to indicate the name of the person to whom the SOP will be sent.

4.22 Make a copy of the original SOP and stamp it in red ink as "official copy".

4.23 Only official copies of SOPs shall be controlled. SOPs not having a red stamp will be considered non-official and uncontrolled SOPs.

4.24 The person shall sign and date (in the appropriate space in the table (see Addendum A, point 6) on the original SOP), as proof of receipt of the SOP.

4.25 When the SOP is reviewed and amended, copies of the superseded SOP should be retrieved from all those who hold a copy when the new version is distributed.

4.26 When replacing the superseded SOP, the persons from whom it has been retrieved should sign (and date) the appropriate space on the distribution table in the original SOP.

4.27 Mark the original SOP as "superseded" on each page and file in the "superseded SOP" file.

4.28 Destroy all retrieved copies of superseded SOPs.

G. Review date

A date should be assigned on which the SOP will be reviewed to determine whether any changes are required to keep it up to date.

H. Revision history

4.29 To maintain a record of the history of the information on the SOP, complete the table regarding the history of the changes to the SOP (see Addendum A, point 7).

4.30 Each SOP should have a time limit for validity and should be reviewed before the end of the period of validity. This is an opportunity to consider whether the SOP still meets all its objectives and is appropriate for the work to be done and the methods of working. The updated SOP should go through the same writing and revision process.

5. Addenda

Addendum A contains an outline of the format of an SOP.

6. Distribution and retrieval

	Distribution		Retrieval	
Name	Signature	Date	Signature	Date

7. History

Date	Reason for change
	New SOP

Addendum A: Format of a standard operating procedure

WHO Logo Review date: 2006 **Standard operating procedure**	Document no.

1. Title

(indicate title)

	Signature	Date
Prepared by		9 May 2006
Authorized by		

2. Policy and objective

3. Responsibility

4. Action

4.1

4.2

4.3

5. Addenda

6. Distribution and retrieval

	Distribution		Retrieval	
Name	Signature	Date	Signature	Date

7. History

Date	Reason for change

Appendix 5

Example of an invitation for expression of interest

SIXTH INVITATION FOR EXPRESSION OF INTEREST (EOI)

In the context of dramatically increasing the access to, and affordability of, HIV/AIDS-related care and treatment, WHO, together with UNICEF, UNAIDS and UNFPA are inviting **expressions of interest** from manufacturers of pharmaceutical products in respect to the provision of drugs for the management of HIV-related diseases. The World Bank is in support of this effort.

This sixth invitation is published in order to increase the range of possible products and sources as a follow up to the interest that was expressed as a result of the first, second, third, fourth and fifth invitations published in 2000, 2001, 2002, 2003 and 2004.

Manufacturers should be committed to providing the above-mentioned products at **preferential prices** to **developing countries**. Interested manufacturers are encouraged to submit documentation and samples as specified below for various dosage forms and strengths of the products in the following categories:

I) Antiretrovirals as single-ingredient formulations for use in adults and adolescents:

- **Nucleoside/Nucleotide Reverse Transcriptase Inhibitors, including**
  Abacavir
  Didanosine
  Lamivudine
  Stavudine
  Tenofovir
  Zidovudine
- **Non-Nucleoside Reverse Transcriptase Inhibitors, including**
  Efavirenz
  Nevirapine
- **Protease Inhibitors, including**
  Indinavir
  Nelfinavir
  Ritonavir
  Saquinavir

Applications are also encouraged for single-ingredient formulations suitable **for use in paediatric populations**, that support existing international and or national treatment guidelines for paediatric antiretroviral therapy (ART).

As solid dosage formulations are the preferred formulations for treating children except for in the very young infant, manufacturers should also apply for reduced and/or scored solid dosage formulations of:

Zidovudine
Abacavir
Lamivudine
Nevirapine
Efavirenz

Also sought are syrups, solutions or dissolvable nucleoside/nucleotide and non-nucleoside formulations of the following products:

Zidovudine
Abacavir
Lamivudine
Nevirapine

For further information on paediatric formulations please consult:
http://www.who.int/3by5/paediatric/en/

II) Antiretrovirals as fixed-dose combinations (FDC):

Applications are also encouraged for fixed-dose combinations of any first-line ARV regimens as described in the *WHO Guidelines for Scaling Up Antiretroviral Therapy in Resource Limited Settings – 2003 Revision*. For further information please consult:
http://webitpreview.who.int/entity/3by5/publicatons/documents/arv_guidelines/en/

Fixed-dose combinations listed below:

For use in adults and adolescents:

- **Reverse Transcriptase Inhibitors**
  Lamivudine + Stavudine
  Lamivudine + Zidovudine
  Lamivudine + Stavudine + Efavirenz
  Lamivudine + Stavudine + Nevirapine
  Lamivudine + Zidovudine + Efavirenz
  Lamivudine + Zidovudine + Nevirapine
  Lamivudine + Zidovudine + Abacavir
  Tenofovir + Emtricitabine

- **Protease Inhibitors**
  Lopinavir + Ritonavir

For paediatric use, reduced and/or scored solid dosage formulations of:

- **Reverse Transcriptase Inhibitors**
  Lamivudine + Stavudine
  Lamivudine + Zidovudine

Lamivudine + Stavudine + Nevirapine
Lamivudine + Zidovudine + Nevirapine
Lamivudine + Zidovudine + Abacavir

- **Protease Inhibitors**
  Lopinavir + Ritonavir

Co-packaged preparations of the standard ARV combinations, for adult, adolescent and paediatric use are also sought. for further information on paediatric fixed dose and/or co-packaged formulations please consult: http://www.who.int/3by5/paediatric/en/

- **Anti-infective drugs listed below:**
  Antibacterial and antimycobacterial agents (other than MTB)
  Azithromycin
  Ceftriaxone
  Cefixime
  Ciprofloxacin
  Clarithromycin
  Clindamycin
  Rifabutin
  Spectinomycin

  Antiprotozoal and Antifungal agents
  Amphotericin B
  Dapsone
  Folinic acid
  Fluconazole
  Itraconazole
  Pentamidine
  Pyrimethamine
  Sulfadiazine
  Trimethoprim/Sulphamethoxazole

  Antiviral agents
  Acyclovir
  Ganciclovir

- **Anti-cancer drugs**
  Bleomycin
  Etoposide
  Vinblastine
  Vincristine

- **Palliative care drugs**
  Amitriptyline
  Codeine

Chlorpheniramine
Ibuprophen
Loperamide
Morphine (oral formulation)

The medicines listed in this Invitation for Expression of Interest are those for which a need has been identified by the HIV/AIDS department, WHO. The submitted products should be of assured pharmaceutical quality and relevant data to support efficacy should be provided.

Procedure for submission of EOI

1. Submit a covering letter expressing the interest in participating in the project, confirming that the information submitted in the product dossiers is correct.

2. Submit a product dossier in the recommended format* as specified in the Guideline for submission of a product file which can be obtained by electronic mail from oakesl@who.int, also available on the the web page http://mednet3.who.int/prequal. The dossier should be accompanied by a sample of the product to enable analyses (e.g. 1 × 100 tablets).

   *If the dossier is compiled in a different format (e.g. EU), then such a dossier can be submitted with a covering letter cross-referencing the pages where the relevant data can be found in accordance with the above-mentioned Guideline.

   Submitted documentation reaching UNICEF Supply Division will be evaluated during March, May, July, September and November 2005. Documentation should be provided in English.

   Interested manufacturers should submit the above-mentioned information to:
   UNICEF Supply Division
   Reference: Accelerated Access to HIV/AIDS Care
   SIXTH EOI
   UNICEF Plads - Freeport
   DK-2100 Copenhagen
   Denmark
   E-mail: supply@unicef.org
   Tel: (45) 35 27 35 27 Fax: (45) 35 26 50 48

3. Submit a site master file for each manufacturing site as listed in the product dossier, in the recommended format, also available by electronic mail and on the web page http://mednet3.who.int/prequal/ to
   The Secretary
   WHO/HTP/PSM/QSM
   20 Ave Appia
   1211 Geneva 27
   Switzerland

Products and manufacturing sites assessed for acceptability and meeting the specified standards will be added to the list published on the project web page (http://mednet3.who.int/prequal/). Products and manufacturers included in this list may be invited to bid for the supply of products, individually or collectively, directly by member governments, by the aforesaid United Nations agencies and/or by associated NGOs.

The following criteria will be taken into account in the quality assessment process.

- Valid manufacturer's licence for production.
- Product registered or licensed in accordance with national requirements.
- Products manufactured in compliance with GMP as certified by the national regulatory authority and/or certified GMP inspectors.
- Product certificates exist in accordance with the WHO Certification scheme on the quality of pharmaceutical products moving in international commerce.
- Product dossiers of acceptable quality submitted and outcome of the assessment in respect of the prequalification procedure.
- Outcome of the inspection performed by or on behalf of the above-mentioned agencies.
- Manufacturer demonstrates sound financial standing.

Only manufacturers THAT CAN SUPPLY APPROPRIATE PRODUCTS OF ACCEPTABLE QUALITY COMPLIANT WITH APPLICABLE REGULATORY REQUIREMENTS, WHO GUIDELINES AND LEGISLATION will be considered.

The United Nations procurement agencies reserve the right to determine specific conditions, as for example the exclusion of companies using child labour, or engaged in the manufacture of land mines or parts thereof.

Further references

For background information on drugs for the treatment of opportunistic infections in HIV/AIDS, please refer to www.aidsinfo.nih.gov/guidelines

For background information on palliative care drugs, please refer to http://www.who.int/3by5/publications/documents/en/genericpalliativecare082004.pdf

Appendix 6

Pharmaceutical product questionnaire

I Product identification

Active pharmaceutical ingredient(s) (use INN if any): _____
Generic name of the product: _____
(Trade name requires prior approval by UNICEF)
Dosage form:
☐ Tablets ☐ Capsules ☐ Ampoules ☐ Vials ☐ Other: _____
Strength per dosage unit: _____
Route of administration:
☐ Oral ☐ IM ☐ IV ☐ SC ☐ Other: _____
Pack size (ml): ☐ 50 ☐ 100 ☐ 1000 ☐ Other: _____
Description of primary packaging materials: _____
Description of secondary packaging materials: _____

II Manufacturer of the product

Name, address and activities of the manufacturer(s) (or contract manufacturer(s)):

Name	Physical address	Telephone number, Facsimile number and e-mail contact details	Activity (e.g. packaging)

Are all sites listed above licensed by the relevant authority to perform the activity?
☐ Yes ☐ No

Is the manufacturing site for THIS product prequalified by the procurement agency?
☐ Yes ☐ No

Has the manufacturing method for each standard batch size been validated?
☐ Yes ☐ No

List the standard batch size quantities: _____

III Supplier identification

(to be filled in if not identical to that indicated in question II)

Name: _____
Address: _____
Telephone number: _____
Facsimile number:_____
E-mail contact details: _____

Link with the product:
☐ Marketing licence holder ☐ Distributor ☐ Manufacturer
☐ Other: _____

IV Regulatory situation (licensing status) in the country of manufacture

☐ Product registered and currently marketed: Licence number: _____

☐ Product registered for marketing in the country of manufacture but not currently marketed: Licence number: _____

☐ Product registered for export only: Licence number:_____

☐ Product not registered (please clarify): _____
_____
_____

Please attach a Certificate of Pharmaceutical Product according to the WHO Certification scheme (WHO Technical Report Series, No. 863). Earlier version is not acceptable.

V Regulatory situation (licensing status) in other countries

List other countries where the product is registered and is currently marketed:

_____
_____
_____

VI Finished product specifications

☐ British Pharmacopoeia Edition (BP)
☐ United States Pharmacopeia Edition (USP)
☐ International Pharmacopoeia Edition
☐ Other: _____

Please attach a copy of the finished product specification, if different from BP, USP or International Pharmacopoeia specification.

Limits in % for the assay in active ingredient(s):
☐ 95–105% ☐ 90–110 % ☐ Other: _____

Additional specifications to those in the pharmacopoeia (e.g. dissolution, syringeability): _____

_____

_____

Please attach a copy of the model certificate of analysis for batch release.

Are you willing to provide necessary information (analytical method) for the tests to be replicated by another control laboratory?
☐ Yes ☐ No

VII Stability

Stability testing data available:
☐ Yes ☐ No

If yes, type and conditions of testing:
☐ Accelerated testing ☐ 40 °C/ 75 % RH/ 6 months ☐ Other:____

In the same packaging as specified under point I (page 1): ☐ Yes ☐ No

Real-time testing temperature:
☐ ambient ☐ 25 °C ☐ 30 °C ☐ Other: _____

Relative humidity:
☐ non-controlled ☐ 45% ☐ 65% ☐ Other: _____

Period of time:
☐ 1 year ☐ 2 years ☐ 3 years ☐ Other: _____

In the same packaging as specified under point I (page 1): ☐ Yes ☐ No

Can a stability report be forwarded within one week of being requested?
☐ Yes ☐ No

Was the stability testing done on a product of the same formula, manufactured on the same site and packed in the same packaging material as the product that will be supplied?
☐ Yes ☐ No

VIII Label and insert information

Shelf-life (years): ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ Other: _____

Storage conditions *(e.g. "Do not store above 30 °C – Protect from light")*:

_____

Label language:
☐ Bilingual English/French ☐ English ☐ French ☐ Other: _____

Package insert: ☐ Yes *(attach a copy)* ☐ No

IX Samples

Can free non-returnable samples be obtained upon request within one week of being requested? ☐ Yes ☐ No

X Therapeutic equivalence

☐ Demonstrated:
☐ by in vivo bioequivalence studies: Reference product: _____
Number of volunteers: ____ Country of study: _____
Year performed: _____
☐ by another method claimed by the supplier/manufacturer (please describe briefly): _____
_____
_____
_____

☐ by in vitro dissolution tests: Reference product: _____

☐ not demonstrated ☐ not relevant ☐ unknown

Can a copy of the report be obtained upon request within one week of being requested?
☐ Yes ☐ No

Is the product used in the trial or test essentially the same as the one that will be supplied (same materials from the same suppliers, same formula, same manufacturing method)?
☐ Yes ☐ No

XI Active pharmaceutical ingredient(s) (APIs)

(In case more than one active ingredient is used, please replicate this question.)

Do specifications and standard test methods exist for each API and excipient?
☐ Yes ☐ No

Each API used (in INN if any):
☐ has a Certificate of suitability to the European Pharmacopoeia (CEP)
Certificate no.: _____
☐ The CEP is in our possession (including annex if any) _____
☐ The CEP is in the possession of the finished product manufacturer (including annex if any) _____

☐ has a drug master file (DMF)
registered in: (country)_____ registration no. _____
☐ The full or open part of the DMF is in our possession .....
☐ The full or open part of the DMF is in the possession of the finished product manufacturer

Quality standard:
☐ BP ☐ USP ☐ EP ☐ International Pharmacopoeia
☐ Other (e.g. "in-house"; specify): _____
☐ No pharmacopoeia monograph exists*

*If there is no monograph in a recognized pharmacopoeia, then the following information should be provided and evaluated:

- chemical structure;
- if relevant, the isomeric nature of the active ingredient, including stereochemical configuration (e.g. racemate, pure (S)-isomer, 50/50 mixture of (Z)- and (E)-isomers;
- the solubility of the active ingredient in water at 25 or 35 °C;
- the solubility of the active ingredient in other solvents such as ether, ethanol, acetone and buffers of different pH (if the active ingredient is acidic or basic);
- other relevant physicochemical characteristics of the active ingredient such as partition coefficient (usually octanol/water) and the existence of polymorphs;
- copies of infrared, nuclear magnetic resonance (proton and C-13), ultraviolet and mass spectra;
- information on the chemical stability of the API, and on physicochemical stability if relevant (e.g. formation of a hydrate, change of polymorphic form).

Manufacturer (name, physical address + country): _____
_____
_____

GMP certified:
☐ Yes *(attach a copy of the GMP certificate if any)* ☐ No ☐ Unknown
Certified by: _____

XII Commitment

I, the undersigned,_____
_____
(position in the company, e.g. General Manager, Authorized Person, Responsible Pharmacist), acting as responsible for the company:_____
_____ *(name of the company)*, certify that the information provided (above) is correct and true.

(If the product is marketed in the country of origin, tick the following boxes as applicable:)

☐ and I certify that the product offered is identical in all aspects of manufacturing and quality to that marketed in:_____ *(country of origin)*, including formulation, method and site of manufacture, sources of active and excipient starting materials, quality control of the product and starting material, packaging, shelf-life and product information;

☐ and I certify that the product offered is identical to that marketed in: _____ *(name of country)*, except:

_____

_____

(e.g. formulation, method and site of manufacture, sources of active and excipient starting materials, quality control of the finished product and starting material, packaging, shelf-life, indications, product information)

Date: _____ Signature: _____

Appendix 7

Example of a standard operating procedure for screening and assessing product information

1. Title

Assessing product files

	Signature	Date
Prepared by		9 May 2005
Authorized by		

2. Policy and objective

2.1 Each product file submitted by an interested manufacturer should be assessed as part of the prequalification process.

2.2 Each product file should go through a screening procedure.

2.3 Product files found to comply with the screening requirements will be retained for assessment.

2.4 The objective is to screen product files to determine whether these comply with the requirements. This will prevent loss of valuable assessment time, should the product files be incomplete when received.

2.5 The objective of the assessment process is to verify that the required information regarding safety, efficacy and quality of the product is documented and submitted in the required format. Where possible during inspections, and as a part of the verification process, the data and results should be verified to ensure that correct, accurate and reliable data have been submitted to the procurement agency.

3. Responsibility

Project Manager
Evaluators

4. Action

A. *Screening*

4.1 Unpack each product file onto the working surface in the presence of at least two other persons. Sign a sheet indicating the names of the persons responsible for opening the containers on that date.

4.2 Complete the relevant details in the "product received register".

4.3 Record details such as the product number, date, product detail (INN), name of supplier, name of manufacturer(s), country of manufacturer(s), screening outcome, date manufacturer informed (Addendum A).

4.4 Allocate the product number in numerical order starting from 001.

4.5 The number should start with the year, e.g. 01 (for 2001).

4.6 Identify the project for which the product was submitted, e.g. HA for HIV/AIDS. The first product for the project would thus be numbered 01HA001.

4.7 Open a WHO file for the product. Write the product name, number and the name of the manufacturer on the outer page.

4.8 Write the product number on the product file and screening form for the product.

4.9 Screen the product file to assess its completeness. Confirm that all the required information, data and forms have been submitted by the manufacturer/supplier.

4.10 Use the attached screening form for this purpose (Addendum B).

4.11 Enter the relevant information in the appropriate column of the screening form as part of the screening process.

4.12 Once the screening is complete, make a copy of the screening form.

4.13 File the copy of the screening form in the screening form file.

4.14 Place the original of the completed screening form in the front of the product file.

4.15 If the product file is complete, place the product file in numerical order in the designated area marked "For evaluation".

4.16 If the product file is incomplete, place the file in the designated area, marked "Incomplete files".

4.17 Enter the outcome in the "product received register".

4.18 For each product file received, send a letter of acknowledgement of receipt to the manufacturer. For an "Incomplete file", inform the manufacturer

in writing that the product file submitted was incomplete and cannot be considered for evaluation or assessment (see Addendum C for a model letter).

B. *Assessing product files*

Note: Each product file must be assessed by at least three evaluators.

Three evaluators should evaluate Part I (quality aspects) and at least two evaluators should evaluate Part II (bioavailability, safety and efficacy aspects).

Step 1 (Evaluator 1)

4.19 Take a product file from the section marked "For evaluation".

4.20 Use the attached product assessment report (Addendum D) for the purpose of evaluating the product information.

4.21 Go through each section and assess compliance with the required standards for the submission of the relevant information.

4.22 Record your findings in the report form.

4.23 On completion of the assessment record your name, signature and the date on the report form.

4.24 Record any specific problem associated with the evaluation of the product on a separate report form, entitled "Product-specific problem report" (Addendum E).
If you are evaluating Part 2, "Bioequivalence (safety and efficacy)", and the efficacy part of the dossier is not included for all oral preparations, except aqueous solutions, at the time of administration, inform the manufacturer in writing that the product file was submitted without bioavailability aspects and cannot be evaluated at present.

4.25 Place the report forms in the front of the product file.

4.26 Replace the file in the section "For evaluation".

Step 2 (Evaluator 2)

Perform steps equivalent to steps 4.19 to 4.26 above.

Step 3 (Evaluator 3)

Perform steps equivalent to steps 4.19 to 4.26 above.

Step 4

4.27 If a file contains the evaluation reports signed by three evaluators (quality aspects) and two evaluators (bioavailability), place the file in the area marked "Evaluation completed".

4.28 Assess whether the relevant number of evaluators (three for quality aspects, and two for bioavailability) have evaluated each product adequately.

4.29 Collate the information in the reports. If additional information is required from the manufacturer or supplier, draft the letter on the basis of the information contained in the reports.

4.30 Request the additional information to be submitted within the specified period. Remind the manufacturer that failure to supply the requested information within the timescale requested may lead to exclusion of the product from further consideration.

4.31 Record the recommendation of evaluators on the list for the inspection of the manufacturing site.

5. Addenda

Addendum A: Product details
Addendum B: Screening form to assess the quality of the submission of EOI
Addendum C: Product information receipt
Addendum D: Product assessment report
Addendum E: Product-specific problem report

6. Distribution and retrieval

The record of distribution and retrieval of the SOP should be entered in a table; see the model below.

	Distribution		Retrieval	
Name	Signature	Date	Signature	Date

7. History

The history of changes to the SOP should be recorded in a table; see the model below.

Date	Reason for change

Addendum A: Product details

Product Number	Date	Product details (INN)	Name of supplier	Name of manufacturer(s)	Country of manufacture	Screening outcome	Date manufacturer informed	Inspection planned (Y/N)

Addendum B: Screening form to assess the quality of the submission of an expression of interest

Access to drugs and diagnostics of acceptable quality
Pilot procurement quality and sourcing project

Complete the following: Product submission number:

Product name			
Active pharmaceutical ingredient			
Strength			
Dosage form			
Pack size			
Name of supplier of drug products			
Address of supplier of drug products			
Name and address of manufacturer if different from that of the supplier above			
Name and address of manufacturer (and if appropriate of supplier) of the active pharmaceutical ingredient			
Date of submission			
Country of origin of the submission	Supplier: _____ Manufacturer: _____		
Is the product licensed in	Japan USA EU*	YES YES YES	NO NO NO
If "Yes", proceed to Appendix 1 If "No", proceed to Appendix 2			

* (EU countries: Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, Netherlands, Portugal, Spain, Sweden, United Kingdom)

Appendix 1

The following is included in the submission:

A WHO-type certificate of a pharmaceutical product (CPP) issued by one of the regulatory authorities of ICH regions	YES	NO
The summary of product characteristics (SmPC)		
Assessment report(s) issued by the respective regulatory authority		
WHO-type batch certificate from the manufacturer		
The packaging of the product is the same as that approved by the drug regulatory authorities of the ICH regions		[1]
The product information is the same as on the WHO-type CPP for at least:	_____	_____
Formulation		[2]
Strength		[2]
Specifications		[2]

[1] Stability testing data are submitted

[2] Arguments and/or data to support the applicability of the certificate(s) despite the differences are submitted.

If the answers to 1 and 2 are “no”, then the EOI should be rejected.

Appendix 2

Check that the following has been submitted in the product documentation for EOI:

	YES	NO
Details of the product (Name of the product; approved generic name(s) (use INN, if any); visual description of the product; visual description of the packaging; strength per unit dosage and dosage form)		
Regulatory situation in other countries (Marketing authorization, withdrawn from the market, application rejected, deferred or withdrawn.)		
API		
Properties Chemical structure; solubility in water, other solvents such as ether, ethanol, acetone and buffers of different pH; its isomeric nature including stereochemical configuration; partition coefficient and the existence of polymorphs; copies of infrared, nuclear magnetic resonance (proton and C-13), ultraviolet and mass spectra; information on the chemical and physico-chemical stability if relevant (e.g. formation of a hydrate, change of polymorphic form)		
Sites of manufacture Name and street address of each facility of manufacture (synthesis, production), including any alternative manufacturers GMP certificate attached (including for all alternative sites of manufacture being submitted)		
Route(s) of synthesis 1. Including reagents and reaction conditions; specifications for starting materials, reagents, solvents, catalysts and intermediates in the synthesis; synthetic by-products and degradation products 2. If a European certificate of suitability with any appendices is submitted, then an outline of the route of synthesis is sufficient 3. The manufacturer of the finished product should know the full details of the synthesis of the substance so that they are able to conduct a full set of tests on each batch. The results of such testing should be presented for at least two batches. The last option can be used only if the quality of API is described in a pharmacopoeia		
Specifications		
Pharmacopoeial requirements: copy of the monograph and tests, additional specifications, certificates of analysis, two batches, including results for impurities		
Non-pharmacopoeia: tests and limits, methods, results of validation		
Stability testing Results of stability, physical as well as chemical tests, methodology used (WHO guidelines or ICH guidelines), validation		
Finished product		
Formulation Formulation and administration unit, excipients not present in final formulation, the qualitative and quantitative composition, overages, function(s) of each excipient, ranges in the content of excipients justified and explained		
Sites of manufacture Name and street address of each facility. Indicate the activity, alternative manufacturers, major production step(s) – certificate issued, product information approved, summary basis of approval		

	YES	NO
Manufacturing procedure Outline of manufacturing and packaging Copy of the master formula and a copy of a manufacturing record Details of sterilization Stages of sampling and in-process control tests		
Specifications for excipients Pharmacopoeia: copy of the monograph, test methods referenced Additional specifications Non-pharmacopoeia: list of tests and for each excipient, including solvents, liquids to adjust pH, coatings, capsule shell, and inked imprint (on the dosage form), description of test methods, microbiological limits, colours EU/FDA/Japan		
Specifications for the finished product Two specifications: at release and end of shelf-life List general characteristics, specific standards: tests and limits for results for the finished product must be provided Analytical test procedures described (physicochemical properties, identity of API) Quantitative determination of active, deviations, purity tests, pharmaceutical tests, colouring antimicrobial or chemical preservatives, results of validation studies, comments on the choice of routine tests and standards provided Copy of pharmacopoeia monograph and verification data Results of batch analysis (inc. date of manufacture, place of manufacture, batch size and use of batch tested)		
Container/closure system(s) and other packaging Detailed description (inc. liner or wadding, details of composition); describe other (e.g. outer) packaging; state materials and specifications for part in contact with the product, or if protective. Parenteral: BP, EP, JP or USP		
Stability testing Results for each pack, methodology, validated (accuracy and precision recorded) Related compounds and decomposition: sensitivity, accelerated and real-time data, accelerated 40 °C and 75% RH for six months, real time 30 °C and 70% RH		
Container labelling Name, active ingredients, amount of each, batch number, expiry date, storage conditions, directions, warnings or precautions, name and address of the manufacturer, excipients known to be a safety concern		
Product information Copy approved by competent authority		
Patient information and package inserts Copies of package inserts and information for distribution		
Justification for any differences Arguments provided and/or data to support, validation data. Only minor differences are likely to be acceptable		
Interchangeability Multisource (generic): bioequivalence study. Bioequivalence of all oral preparations except aqueous solutions. Orally or parenterally administered aqueous solutions: chemical–pharmaceutical characteristics. Comparative clinical trial using clinical or pharmacodynamic end-points can be presented. End-points justified and validated for the compound and trial should be designed to show equivalence. Trial showing the absence of significant difference cannot be accepted Bioequivalence study report included		

	YES	NO
Report Study design, investigators, study site, study dates, preparations used, characterization of study subjects, study procedures, drug determination methods, measured drug concentrations, calculation methodology of pharmacokinetic parameters, statistical methodology and results of statistical calculations		
Summary of pharmacology, toxicology and efficacy of the product New active ingredients and new combinations of active ingredients: full safety and efficacy (EU, FDA, Japan)		

☐ Accept ☐ Reject ☐ Hold

Reasons for rejecting or holding an application: _____

_____

_____

_____

_____

Addendum C: Product information receipt

Dear …

Prequalification of manufacturers and suppliers of drug products

Thank you for submitting a product file after having indicated your company's interest in supplying drug products as part of the prequalification process of drug products to the United Nations organizations and interested procurement agencies.

We herewith acknowledge receipt of your product information sent to this office as part of the prequalification process.

The product information submitted has been screened to assess completeness of the submission in accordance with the guidelines that were sent to you after receiving your Expression of Interest (EOI) in participating in the prequalification programme.

Kindly note that your submission is now pending the full assessment. It is possible that an inspection of the manufacturing site(s) will be performed in due course. Details of this will be advised to you once all the necessary arrangements have been completed.

OR

Kindly note that your submission was found to be incomplete. We therefore regret to inform you that no further evaluation will take place with regards to your product file, and that the manufacturer will be not be included in the prequalification process. Would you kindly contact this office within 30 days to enable us to make the necessary arrangements for the return of the information already submitted.

OR

Kindly note that your submission was found to be incomplete. It is missing the following information.

If you provide the missing data within X days, and it is of satisfactory quality, then your submission will go forward to full assessment.

Your cooperation is appreciated.

Addendum D: Product assessment report

Access to drugs and diagnostics of acceptable quality
Pilot procurement quality and sourcing project

Product number:		
Product name (API):		
Manufacturer:		
Product manufactured and registered/licensed in EU, Japan or USA	YES[1]	NO[2]

This product evaluation report consists of two parts. Both parts should be completed as part of the assessment. The report should be written in clear unambiguous language referring to shortcomings or lack of data submitted, as communication with the manufacturer may result from the assessment.

Part One should be completed by at least three evaluators from different countries, responsible for assessing product quality including pharmaceutical and analytical aspects. (The report should be no longer than six pages.)

Part Two should be completed by an evaluator responsible for the assessment for bioavailability. (The report should be no longer than two pages.)

The report should be signed off by the person responsible for the evaluation and assessment of the product files.

Part I: Quality aspects

[1] Product licensed/registered in the EU, Japan or the USA. Review the data submitted and comment (see also guidelines):

A WHO-type certificate of a pharmaceutical product (CPP) issued by one of the regulatory authority of ICH regions (EU, Japan, USA)
The summary of product characteristics (SmPC)
Assessment report(s) issued by the respective regulatory authority
WHO-type batch certificate from the manufacturer
The packaging of the product is the same as those approved by the drug regulatory authorities of the ICH regions
The product information is the same as on the WHO-type CPP for at least:

Formulation
Strength
Specifications

[2] Product not licensed/registered in the EU, Japan or the USA. Review the data submitted and comment:

Details of the product
Regulatory situation in other countries
Active pharmaceutical ingredient(s) (API) Properties of the API(s)
Sites of manufacture
Route(s) of synthesis
Specifications API described in a pharmacopoeia (specify the pharmacopoeia, its edition, and any supplement if relevant). The latest edition of the relevant pharmacopoeia should always be used. API not described in a pharmacopoeia
Stability testing
Finished product
Formulation
Sites of manufacture
Manufacturing procedure
Specifications for excipients

Specifications for the finished product
Container/closure system(s) and other packaging
Stability testing
Container labelling
Product information
Patient information and package inserts
Justification for any differences of the product in the country or countries issuing the submitted WHO-type certificate(s)

Evaluator (name):	Signature:	Date:
1		
2		
3		

Part II: Bioavailability (safety and efficacy)

(See also guidelines)

Bioequivalence study report
Summary of pharmacology, toxicology and efficacy

Evaluator (name):	Signature:	Date:
1		
2		
3		

Addendum E: Product-specific problem report

Access to drugs and diagnostics of acceptable quality
Pilot procurement quality and sourcing project

API:	

This product-specific problem report should highlight any specific problems identified during the evaluation of products. No mention should be made of the specific manufacturer's product. The objective is to identify any problems associated with a specific product containing a specific API, or specific to any dosage form.

Dosage form	

Problems

General recommendations

Appendix 8

Technical questionnaire for pharmaceutical manufacturers

1. General information on the manufacturer

Name, address, telephone, telefax, Internet address of the company:

Name	
Postal address	
Physical address	
Telephone	
Fax number	
Web site URL	
Contact e-mail address	

2. Affiliates

If the company is owned by another company, or belongs to a group of companies,
Please describe your position within the structure: _____

_____

3. Regulatory issues

3.1 Good manufacturing practice (GMP)

Indicate the GMP standards (WHO, PIC/EU, FDA or other) with which the company complies: _____

Provide a copy of the latest inspection report or certificate whichever is appropriate.

3.2 Manufacturing licence for medicinal products

Please list the pharmaceutical dosage forms you are licensed to manufacture by the national regulatory authority and attach a copy of the manufacturing licence(s): _____

_____

_____

_____

_____

3.3 Inspection

Date of last inspection by a national or other competent drug regulatory authority:

Drug regulatory authority	Date

Please attach a copy of the last inspection report(s) or certificates for review on a confidential basis.

4. Manufacturing

4.1 Manufacturing site

Please state all the names and addresses at which manufacturing of pharmaceutical products to be prequalified takes place, and indicate in which year the factory was built. Include dates of upgrading and adaptation, as well as a description of the activity:

Name	Physical address	Year built and recent upgrades	Activity (e.g. all, compression, packaging, etc.)

4.2 Personnel

Please indicate the name, qualification and years of experience of the following key staff:

Position	Name	Qualification	Experience
Managing Director			
Technical Director			
Production Manager			
Quality Control Manager			
Quality Assurance Manager			

Number of personnel in total: _____
Number of personnel in production: _____
Number of personnel in quality assurance/control: _____

4.3 Ventilation system

Please indicate whether the manufacturing areas are equipped with controlled ventilation systems ☐ Yes ☐ No

If "Yes", please give a brief description of the ventilation system. *(A diagram complementing the description can be submitted.)*

If "No", explain reasons: _____

_____

_____

4.4 Quality control

Instrumentation?

Chemical laboratory	in-house ☐	contracted out ☐
Biological laboratory	in-house ☐	contracted out ☐
Microbiological laboratory	in-house ☐	contracted out ☐

4.5 Contract manufacture

Do you undertake contract manufacture for other companies? ☐ Yes ☐ No

If "Yes", please indicate the type of products (e.g. pesticides, antibiotics, hormones, cytotoxics, etc.) _____

Do you subcontract to other companies? ☐ Yes ☐ No

If "Yes", please list products and/or services that are subcontracted: ____

_____

_____

4.6 Sterile products

Do you manufacture sterile products? ☐ Yes ☐ No

Give a brief description of the method of sterilization used: _____

_____

_____

4.7 Beta-lactam, highly sensitizing compounds, hormones, cytotoxic products

Do you manufacture penicillins or other beta-lactam, highly sensitizing compounds, hormones or cytotoxic products? ☐ Yes ☐ No

If yes, does this production take place in a separate building provided with its own dedicated air-handling system? ☐ Yes ☐ No

4.8 Complaints and recalls

Do you have a recall procedure, which enables you to recall any product effectively and promptly within 24 hours from the distribution points or market? ☐ Yes ☐ No

Do you have a procedure for handling complaints? ☐ Yes ☐ No

Does it cover analysis of trends? ☐ Yes ☐ No

Please list significant product complaints and any recalls during the last three years:

Product	List complaints		
	Year 1	Year 2	Year 3

4.9 Research and development activities

Please indicate the type of activities and annual investment: ._____

_____

_____

_____

_____

4.10 Production capacity

Product	No. of units per year	Last year's production units
Tablets		
Capsules		
Ampoules		
Vials, liquids		
Vials, dry powder		
Vials, lyophilized		
Ointments		
Liquids		
Powder for oral suspensions		
Suppositories		
Penicillin, tablets/capsules		
Penicillin, powder for oral suspension		

Penicillin, powder for injection		
Other, specify		

Are production capacity figures based on one or more shifts? (Tick appropriate box)

☐ One ☐ Two ☐ Three

4.11 Stock

Do you maintain a permanent stock? ☐ Yes ☐ No

4.12 Quality systems (including quality management and quality assurance)

Give a brief description of the quality management system, with specific reference to aspects such as procurement agency, documentation infrastructure, validation, training, statistical analysis, and other related aspects: __

_____
_____
_____
_____
_____

5. Products

5.1 Product licences

Please enclose a list of all products manufactured by your company for which you seek prequalification and which are authorized for sale. For each licensed product, please complete the table below and categorize as shown.

If possible, please attach an indicative price list.

Product	Marketed in the domestic market (Yes or No)	For export only (Yes or No)	Licences are held in the following countries	Name of contract manufacturer and country

5.2 Documentation

The following product documentation must be made available upon request for each product offered. Please indicate if this documentation

is NOT available for any of the products on the list shown under point 5.1:

Product composition – master formula_____

Starting materials specification_____

Manufacturing and packaging specification_____

In-process test specifications and methods_____

Finished product specification _____

Packaging and labelling specifications_____

Analytical procedures _____

Upon request, "the common product questionnaire" must be completed and returned.

5.3 Samples

Are you willing to provide product samples and batch documentation (on a confidential basis) when requested? ☐ Yes ☐ No

5.4 Starting materials

List starting materials manufactured by the company or by affiliates, and indicate in the table below whether approved drug master files (DMF) or Certificates of suitability of the Monograph of the European Pharmacopoeia (CEP) are available.

Starting material	DMF (Mark ✓, and state number)	CEP (Mark ✓)

5.5 Stability studies and shelf-life

Do you perform initial and continuous stability studies on your products? ☐ Yes ☐ No

Give a brief description of the stability procedure and programme. If "No", explain reasons: _____

_____

_____

_____

What type(s) of studies do you carry out?

Type *(Mark with ✓)*		Test conditions	
		Temperature *(indicate)*	Relative humidity *(indicate)*
	Accelerated studies		
	Real-time studies		

Explain if necessary: _____

_____

_____

_____

How do you determine the shelf-life of your products? _____

_____

_____

_____

_____

5.6 Bioequivalence

Have you conducted in vivo bioequivalence studies for some of your products? ☐ Yes ☐ No

If "yes", list the products studied and the reference products:

Product	Reference product	Country of study

5.7 Retention samples

Do you keep retention samples? ☐ Yes ☐ No

Samples:	Yes	No	Retention period	Storage conditions
Every finished product				
Active pharmaceutical ingredients				
Excipients				

6. Audit

Can we or any other representative designated by us perform a GMP audit of the manufacturing site? ☐ Yes ☐ No

Can (a) representative(s) from the national regulatory authority participate as observer(s) in the audit? ☐ Yes ☐ No

May we share the inspection report with the other procurement agencies "signatory" to this questionnaire? ☐ Yes ☐ No

Is a site master file (PIC or WHO format) available upon request? ☐ Yes ☐ No

Will any required additional information be provided if we wish to perform an audit of the company? ☐ Yes ☐ No

7. Other information

Contact person (commercial issues):

Name:	
Telephone no.:	
Fax:	
e-mail:	

Contact person (quality issues):

Name:	
Telephone no.:	
Fax:	
e-mail:	

Any additional information: _____

_____

_____

_____

_____

I hereby certify that the information given in this questionnaire and the attachments is correct.

Date	**Signature**
Name	Position in company

Appendix 9

Example of a standard operating procedure for planning of inspections

1. Title

Inspection, planning of site inspections

	Signature	Date
Prepared by		1 July 2006
Authorized by		

2. Policy and objective

2.1 Manufacturing sites should be inspected as part of the prequalification process. To enable the procurement agency to perform the inspections, they should be properly planned.

2.2 The objective is proper planning of site inspections to ensure that products will be sourced only from manufacturers that comply with international standards.

2.3 Proper planning of inspections should save time and resources (e.g. financial and human) through procurement agency planning.

3. Responsibility

Head of the Section or Department
Project Manager
Evaluator

4. Action

4.1 When assessing product information, make a list of all the products received (see Addendum A). Complete the table.

4.2 On the basis of the outcome of the assessment of the product information, decide which manufacturers should be inspected for prequalification.

4.3 Dossiers lacking information, or of unacceptably low quality, may lead to the manufacturing site failing to qualify for the inspection.

4.4 Group all the manufacturers in one country together to ensure that when a trip is undertaken to one country, more than one manufacturer can be included in the inspection trip where relevant.

4.5 Consult a map to see where the sites are located and plan the trip so as to prevent unnecessary loss of time through travelling.

4.6 Plot the sites on a table (calendar) and allocate at least 3 days for inspection of each manufacturing site, depending on the dosage forms manufactured and the size of the facilities.

4.7 Write a letter to the company informing them of the tentative date allocated for the site inspection. Request the company to indicate whether the dates are suitable to them, and also request them to submit a site master file.

4.8 Appoint inspectors for the inspection team. There should be at least two inspectors on the team, including the representative from WHO.

4.9 Send a letter to the national regulatory authority inviting an inspector from the inspectorate to participate in the inspection.

4.10 Inform the inspectors of the proposed dates for the inspection.

4.11 When the manufacturer confirms the dates for inspection confirm the date with the company and request the information listed in Addendum B.

4.12 Confirm the dates with the inspectors.

4.13 Send the inspectors copies of the SOPs needed to perform the inspections, as well as the terms of reference, confidentiality clause, no conflict of interest declaration and agreement for performance of work.

4.14 Make the relevant bookings (air travel, transport in the country where the inspection will be performed and hotel accommodation).

5. Addenda

Addendum A: Summary list of dossiers received

Addendum B: Manufacturer information

6. Distribution and retrieval

The record of distribution and retrieval of the SOP should be entered in a table; see the model below.

	Distribution		Retrieval	
Name	Signature	Date	Signature	Date

7. History

The history of changes to the SOP should be entered in a table; see the model below.

Date	Reason for change

Addendum A: Summary list of dossiers received

No	API	Strength	Dosage form	Supplier/ Manu-facturer	Manu-facturing site	Country	Sample

Addendum B:Manufacturer information

1. General information

Name	
Physical address of head office	
Postal address	
Telephone number	
Fax number	
Contact person	
E-mail address	

2. Manufacturing licence

Please attach the manufacturing licence.

3. Product list

Please attach a list of products manufactured at this particular manufacturing site.

4. Inspections by the national regulatory authority

Date of last inspection by the national regulatory authority (NRA)		
List the NRA of other countries that have inspected the site, and dates of inspection	Country	Date

5. Manufacturing and testing

Physical address of manufacturing sites for the products indicated in the submission	
Telephone number	
Fax number	
Physical address of quality control laboratories (chemical and microbiological) used for testing the products in the submission	
Telephone number	
Fax number	
E-mail	

6. Recalls

Please list the products and reasons for implementing a product recall in the last 5 years.

Product and batch number (INN, strength and dosage form)	Reason	Date of recall

7. Complaints

If the company has had any product complaints in the last year, please complete the table below.

Products and batch number (INN, strength and dosage form)	Complaint and source	Corrective action taken

8. Site master file (SMF)

If the SMF for the manufacturing site was submitted previously:

Date submitted	
SMF number	

If the SMF has not yet been submitted to WHO, please attach it now. Please note that the SMF must conform to the requirements specified previously.

9. Audit/inspection

We herewith grant WHO permission to perform the inspection of the manufacturing site to assess compliance with good manufacturing practice, for the purpose of the prequalification of the manufacturing site and product.

I declare that the information given above is true and correct.

_____ _____

Signature: Date:

Name: _____

Position: _____

Appendix 10

Example of a standard operating procedure for preparing for an inspection

1. Title

Preparation for an inspection

	Signature	Date
Prepared by		11 May 2006
Authorized by		

2. Policy and objective

2.1 Each manufacturer should be inspected by the procurement agency to assess compliance with good manufacturing practices.

2.2 All inspectors should follow the SOP in preparing for the inspection(s).

2.3 The objective is to ensure that a standardized procedure is followed by all inspectors when preparing for the inspections to prevent inspections being performed by different inspectors in different ways. This should ensure consistency in performance between inspectors.

3. Responsibility

Project Manager
Inspectors

4. Action

All actions described here are taken from the details provided by the WHO publication *Quality assurance of pharmaceuticals*, Volume 2, Chapter 4: Inspection of pharmaceutical manufacturers and inspection of drug distribution channels. These guidelines or other similar systems operated by national drug regulatory agencies should be followed in detail.

4.1 Once the inspection has been allocated to the inspector, he or she should plan for the performance of the inspection according to the steps outlined below.

4.2 Verify the objective of the inspection that is to be carried out.

4.3 Clarify which type of inspection will be performed, e.g. routine GMP or follow-up inspection.

4.4 Decide whether the inspection will cover the entire factory or just part of it.

4.5 Determine what the scope and depth of the inspection will be to enable you to prepare for it properly. (For a company producing sterile products, prepare by reviewing the guidelines for sterile product manufacture in addition to the general GMP guidelines.)

4.6 Scrutinize the product information for the products in the prequalification procedure manufactured at this manufacturing site.

4.7 Decide how long it will take to carry out the inspection and plan the date when the inspection will take place.

4.8 Inform the manufacturer(s) in question of the proposed date for the inspection.

4.9 Ensure that the proposed date for the inspection is suitable for all members of the inspection team.

4.10 Decide on a chief or lead inspector to coordinate and lead the inspection.

4.11 The lead inspector will be the main spokesperson during the closing or exit meeting at the end of an inspection, and has the overall responsibility for the inspection report.

4.12 Inform other interested parties of the proposed or planned inspection, e.g. a regional office of the procurement agency or agency, or the national regulatory authority.

4.13 Review documentation relating to the manufacturer to be inspected such as a completed questionnaire.

4.14 In case of a follow-up inspection, and where the procurement agency or agency has a company file in which general correspondence and previous inspection reports are filed, review the correspondence.

4.15 If a site master file (SMF) exists and is available, study the SMF and make notes to be followed up during the inspection (e.g. available equipment, SOPs and records)

4.16 Study the layout and design of the manufacturing facility, and some of the systems the manufacturer has in place to ensure quality in manufacture of products.

4.17 Look at the information provided on the manufacturing licence and product licence. Make notes of the aspects that need to be inspected to

confirm compliance with licence conditions, and to verify data during the inspection.

4.18 Review the reports of previous inspections, reports of adverse drug experiences and complaints, if any exist, as investigations and corrective action taken by the manufacturer should be verified during inspections.

4.19 For a special inspection, review records of the company in relation to complaints and recalls, and regulatory test results (surveillance) where available.

4.20 If an annual report is available, scrutinize the report and note the information in relation to financial aspects of the company, personnel issues and products manufactured.

4.21 If any complaints had been received about the manufacturer or products previously supplied, review the contents of the complaint, investigation, outcome and corrective action.

4.22 If self-inspection/internal audit reports were requested from the manufacturer, review the contents. (Such reports are normally not requested as some manufacturers consider that the inspectors should assess GMP compliance themselves, and not look at the company's own findings of inspections. Requesting such reports would be dependent on the policy of the procurement agency.)

4.23 Study the diagram of the facility to get a better understanding of the flow of material, personnel and processes in the facility.

4.24 If any manuals and/or procedures were submitted by the manufacturer, review these and prepare specific questions relating to the quality policy, validation policy and procedure for performing certain activities.

4.25 Draw up a checklist or aide-memoire of points to be verified during the inspection.

4.26 Draw up a programme for the inspection. Produce an outline of what will be covered each day and clarify what each member of the team will be doing every day or half-day of the visit. Indicate in the programme which sections or departments will be inspected, and when (for an example, see Addendum A).

4.27 Distribute the programme to the team members. In the case of an announced inspection, inform the company of the proposed inspection programme.

5. Addenda

Addendum A: Example of an inspection plan

6. Distribution and retrieval

The record of distribution and retrieval of the SOP should be entered in a table; see the model below.

	Distribution		Retrieval	
Name	Signature	Date	Signature	Date

7. History

The history of changes to the SOP should be entered in a table; see the model below.

Date	Reason for change

Addendum A: Example of an inspection plan

Manufacturer	
Address	
Date	
Inspectors	

Day 1

Time	Activity
08:30	Arrival
08:45	Opening meeting and company presentation
09:15	Receiving area and stores
10:15	Sampling
11:00	Tea
11:15	Weighing
12:00	Packaging components
13:00	Lunch
14:00	Manufacturing (organize time depending on the dosage form(s))
17:00	Summary of the day's observations

Day 2

08:30	Manufacturing, continued
10:00	Tea
10:15	Quality control
12:00	Heating, ventilation and air-conditioning, water and other utilities
13:00	Lunch
14:00	Documentation
17:00	Summary
17:30	Closing meeting

Appendix 11

Example of a standard operating procedure for performing an inspection

1. Title

Performance of inspection

	Signature	Date
Prepared by		1 July 2006
Authorized by		

2. Policy and objective

2.1 Each manufacturer should be inspected by the procurement agency to assess compliance with good manufacturing practices.

2.2 All inspectors should follow the SOP for performing inspections.

2.3 The objective is to ensure that a standardized procedure is followed by all inspectors when performing inspections to prevent inspections being performed by different inspectors in different ways. This should ensure consistency in performance between inspectors.

2.4 One of the objectives is to control and enforce the general standards of production for products that may be sourced as a result of the prequalification procedure.

2.5 Through sequential examination of production and control activities of the manufacturer, the manufacturer of pharmaceutical products may be included on the prequalification list as a manufacturer of pharmaceutical products for possible supply of specified products to procurement agencies and other agencies.

2.6 During inspections, the performance of manufacture of products and data submitted in the relevant product information files should be verified.

3. Responsibility

Project Manager
Inspectors

4. Action

All actions described here are taken from the details provided in the WHO publication *Quality Assurance of Pharmaceuticals*,Volume 2, Chapter 4: Inspection of pharmaceutical manufacturers and inspection of drug distribution channels. These guidelines or other similar systems operated by national drug regulatory authorities should be followed in detail.

4.1 Clarification and definitions

4.1.1 Different types of inspections are identified in the WHO text referred to above. These include:

— routine inspection;
— concise inspection;
— follow-up inspection;
— special inspection; and
— quality systems review.

4.2 The performance of the inspection is dependent on the type of inspection; however, in principle, the basic aspects of this procedure can be followed for performance of an inspection.

4.3 A routine inspection is a full review of all aspects and components of GMP within a facility. It is appropriate to perform a routine inspection under the following circumstances:

- When there is a new expression of interest (EOI) from a manufacturer or a newly established manufacturer.
- When the listing on the prequalification list is due for renewal.
- If there have been significant changes such as new products or new product lines; modification to manufacturing methods or processes; or changes in key personnel, premises and/or equipment.
- If an inspection has not been carried out within the past 3–5 years.

4.4 A concise inspection is the evaluation of limited aspects relating to GMP compliance within a facility. (It is known as an abbreviated inspection in some countries.) A limited number of GMP requirements are selected by the inspector to serve as indicators of overall GMP compliance by the manufacturer. The inspector also has to identify and evaluate any significant changes that could have been introduced by the manufacturer since the last inspection.

4.4.1 Collectively, the selected indicators and the changes identified indicate the manufacturer's attitude towards GMP.

4.4.2 A concise inspection is appropriate under the following circumstances:

- Where a manufacturer has a consistent record of compliance with GMP through routine inspections in the past.

- Where a sample of aspects can be taken as a good indication of the overall level of compliance with GMP.

4.4.3 However, if the concise inspection uncovers evidence that the level of GMP compliance has fallen, a more comprehensive or full GMP inspection should be performed soon after the concise inspection.

4.5 A follow-up inspection is also referred to as a re-inspection or a reassessment of the manufacturer.

4.5.1 A follow-up inspection is performed specifically to monitor the result of corrective actions of the manufacturer following a previous inspection.

4.5.2 Depending on the nature of the defects and the work required, the follow-up inspection could be carried out between 6 weeks and 6 months after the original inspection took place.

4.5.3 The follow-up inspection is limited to specific GMP requirements that have not been observed or that have been inadequately implemented by the manufacturer.

4.6 There are a number of circumstances in which special visits or inspections may be necessary. A special inspection is undertaken to do spot checks. Spot checks could focus on one product, a group of related products, or specific operations e.g. mixing, or labelling. If there have been complaints about a specific product that suggest there may be defects, a special inspection could be performed to investigate the quality defects of the product. If there has been a product recall, this can also trigger an inspection, as would adverse drug reactions. In the above cases, the inspection would focus on the specific product or aspect of production that is suspect. A special inspection could also be performed to gather specific information, or to investigate specific operations of the manufacturer.

4.7 The purpose of a quality systems review is to review the manufacturer's quality system and to ascertain whether it has been shown to operate satisfactorily.

4.8 Plan the inspection to ensure that all areas for assessment are covered in the allocated timeframe. The length of time needed for an inspection is determined by a number of factors, including the type of inspection to be performed, the number of inspectors, the size of the company and the purpose of the inspection or visit.

4.9 An inspection can be performed over a period of a few days to several weeks.

4.10 The time taken will also depend on the size of the inspection team. One or more inspectors can perform the inspection as part of an inspection team.

4.11 If necessary, appoint a specialist to accompany the team during the inspection, e.g. for particular dosage forms, chemistry or another aspect, e.g. the manufacture of biologicals.

5. Addenda

Addendum A: Inspection programme

Addendum B: Documentation required for verification during the inspection

6. Distribution and retrieval

The record of distribution and retrieval of the SOP should be entered in a table; see the model below.

	Distribution		Retrieval	
Name	Signature	Date	Signature	Date

7. History

The history of changes to the SOP should be entered in a table; see the model below.

Date	Reason for change

Addendum A: Inspection programme

Manufacturer	
Address	
Date	
Inspectors	

Day 1

08:30 Arrival
08:35 Opening meeting
08:45 Company presentation
09:00 Receiving area and stores
10:30 Tea
10:45 Sampling and weighing areas
11:15 Packaging material stores and control
12:30 Lunch
13:15 Manufacturing areas
15:30 Tea
15:45 Manufacturing (cont.)
16:30 Summary of findings, day 1

Day 2

08:30 Arrival
08:35 Manufacturing area (cont.)
10:30 Tea
10:45 Laboratories
12:30 Lunch
13:15 Laboratories (cont.)
15:30 Tea
15:45 Utilities
16:30 Summary of findings, day 2

Day 3

08:30 Arrival
08:35 Utilities (cont.)
10:30 Tea
10:45 Documentation
12:30 Lunch
13:15 Documentation (cont.)
15:30 Tea
15:45 Preparation for closing meeting
16:00 Closing meeting

Addendum B: Documentation required for verification during the inspection

1. Organigram
2. Job descriptions
3. Quality policy (e.g. quality manual)
4. Validation policy (e.g. validation master plan or programme)
5. Raw material specifications (for specific products)
6. Packaging material specifications
7. Manufacturing formula and method masters
8. Packing instructions master
9. Batch manufacturing records (verification against master documents)
10. SOP index
11. SOP: self inspection
12. SOP: recalls
13. SOP: complaints plus records
14. SOP: batch number allocation
15. SOP: planned preventive maintenance
16. SOP and record: planned preventive maintenance of specific equipment
17. SOP: training (plus record of personnel)
18. SOP: environmental monitoring plus records
19. SOP: water sampling and testing plus records
20. Validation protocol and report for specific products
21.
22.
23.
24.
25.
26.
27.
28.
29.
30.

Appendix 12

Example of a checklist for good manufacturing practices

It is recommended that inspectors prepare an aide-memoire to remind them of points to be checked during an inspection.

Aide-memoires can be prepared to cover one or more aspects, e.g.

- production
- quality control
- utilities
- lyophilization

The aide-memoire should contain key words to remind the inspector of aspects to be inspected.

An example of an aide-memoire is shown below.

Example: Aide-memoire for inspection of the lyophilization process:

Points to check	Notes
Dissolving Filtration Filling and stoppering Transfer Loading Freezing Vacuum Heating Stoppering Capping	
Validation: Design qualification (DQ) Installation qualification (IQ) Operational qualification (OQ) Commissioning Process qualification (PQ) Media fills Air samples Surface swabs Operator swabs Daily clothing Simulate process with media (not freeze) Smoke test (transport area) Transport Frequent fill volume Pre-cooling of shelves (no ice)	

Points to check	Notes
Freezing Cycle Rate – (slow = crystals, polymorphism) Manner Drying temp. < eutectic point Determine eutectic point, consistent Shelf loading variations *Validate:* shelf temperature product temperature condenser temperature pressure (chamber) pressure (condenser) time, temperature, pressure leakage in contamination (thermal fluid, oil) cleaning	
Cycle Eutectic point determination Scale up Vial size Batch size	
Sterilization of lyophilizer Moist heat used Each cycle Residue if applicable Biological Indicators Design: single door (double door, air class!)	

Appendix 13

Guidance on good manufacturing practices: inspection report

Guidance on Good Manufacturing Practices (GMP): inspection report. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations, Thirty-seventh report*. Geneva, World Health Organization, 2003 (WHO Technical Report Series No. 908), Annex 6.

Available at:
http://www.who.int/medicines/areas/quality_safety/quality_assurance/inspections/en/

Appendix 14

Good storage practices

For a guide to good storage practices for pharmaceuticals, see: *WHO Expert Committee on Specifications for Pharmaceutical Preparations, Thirty-seventh report*. Geneva, World Health Organization, 2003 (WHO Technical Report Series No. 908), Annex 9.

Available at:
http//:www.who.int/medicines/areas/quality_safety/quality_assurance/distribution/en/

Appendix 15

Good trade and distribution practices

For a guide to good trade and distribution practices for pharmaceutical starting materials, see: *WHO Expert Committee on Specifications for Pharmaceutical Preparations, Thirty-eighth report*. Geneva, World Health Organization, 2003 (WHO Technical Report Series, No. 917), Annex 2.

Available at:
http://www.who.int/medicines/strategy/quality_safety/tr917ann2.pdf

Appendix 16

Quality system recommendations for pharmaceutical inspectorates

For a guide to Quality systems requirements for national good manufacturing practice inspectorates, see: *WHO Expert Committee on Specifications for Pharmaceutical Preparations, Thirty-sixth report*. Geneva, World Health Organization, 2002 (WHO Technical Report Series, No. 902), Annex 8.

Available at:
http://who.int/medicines/areas/quality_safety/quality_assurance/inspections/en/

WHO Technical Report Series, No. 937, 2006

Annex 7

Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability

1. Introduction

These guidelines are intended to provide recommendations to sponsors on the requirements for approval of multisource (generic) pharmaceutical products in their respective countries. The guidance provides appropriate in vivo and in vitro requirements to assure interchangeability of the multisource product without compromising the safety, quality and efficacy of the pharmaceutical product.

The national health and drug regulatory authorities should ensure that all pharmaceutical products subject to their control conform to acceptable standards of safety, efficacy and quality, and that all premises and practices employed in the manufacture, storage and distribution of these products comply with good manufacturing practice (GMP) standards so as to ensure the continued conformity of the products with these requirements until they are delivered to the end-user.

All pharmaceutical products, including multisource products, should be used in a country only after approval by the local authority. Regulatory authorities should require the documentation of a multisource pharmaceutical product to meet the following:

— GMP;
— quality control specifications; and
— pharmaceutical product interchangeability.

Multisource pharmaceutical products need to conform to the same appropriate standards of quality, efficacy and safety as those required of the innovator's (comparator) product. In addition, reasonable assurance must be provided that the multisource product is therapeutically equivalent and interchangeable with the comparator product. For some classes of product, including – most evidently – parenteral formulations of highly water-soluble compounds, interchangeability is adequately assured by implementation of GMP and evidence of conformity with relevant pharmacopoeial specifications. For a wide range of pharmaceutical products the concepts and approaches covered by these guidelines will enable the national regulatory authority to decide whether a given multisource product can be approved. This guidance is generally applicable to orally administered multisource products, as well as to non-orally administered pharmaceutical products for which systemic exposure measures are suitable for documenting bioequivalence (e.g. transdermal delivery systems and certain parenteral, rectal and nasal pharmaceutical products). For yet other classes of products, including many biologicals such as vaccines, animal sera, products derived from human blood and plasma, and products manufactured by biotechnology, the concept of interchangeability raises complex considerations that are beyond the scope of this document, and these products are consequently excluded from consideration.

To ensure interchangeability, the multisource product must be therapeutically equivalent to the comparator product. Types of in vivo bioequivalence studies include pharmacokinetic studies, pharmacodynamic studies and comparative clinical trials. Direct practical demonstration of therapeutic equivalence in a clinical study usually requires large numbers of patients. Such studies in humans can be financially daunting, are often unnecessary and may be unethical. For these reasons the science of bioequivalence testing has been developed over the last 40 years. According to the tenets of this science, therapeutic equivalence can be assured when the multisource product is both pharmaceutically equivalent/alternative and bioequivalent. Assuming that in the same subject an essentially similar plasma concentration time course will result in essentially similar concentrations at the site(s) of action and thus an essentially similar therapeutic outcome, pharmacokinetic data may be used instead of therapeutic results. In selected cases, in vitro comparison of dissolution profile of the multisource product with that of the comparator product, or dissolution studies, may be sufficient to provide indication of equivalence.

It should be noted that the concept of interchangeability includes the equivalence of the dosage form as well as of the indications and instructions for use. Alternative approaches to the principles and practices described in this document may be acceptable provided they are supported by adequate scientific justification. These guidelines should be interpreted and applied without prejudice to obligations incurred through existing international agreement on trade-related aspects of intellectual property rights (*1*).

2. Glossary

Some important terms used in these guidelines are defined below. They may have different meanings in other contexts.

bioavailability

The rate and extent to which the active moiety is absorbed from a pharmaceutical dosage form and becomes available at the site(s) of action. Reliable measurements of drug concentrations at the site(s) of action are usually not possible. The substance in the general circulation, however, is considered to be in equilibrium with the substance at the site(s) of action. Bioavailability can be therefore defined as the rate and extent to which the active pharmaceutical ingredient or active moiety is absorbed from a pharmaceutical dosage form and becomes available in the general circulation. Based on pharmacokinetic and clinical considerations it is generally accepted that in the same subject an essentially similar plasma concentration time course will result in an essentially similar concentration time course at the site(s) of action.

bioequivalence

Two pharmaceutical products are bioequivalent if they are pharmaceutically equivalent or pharmaceutical alternatives, and their bioavailabilities, in terms of peak (C_{max} and T_{max}) and total exposure (area under the curve (AUC)) after administration of the same molar dose under the same conditions, are similar to such a degree that their effects can be expected to be essentially the same.

Biopharmaceutics Classification System (BCS)

The BCS is a scientific framework for classifying active pharmaceutical ingredients based upon their aqueous solubility and intestinal permeability. When combined with the dissolution of the pharmaceutical product, the BCS takes into account three major factors that govern the rate and extent of drug absorption (exposure) from immediate-release oral solid dosage forms: dissolution, solubility, and intestinal permeability.

biowaiver

The term biowaiver is applied to a regulatory drug approval process when the dossier (application) is approved based on evidence of equivalence other than through in vivo equivalence testing.

comparator product

The comparator product is a pharmaceutical product with which the multisource product is intended to be interchangeable in clinical practice. The comparator product will normally be the innovator product for which efficacy, safety and quality have been established. The selection of the comparator product is usually made at the national level by the drug regulatory authority (see section 6.5.2).

dosage form

The form of the completed pharmaceutical product, e.g. tablet, capsule, elixir or suppository.

equivalence requirements

In vivo and/or in vitro testing requirements for approval of a multisource pharmaceutical product and marketing authorization.

equivalence test

A test that determines the equivalence between the multisource product and the comparator product using in vivo and/or in vitro approaches.

fixed-dose combination (FDC)

A combination of two or more active pharmaceutical ingredients in a fixed ratio of doses. This term is used generically to mean a particular combination of active pharmaceutical ingredients irrespective of the formulation or

brand. It may be administered as single-entity products given concurrently or as a finished pharmaceutical product.

fixed-dose combination finished pharmaceutical product (FDC-FPP)

A finished pharmaceutical product that contains two or more active pharmaceutical ingredients.

generic product

See *multisource pharmaceutical products.*

innovator pharmaceutical product

Generally, the innovator pharmaceutical product is that which was first authorized for marketing, on the basis of documentation of quality, safety and efficacy.

interchangeable pharmaceutical product

An interchangeable pharmaceutical product is one which is therapeutically equivalent to a comparator product and can be interchanged with the comparator in clinical practice.

in vitro equivalence test

An in vitro equivalence test is a dissolution test that includes comparison of the dissolution profile between the multisource product and the comparator product in three media: pH 1.2, pH 4.5 and pH 6.8.

in vitro quality control dissolution test

A dissolution test procedure identified in the pharmacopoeia, generally a one time point dissolution test for immediate-release products and a three or more time points dissolution test for modified release products.

multisource pharmaceutical products

Pharmaceutically equivalent or pharmaceutically alternative products that may or may not be therapeutically equivalent. Multisource pharmaceutical products that are therapeutically equivalent are interchangeable.

pharmaceutical alternatives

Products are pharmaceutical alternative(s) if they contain the same molar amount of the same active pharmaceutical moiety(s) but differ in dosage form (e.g. tablets versus capsules), and/or chemical form (e.g. different salts, different esters). Pharmaceutical alternatives deliver the same active moiety by the same route of administration but are otherwise not pharmaceutically equivalent. They may or may not be bioequivalent or therapeutically equivalent to the comparator product.

pharmaceutical equivalence

Products are pharmaceutical equivalents if they contain the same molar amount of the same active pharmaceutical ingredient(s) in the same dosage

form, if they meet comparable standards, and if they are intended to be administered by the same route. Pharmaceutical equivalence does not necessarily imply therapeutic equivalence, as differences in the excipients and/or the manufacturing process and some other variables can lead to differences in product performance.

therapeutic equivalence

Two pharmaceutical products are considered to be therapeutically equivalent if they are pharmaceutically equivalent or pharmaceutical alternatives and after administration in the same molar dose, their effects, with respect to both efficacy and safety, are essentially the same when administered to patients by the same route under the conditions specified in the labelling. This can be demonstrated by appropriate bioequivalence studies, such as pharmacokinetic, pharmacodynamic, clinical or in vitro studies.

3. Documentation of equivalence for marketing authorization

Multisource pharmaceutical products must be shown, either directly or indirectly, to be therapeutically equivalent to the comparator product if they are to be considered interchangeable. Suitable test methods to assess equivalence are:

— comparative pharmacokinetic studies in humans, in which the active pharmaceutical ingredient (API) and/or its metabolite(s) are measured as a function of time in an accessible biological fluid such as blood, plasma, serum or urine to obtain pharmacokinetic measures, such as AUC and C_{max} that are reflective of the systemic exposure;
— comparative pharmacodynamic studies in humans;
— comparative clinical trials; and
— comparative in vitro tests.

The applicability of each of these four methods is discussed below. Detailed information is provided on conducting an assessment of equivalence studies using pharmacokinetic measurements and in vitro methods, which are currently the methods most often used to document equivalence for most orally administered pharmaceutical products for systemic exposure.

Acceptance of any test procedure in the documentation of equivalence between two pharmaceutical products by a drug regulatory authority depends on many factors, including the characteristics of the API and the pharmaceutical product. Where an API produces measurable concentrations in an accessible biological fluid such as plasma, comparative pharmacokinetic studies can be performed. Where appropriate, in vitro testing and BCS-based biowaivers for immediate-release pharmaceutical products can assure

equivalence between the multisource product and the comparator product (see sections 5 and 9). Where an API does not produce measurable concentrations in an accessible biological fluid, comparative pharmacodynamic studies are an alternative method for documenting equivalence. In certain cases when it is not possible to determine the pharmacokinetic profile or to find suitable pharmacodynamic end-points, comparative clinical trials may be considered appropriate.

The criteria that indicate when equivalence studies are necessary are discussed in the following two sections of the guideline.

4. When equivalence studies are not necessary

The following types of multisource pharmaceutical product are considered to be equivalent without the need for further documentation:

(a) when the pharmaceutical product is to be administered parenterally (e.g. intravenously, subcutaneously or intramuscularly) as an aqueous solution containing the same API in the same molar concentration as the comparator product and the same or similar excipients in comparable concentrations as in the comparator product. Certain excipients (e.g. buffer, preservative and antioxidant) may be different provided it can be shown that the change(s) in these excipients would not affect the safety and/or efficacy of the pharmaceutical product;
(b) when pharmaceutically equivalent products are solutions for oral use (e.g. syrups, elixirs and tinctures), contain the API in the same molar concentration as the comparator product, and contain essentially the same excipients in comparable concentrations. Excipient(s) known to affect gastrointestinal (GI) transit, GI permeability and hence absorption or stability of the API in the GI tract should be critically reviewed;
(c) when pharmaceutically equivalent products are in the form of powders for reconstitution as a solution and the resultant solution meets either criterion (a) or criterion (b) above;
(d) when pharmaceutically equivalent products are gases;
(e) when pharmaceutically equivalent products are otic or ophthalmic products prepared as aqueous solutions and contain the same API(s) in the same molar concentration and essentially the same excipients in comparable concentrations. Certain excipients (e.g. preservative, buffer, substance to adjust tonicity or thickening agent) may be different provided their use is not expected to affect safety and/or efficacy of the product;
(f) when pharmaceutically equivalent products are topical products prepared as aqueous solutions and contain the same API(s) in the same molar concentration and essentially the same excipients in comparable concentrations;

(g) when pharmaceutically equivalent products are aqueous solutions for nebulizer inhalation products or nasal sprays, intended to be administered with essentially the same device, and contain the same API(s) in the same concentration and essentially the same excipients in comparable concentrations. The pharmaceutical product may include different excipients provided their use is not expected to affect safety and/or efficacy of the product.

For situations (b), (c), (e), (f) and (g) above, it is incumbent upon the applicant to demonstrate that the excipients in the pharmaceutically equivalent product are essentially the same and in concentrations comparable to those in the comparator product or, where applicable (i.e. (e) and (g)), that their use is not expected to affect the safety and/or efficacy of the product. In the event that this information cannot be provided by the applicant and the drug regulatory authority does not have access to the relevant data, it is incumbent upon the applicant to perform appropriate studies to demonstrate that differences in excipients or devices do not affect product performance.

5. When in vivo equivalence studies are necessary and types of study required

Except for the cases discussed in section 4, these guidelines recommend that documentation of equivalence with the comparator product be required by registration authorities for a multisource pharmaceutical product. Studies must be carried out using the product intended for marketing (see also section 6.5).

5.1 In vivo studies

For certain medicines and dosage forms, in vivo documentation of equivalence, through either a pharmacokinetic bioequivalence study, a comparative pharmacodynamic study or a comparative clinical trial, is regarded as especially important. In vivo documentation of equivalence is needed when there is a risk that possible differences in bioavailability may result in therapeutic inequivalence (*2*). Examples are listed below.

(a) Oral immediate-release pharmaceutical products with systemic action when one or more of the following criteria apply:

- critical use medicines;
- narrow therapeutic range (efficacy/safety margins), steep dose–response curve;
- documented evidence for bioavailability problems or bioinequivalence related to the API or its formulations (unrelated to dissolution problems);
- there is scientific evidence to suggest that polymorphs of API, the excipients and/or the pharmaceutical processes used in manufacturing could affect bioequivalence.

(b) Non-oral, non-parenteral pharmaceutical products designed to act systemically (such as transdermal patches, suppositories, nicotine chewing gum, testosterone gel and skin-inserted contraceptives).
(c) Modified-release pharmaceutical products designed to act systemically.[1]
(d) Fixed-combination products with systemic action, where at least one of the APIs requires an in vivo study (*3*).
(e) Non-solution pharmaceutical products, which are for non-systemic use (e.g. for oral, nasal, ocular, dermal, rectal or vaginal application) and are intended to act without systemic absorption. In these cases, the equivalence is established through, e.g. comparative clinical or pharmacodynamic, dermatopharmacokinetic studies and/or in vitro studies. In certain cases, measurement of the concentration of the API may still be required for safety reasons, i.e. in order to assess unintended systemic absorption.

5.2 In vitro studies

For certain medicines and dosage forms, in vitro documentation of equivalence may be appropriate. These studies are addressed in section 9.

6. Bioequivalence studies in humans

6.1 General considerations

6.1.1 *Provisions for studies in humans*

Pharmacokinetic, pharmacodynamic and clinical studies are all clinical trials and should therefore be carried out in accordance with the provisions and prerequisites for a clinical trial, as outlined in the WHO guidelines for good clinical practice (GCP) for trials on pharmaceutical products (*4*). Additional guidance for organizations performing in vivo bioequivalence studies is available from WHO (*5*).

All research involving human subjects should be conducted in accordance with the ethical principles contained in the current version of the Declaration of Helsinki, including respect for persons, beneficence ("maximize benefits and minimize harms and wrongs") and non-maleficence ("do no harm"). As defined by the current revision of the International Ethical Guidelines for Biomedical Research Involving Human Subjects issued by the Council for International Organizations of Medical Sciences (CIOMS), or laws and regulations of the country in which the research is conducted, whichever represents the greater protection for subjects.

[1] In some instances, the product marketing authorization may be based on in vitro-in vivo correlation (IVIVC) information and in vitro data of modified release drug products, provided it is not the first (original) approval of the modified-release dosage form.

6.1.2 *Justification of human bioequivalence studies*

Most pharmacokinetic and pharmacodynamic equivalence studies are non-therapeutic studies in which no direct clinical benefit accrues to the subject.

It is important for anyone preparing a trial of a medicinal product in humans that the specific aims, problems and risks or benefits of the proposed human study be thoroughly considered and that the chosen design be scientifically sound and ethically justified. It is assumed that people involved in the planning of a study are familiar with pharmacokinetic theories underlying bioavailability and bioequivalence studies. The overall design of the bioequivalence study should be based on the knowledge of the pharmacokinetics, pharmacodynamics and therapeutics of the API. Information about manufacturing procedures and data from tests performed on the product batch to be used in the study should establish that the product under investigation is of suitable quality.

6.1.3 *Selection of investigators*

The investigator(s) should have the appropriate expertise, qualifications and competence to undertake the proposed study. Prior to the trial, the investigator(s) and the sponsor should draw up an agreement on the protocol, monitoring, auditing, standard operating procedures (SOP) and the allocation of trial-related responsibilities. The identity and duties of the individuals responsible for the study and safety of the subjects participating in the study must be specified. The logistics and premises of the trial site should comply with requirements for the safe and efficient conduct of the trial.

6.1.4 *Study protocol*

A bioequivalence study should be carried out in accordance with a protocol agreed upon and signed by the investigator and the sponsor. The protocol and its attachments and/or appendices should state the aim of the study and the procedures to be used, the reasons for proposing the study to be undertaken in humans, the nature and degree of any known risks, assessment methodology, criteria for acceptance of bioequivalence, the groups from which it is proposed that trial subjects be selected and the means for ensuring that they are adequately informed before they give their consent. The investigator is responsible for ensuring that the protocol is strictly followed. Any change(s) required must be agreed on and signed by the investigator and sponsor, and appended as amendments, except when necessary to eliminate an apparent immediate hazard or danger to a trial subject.

The protocol and attachments/appendices should be scientifically and ethically appraised by one or, if required by local laws and regulations, more review bodies (e.g. institutional review board, peer review committee, ethics

committee, drug regulatory authority), constituted appropriately for these purposes and independent of the investigator(s) and sponsor.

A signed and dated study protocol together with the study report should be presented to the authorities in order to obtain the marketing authorization for the multisource product.

6.2 Study design

Bioequivalence studies are designed to compare the in vivo performance of a multisource product with that of a comparator product. Pharmacokinetic bioequivalence studies on products designed to deliver the API for systemic exposure serve two purposes:

- as a surrogate for clinical proof of equivalence; and
- they provide an in vivo measure of pharmaceutical quality.

The design of the study should minimize the variability that is not caused by formulation effects and eliminate bias as far as possible. Test conditions should reduce variability within and between subjects. In general, for a pharmacokinetic bioequivalence study involving a multisource and a comparator product, a two-period, single-dose, cross-over study in healthy volunteers will suffice. However, in certain circumstances, an alternative, well-established and statistically appropriate study design may be adopted.

A two-period, two-sequence, single-dose, cross-over, randomized design is the first choice for pharmacokinetic bioequivalence studies. Each subject is given the multisource and the comparator product in randomized order. An adequate wash-out period should follow the administration of each product. The interval (wash-out period) between doses of each formulation should be long enough to permit the elimination of essentially all of the previous dose from the body. The wash-out period should be the same for all subjects and should normally be more than five times the terminal half-life of the API. Consideration will need to be given to extending this period if active metabolites with longer half-lives are produced and under some other circumstances. For example, if the elimination rate of the product has high variability between subjects, the wash-out period may be longer to allow for the slower elimination in subjects with lower elimination rates. Just prior to administration of treatment during the second study period, blood samples are collected and assayed to determine the concentration of the API or metabolites. The minimum wash-out period should be at least seven days. The adequacy of the wash-out period can be estimated from the pre-dose concentration of the API and should be less than 5% of C_{max}.

It is currently not foreseen that there would be a need for blood samples to be collected for more than 72 hours.

6.2.1 *Alternative study designs for studies in patients*

For APIs that are very potent or too toxic to administer in the usual dose to healthy volunteers (e.g. because of the potential for serious adverse events, or the trial necessitates a high dose) it is recommended that the study be conducted using the API at a lower strength. However, if the pharmacokinetics are not proportional or if the solubility of the API is an issue, it will not be appropriate to extrapolate the bioequivalence results of the studies at lower strength to those at higher strengths. For APIs that show unacceptable pharmacological effects in volunteers, a multiple-dose, steady-state, cross-over study in patients or a parallel group design study in patients may be required. The alternative study design should be justified by the sponsor who should attempt to recruit patients whose disease process is stable for the duration of the pharmacokinetic bioequivalence study.

6.2.2 *Considerations for drugs with long elimination half-lives*

A single-dose cross-over pharmacokinetic bioequivalence study of an orally administered product with a long elimination half-life can be conducted provided an adequate wash-out period is used between admnistrations of the treatments. The interval between study days should be long enough to permit elimination of essentially all of the previous dose from the body. Ideally, the interval should not be less than five terminal elimination half-lives of the active compound or metabolite, if the latter is measured. Normally the interval between study days should not exceed 3–4 weeks. If the cross-over study is problematic, a pharmacokinetic bioequivalence study with a parallel design may be more appropriate.

For both cross-over and parallel-design studies, sample collection time should be adequate to ensure completion of gastrointestinal transit (approximately 2–3 days) of the pharmaceutical product and absorption of the API. Blood sampling up to 72 hours following administration should be carried out, unless shorter periods can be justified. The number of subjects should be derived from statistical calculations, but generally more subjects are needed for a parallel study design than for a cross-over study design.

6.2.3 *Considerations for multiple-dose studies*

In certain situations multiple-dose studies may be considered appropriate. Multiple-dose studies in patients are most useful in cases where the medicine being studied is considered to be too potent and/or too toxic to be administered to healthy volunteers, even in single doses (see also 6.2.1). In this case, a multiple-dose cross-over study in patients may be performed without interrupting therapy. Evaluation of such studies can be based on either pharmacokinetic or pharmacodynamic end-points, although it is likely that using pharmacodynamic end-points would require a larger number of patients than pharmacokinetic end-points.

The dosage regimen used in multiple-dose studies should follow the usual dosage recommendations.

Other situations in which multiple-dose studies may be appropriate are as follows:

— drugs that exhibit non-linear kinetics at steady state (e.g. saturable metabolism, active secretion);
— cases where the assay sensitivity is too low to adequately characterize the pharmacokinetic profile after a single dose;
— extended-release dosage forms with a tendency to accumulation (in addition to a single-dose study).

In steady-state studies the wash-out of the last dose of the previous treatment can overlap with the approach to steady state of the second treatment, provided the approach period is sufficiently long (at least three times the terminal half-life). Appropriate dosage administration and sampling should be carried out to document for the attainment of a steady state.

6.2.4 *Considerations for modified-release products*

Modified-release products include extended-release products and delayed-release products. Extended-release products are variously known as controlled-release, prolonged-release and sustained-release products.

To establish the bioequivalence of modified-release products, a single-dose, non-replicate cross-over, fasting study comparing the highest strength of the multisource and the comparator product should be performed. Single-dose studies are preferred to multiple-dose studies as single-dose studies are considered to provide more sensitive measurements of the release of API from the pharmaceutical product into the systemic circulation. Multiple-dose studies may need to be considered (in addition to a single-dose study) for extended-release dosage forms with a tendency to accumulate.

The comparator product in this study should be a pharmaceutically equivalent modified-release product. The pharmacokinetic bioequivalence criteria for modified-release products are basically the same as for conventional-release dosage forms.

Coadministration of food with oral pharmaceutical products may influence drug bioavailability and also in certain cases pharmacokinetic bioequivalence. In addition to physiological changes in the gastrointestinal tract, food can affect the release of the API from the formulation. A concern with modified-release products is the possibility that food may trigger a sudden and abrupt release of the API leading to “dose dumping”. This would most likely be manifested as a premature and abrupt rise in plasma concentration time profile. Therefore, a pharmacokinetic bioequivalence study under fed conditions is generally required for orally administered modified-release

pharmaceutical products. Omission of either the fed or fasting study should be justified by the applicant. A fed-state pharmacokinetic bioequivalence trial should be conducted after the administration of an appropriate standardized meal at a specified time (usually not more than 30 minutes) before taking the medicine (see also section 6.4). A high-fat meal often provides a maximal challenge to the robustness of release from the formulation with respect to prandial state. The composition of the meal should also take local diet and customs into consideration. The composition and caloric breakdown of the test meal should be provided in the study protocol and report.

6.3 Subjects

6.3.1 *Number of subjects*

The number of subjects required for a sound pharmacokinetic bioequivalence study is determined by:

- the error variance (coefficient of variation) associated with the primary parameters to be studied, as estimated from a pilot experiment, from previous studies or from published data;
- the significance level desired (5%);
- the statistical power desired;
- the mean deviation from the reference product compatible with bioequivalence and with safety and efficacy;
- the need for the 90% confidence interval around the geometric mean ratio to be within 80–125% bioequivalence limits for log transformed data.

The number of subjects to be recruited for the study should be estimated by considering the standards that must be met. It should be calculated by appropriate methods (see statistical analysis and acceptance criteria below). The number of subjects recruited should always be justified by the sample-size calculation provided in the study protocol. A minimum of 12 subjects is required.

6.3.2 *Drop-outs and withdrawals*

Sponsors should select a sufficient number of study subjects to allow for possible drop-outs or withdrawals. Because replacement of subjects during the study could complicate the statistical model and analysis, drop-outs generally should not be replaced. Reasons for withdrawal (e.g. adverse drug reaction or personal reasons) must be reported.

Sponsors who wish to replace drop-outs during the study or consider an add-on design should indicate this intention in the protocol. It is appropriate to recruit into the study more subjects than the sample-size calculation requires. These subjects are designated as extras. The protocol should state whether samples from these extra subjects will be assayed if not required for statistical analysis.

If the bioequivalence study was performed with the appropriate number of subjects but bioequivalence cannot be demonstrated because of a larger than expected random variation or a relative difference, an add-on subject study can be performed using not less than half the number of subjects in the initial study, provided this eventuality was anticipated and provided for in the study protocol. Combining data is acceptable only in the case that the same protocol was used and preparations from the same batches were used. Add-on designs must be carried out strictly according to the study protocol and SOPs, and must be given appropriate statistical treatment.

6.3.3 *Selection of subjects*

Pharmacokinetic bioequivalence studies should generally be performed with healthy volunteers. Clear criteria for inclusion and exclusion should be stated in the study protocol. If the pharmaceutical product is intended for use in both sexes, the sponsor may wish to include both males and females in the study. The risk to women will need to be considered on an individual basis, and if necessary, they should be warned of any possible dangers to the fetus if they should become pregnant. The investigators should ensure that female volunteers are not pregnant or likely to become pregnant during the study. Confirmation should be obtained by urine tests just before administration of the first and last doses of the product under study.

Generally subjects should be between the ages of 18 and 55 years, and their weight should be within the normal range according to accepted life tables. The subjects should have no history of alcohol or drug abuse problems and should preferably be non-smokers.

The volunteers should be screened for their suitability using standard laboratory tests, a medical history, and a physical examination. If necessary, special medical investigations may be carried out before and during studies depending on the pharmacology of the individual API being investigated, e.g. an electrocardiogram if the API has a cardiac effect. The ability of the volunteers to understand and comply with the study protocol has to be assessed. Subjects who are being or have previously been treated for any gastrointestinal problems, or convulsive, depressive or hepatic disorders, and in whom there is a risk of a recurrence during the study period, should be excluded.

If the aim of the bioequivalence study is to address specific questions (e.g. bioequivalence in a special population) the selection criteria should be adjusted accordingly.

6.3.4 *Monitoring the health of subjects during the study*

During the study the health of volunteers should be monitored so that onset of side-effects, toxicity, or any intercurrent disease may be recorded, and

appropriate measures taken. The incidence, severity, and duration of any adverse reactions and side-effects observed during the study must be reported. The probability that an adverse effect is drug-induced is to be judged by the investigator.

Health monitoring before, during and after the study must be carried out under the supervision of a qualified medical practitioner licensed in the jurisdiction in which the study is conducted.

6.3.5 *Considerations for genetic phenotyping*

Phenotyping for metabolizing activity can be of importance for studies with high-clearance drugs that are metabolized by enzymes that are subject to genetic polymorphism, e.g. propranolol. In such cases, slow metabolizers will have a higher bioavailability of the parent drug, while the bioavailability of possible active metabolites will be lower. Phenotyping of subjects can be considered for studies of drugs that show phenotype-linked metabolism and for which a parallel group design is to be used, because it allows fast and slow metabolizers to be evenly distributed in the two groups of subjects.

Phenotyping could also be important for safety reasons, determination of sampling times and wash-out periods in cross-over design studies.

6.4 Study standardization

Standardization of study conditions is important to minimize the magnitude of variability other than in the pharmaceutical products. Standardization should cover exercise; diet; fluid intake; posture; and the restriction of the intake of alcohol, caffeine, certain fruit juices and concomitant medicines for a specified time period before and during the study.

Volunteers should not take any other medicine, alcoholic beverages or over-the-counter (OTC) medicines and supplements for an appropriate interval either before or during the study. In the event of emergency, the use of any non-study medicine must be reported (dose and time of administration).

Physical activity and posture should be standardized as far as possible to limit their effects on gastrointestinal blood flow and motility. The same pattern of posture and activity should be maintained for each day of the study. The time of day at which the study drug is to be administered should be specified.

Medicines are usually given after an overnight fast of at least 10 hours, and participants are allowed free access to water. On the morning of the study no water is allowed during the hour prior to drug administration. The dose should be taken with a standard volume of water (usually 150–250 ml). Two hours after drug administration water is again permitted *ad libitum*. A standard meal is usually provided four hours after drug administration.

All meals should be standardized and the composition stated in the study protocol and report.

Some medicines are normally given with food to reduce gastrointestinal side-effects; in certain cases coadministration with food increases bioavailability of orally administered preparations. If the labelling states that the pharmaceutical product should be taken with food then a fed study should be used to assess bioequivalence. Fed state studies are also required in bioequivalence studies of modified release formulations. In these cases the objective is to select a meal that will challenge the robustness of the new multisource formulation to prandial effects on bioavailability (see 6.2.4). The test meal selected should take account of local custom and diet and should be consumed within 20 minutes. The product should be administered according to the protocol and within 30 minutes after the meal has been eaten.

6. 5 Investigational product

6.5.1 *Multisource pharmaceutical product*

The multisource pharmaceutical product used in the bioequivalence studies for registration purposes should be identical to the projected commercial pharmaceutical product. Therefore, not only the composition and quality characteristics (including stability), but also the manufacturing methods (including equipment and procedures) should be the same as those to be used in the future routine production runs. Test products must be manufactured under GMP regulations. Batch-control results of the multisource product, and the lot numbers and expiry dates of both multisource and comparator products should be stated.

Samples should ideally be taken from batches of industrial scale. When this is not feasible pilot or small-scale production batches may be used, provided that they are not smaller than 10% of expected full production batches, or 100 000 units, whichever is higher (unless otherwise justified), and are produced with the similar equipment, machinery and process as that planned for commercial production batches. If the product is subjected to further scale-up, this should be properly validated.

It is recommended that potency and in vitro dissolution characteristics of the multisource and the comparator pharmaceutical products be ascertained prior to performance of an equivalence study. Content of the API(s) of the comparator product should be close to the label claim, and the difference between two products should preferably be not more than +/– 5%.

6.5.2 *Choice of comparator product*

The innovator pharmaceutical product is usually the most logical comparator product for a multisource pharmaceutical product because its quality,

safety and efficacy should have been well assessed and documented in premarketing studies and postmarketing monitoring schemes.

For some pharmaceutical products however, an innovator product cannot be identified; and in some cases no innovator product is available on the market. A generic pharmaceutical product should not be used as a comparator as long as an innovator pharmaceutical product is available, because this could lead to progressively less reliable similarity of future multisource products and potentially to a lack of interchangeability with the innovator.

The selection of the comparator product is usually made at the national level by the drug regulatory authority. In principle, a national drug regulatory authority has the following options which are listed *in order of preference*:

(i) to choose the innovator product for which quality, safety and efficacy has been established if this product has been granted a national marketing authorization ("*nationally authorized innovator*"); or
(ii) to choose the WHO comparator product (for which marketing authorization has been granted, on the basis of quality, safety and efficacy) ("*WHO comparator product*"). The primary manufacturing site is indicated in the WHO comparator list (*6*), and the comparator is to be purchased in that country, or;
(iii) to choose the innovator product for which a marketing authorization has been granted in a well-regulated country (ICH or associated country) on the basis of quality, safety and efficacy ("*ICH et al. innovator*") and which is to be purchased from that market; or
(iv) in the case that no innovator product can be identified – within the context of (i)–(iii) above, the choice of the comparator must be made carefully and must be comprehensively justified by the applicant. The most important selection criteria in order of preference are:

— approval in ICH- and associated countries;
— "prequalified" by WHO;
— extensive documented use in clinical trials reported in peer-reviewed scientific journals; and
— long and unproblematic period of postmarket surveillance ("*well selected comparator*"). Additionally, "well selected comparators" must conform to compendial quality standards, where these exist.

Note: a product that has been approved based on comparison with a non-domestic comparator product may or may not be interchangeable with currently marketed domestic products.

In the context of regional harmonization efforts, it may be advantageous to establish a regional comparator product, for which quality, safety and efficacy has been established, in order to increase access to medicines.

The choice of comparator product should be justified by the applicant. The country of origin of the comparator product should be reported together with lot number and expiry date.

6.6 Study conduct

6.6.1 *Selection of dose*

In bioequivalence studies the molar equivalent dose of multisource and comparator product must be used.

Generally the marketed strength with the greatest sensitivity to bioequivalence assessment should be administered as a single unit. This will usually be the highest marketed strength. A higher dose (i.e. more than one dosage unit) may be employed when analytical difficulties exist. In this case the total single dose should not exceed the maximal daily dose of the dosage regimen. Alternatively, the application of area under the curve (AUC) truncated to 3 × median t_{max} of the comparator formulation would avoid problems of lack of assay sensitivity in many cases. In certain cases a study performed with a lower strength can be considered acceptable if this lower strength is chosen for reasons of safety.

6.6.2 *Sampling times*

Blood samples should be taken at a frequency sufficient for assessing C_{max}, AUC and other parameters. Sampling points should include a pre-dose sample, at least 1–2 points before C_{max}, 2 points around C_{max} and 3–4 points during the elimination phase. Consequently at least seven sampling points will be necessary for estimation of the required pharmacokinetic parameters. For most medicines the number of samples necessary will be higher to compensate for between-subject differences in absorption and elimination rate and thus enable accurate determination of the maximum concentration of the API in the blood (C_{max}) and terminal elimination rate constant in all subjects. Generally, sampling should continue for long enough to ensure that 80% of the AUC ($0 \rightarrow \text{infinity}$) can be accrued, but it is not necessary to sample for more than 72 hours. The exact duration of sample collection depends on the nature of the API and the input function from the administered dosage form (see also 6.11.4).

6.6.3 *Sample fluids and their collection*

Under normal circumstances blood should be the biological fluid sampled to measure the concentrations of the API. In most cases the API or its metabolites are measured in serum or plasma. If the API is excreted predominantly unchanged in the urine, urine can be sampled. The volume of each sample must be measured at the study centre, where possible immediately after collection, and included in the report. The number of samples should be suf-

ficient to allow the estimation of pharmacokinetic parameters. However, in most cases the exclusive use of urine excretion data should be avoided as this does not allow estimation of the t_{max} and the maximum concentration.

Blood samples should be processed and stored under conditions that have been shown not to cause degradation of the analytes. This can be proven by analysing duplicate quality control samples during the analytical period. Quality control samples must be prepared in the fluid of interest (e.g. plasma), including concentrations at least at the low, middle and high segments of the calibration range. The quality control samples must be stored with the study samples and analysed with each set of study samples for each analytical run.

The sample collection methodology must be specified in the study protocol.

6.6.4 *Parameters to be assessed*

In bioavailability studies, the shape of and the area under the plasma concentration versus time curves are mostly used to assess rate (C_{max}, t_{max}) and extent (AUC) of absorption. Sampling points or periods should be chosen such that the concentration versus time profile is adequately defined to allow calculation of relevant parameters. For single-dose studies, the following parameters should be measured or calculated:

- Area under the plasma/serum/blood concentration–time curve from time zero to time *t* ($AUC_{0–t}$), where *t* is the last sampling time point with a measurable concentration of the API in the individual formulation tested. The method of calculating AUC-values should be specified. In general AUC should be calculated using the linear/log trapezoidal integration method. The exclusive use of compartmental-based parameters is not recommended.
- C_{max} is the maximum or peak concentration observed representing peak exposure of API (or metabolite) in plasma, serum or whole blood.

$AUC_{0–t}$ and C_{max} are considered to be the most relevant parameters for assessment of bioequivalence. In addition it is recommended that the following parameters be estimated:

- area under the plasma/serum/blood concentration–time curve from time zero to time infinity ($AUC_{0-\infty}$) representing total exposure, where $AUC_{0-\infty} = AUC_{0–t} + C_{last}/ß$; C_{last} is the last measurable drug concentration and ß is the terminal or elimination rate constant calculated according to an appropriate method;
- t_{max} is the time after administration of the drug at which C_{max} is observed.

For additional information the elimination parameters can be calculated:

- $T_{1/2}$ is the plasma (serum, whole blood) half-life.

For steady-state studies the following parameters can be calculated:

- AUCτ is AUC over one dosing interval (τ) at steady-state;
- C_{max};
- C_{min} is concentration at the end of a dosing interval;
- peak trough fluctuation is percentage difference between C_{max} and C_{min}.

When urine samples are used, cumulative urinary recovery (Ae) and maximum urinary excretion rate are employed instead of AUC and C_{max}.

6.6.5 *Studies of metabolites*

Generally, evaluation of pharmacokinetic bioequivalence will be based upon the measured concentrations of the parent drug released from the dosage form rather than the metabolite. The concentration–time profile of the parent drug is more sensitive to changes in formulation performance than a metabolite, which is more reflective of metabolite formation, distribution and elimination. It is important to state *a priori* in the study protocol which chemical entities (pro-drug, drug (API) or metabolite) will be analysed in the samples.

In some situations it may be necessary to measure metabolite concentrations rather than those of the parent drug:

- The measurement of concentrations of therapeutically active metabolite is acceptable if the substance studied is a pro-drug.
- Measurement of a metabolite may be preferred when concentrations of the parent drug are too low to allow reliable analytical measurement in blood, plasma or serum for an adequate length of time, or when the parent compound is unstable in the biological matrix.

It is important to note that measurement of one analyte, API or metabolite, carries the risk of making a type-I error (the consumer risk) to remain at the 5% level. However, if more than one of several analytes is selected retrospectively as the bioequivalence determinant, then both the consumer and producer risks change (*7*).

When measuring the active metabolites wash-out period and sampling times may need to be adjusted to enable adequate characterization of the pharmacokinetic profile of the metabolite.

6.6.6 *Measurement of individual enantiomers*

A non-stereoselective assay is currently acceptable for most pharmacokinetic bioequivalence studies. When the enantiomers have very different pharmacological or metabolic profiles, assays that distinguish between the enantiomers of a chiral API may be appropriate. Stereoselective assay is also preferred when systemic availability of different enantiomers is demonstrated to be non-linear.

6.6.7 *Use of fed-state studies in bioequivalence determination*

6.6.7.1 *Immediate-release formulations*

Fasted-state studies are generally preferred. When the product is known to cause gastrointestinal disturbances if given to subjects in the fasted state, or if labelling restricts administration to subjects in the fed state, then the fed-state pharmacokinetic bioequivalence study becomes the preferred approach. The composition of the meal may depend on local diet and customs (see also section 6.4).

6.6.7.2 *Modified-release formulations*

Food-effect studies are necessary for all multisource modified-release formulations to ensure the absence of "dose dumping". The latter signals a formulation failure such that the dose is released all at once rather than over an extended period of time. This results in a premature and abrupt rise in the plasma concentration time profile. A high-fat meal often provides a maximal challenge to the robustness of release from the formulation with respect to prandial state. The composition of the meal should also take local diet and custom into consideration (see also section 6.2.4).

6.7 Quantification of active pharmaceutical ingredient

All analytical test methods used to determine the active compound and/or its biotransformation product in the biological fluid must be well-characterized, fully validated and documented. The objective of the validation is to demonstrate that a particular method used for quantitative measurement of analytes in a given biological matrix, such as blood, plasma, serum or urine, is reliable and reproducible for the intended use.

Applicable principles of GLP should be followed in the conduct of chemical analysis (*8*). Bioanalytical methods should meet the requirements of specificity, sensitivity, accuracy, precision and reproducibility. Knowledge of the stability of the API and/or its biotransformation product in the sample material is a prerequisite for obtaining reliable results.

The Bioanalytical Method Validation Conference held in 2000 made several recommendations for the conduct of analyses of biological samples in a pharmacokinetic study (*9*). Some of the important recommendations are:

- Validation comprises pre-study and within-study phases. During the pre-study phase stability of the stock solution and spiked samples in the biological matrix, specificity, sensitivity, accuracy, precision and reproducibility should be provided. Within-study validation proves the stability of samples collected during a clinical trial under storage conditions and confirms the accuracy and precision of the determinations.
- Validation must cover the intended use of the assay.

- The calibration range must be appropriate to the study samples. A calibration curve should be prepared in the same biological matrix as will be used for the samples in the intended study by spiking the matrix with known concentrations of the analyte. A calibration curve should consist of a blank sample, a zero sample, and 6–8 non-zero samples covering the expected range. Concentrations of standards should be chosen on the basis of the concentration range expected in a particular study.
- If an assay is to be used at different sites, it must be validated at each site, and cross-site comparability established.
- An assay which is not in regular use requires sufficient revalidation to show that it still performs according to the original validated test procedures. The revalidation study must be documented, usually as an appendix to the study report.
- Within a study, the use of two or more methods to assay samples in the same matrix over a similar calibration range is strongly discouraged.
- If different studies are to be compared and the samples from the different studies have been assayed by different methods, and the methods cover a similar concentration range and the same matrix, then the methods should be cross-validated.
- Spiked quality control samples at a minimum of three different concentrations in duplicate should be used for accepting or rejecting the analytical run.
- All the samples from one subject (all periods) should be analysed in the same analytical run, if possible.

Validation procedures, methodology and acceptance criteria should be specified in the analytical protocol, and/or the SOP. All experiments used to support claims or draw conclusions about the validity of the method should be described in a report (method validation report). Any modification of the method during the analysis of study samples will require adequate revalidation. The results of study sample determination should be given in the analytical report together with calibration and quality control sample results, repeat analyses (if any), and a representative number of sample chromatograms.

6.8 Statistical analysis

The primary concern in bioequivalence assessment is to limit the risk of a false declaration of equivalence. Statistical analysis of the bioequivalence trial should demonstrate that a clinically significant difference in bioavailability between the multisource product and the comparator product is unlikely. The statistical procedures should be specified in the protocol before the data collection starts.

The statistical method for testing pharmacokinetic bioequivalence is based upon the determination of the 90% confidence interval around the ratio

of the log-transformed population means (multisource/comparator) for the pharmacokinetic parameters under consideration and by carrying out two one-sided tests at the 5% level of significance (*10*). To establish pharmacokinetic bioequivalence, the calculated confidence interval should fall within a preset bioequivalence limit. The procedures should lead to a decision scheme which is symmetrical with respect to the two formulations (i.e. leading to the same decision whether the multisource formulation is compared to the comparator product or the comparator product to the multisource formulation).

All concentration-dependent pharmacokinetic parameters (e.g. AUC and C_{max}) should be log-transformed using either common logarithms to the base 10 or natural logarithms. The choice of common or natural logs should be consistent and should be stated in the study report.

Logarithmically transformed, concentration-dependent pharmacokinetic parameters should be analysed using analysis of variance (ANOVA). Usually the ANOVA model includes the formulation, period, sequence or carry-over and subject factors.

Parametric methods, i.e. those based on normal distribution theory, are recommended for the analysis of log-transformed bioequivalence measures. The general approach is to construct a 90% confidence interval for the quantity $\mu T - \mu R$ and to reach a conclusion of pharmacokinetic equivalence if this confidence interval is within the stated limits. The nature of parametric confidence intervals means that this is equivalent to carrying out two one-sided tests of the hypothesis at the 5% level of significance (*10*, *11*). The antilogs of the confidence limits obtained constitute the 90% confidence interval for the ratio of the geometric means between the multisource and comparator products.

The same procedure should be used for analysing parameters from steady-state trials or cumulative urinary recovery, if required.

For t_{max} descriptive statistics should be given. If t_{max} is to be subjected to a statistical analysis this should be based on non-parametric methods and should be applied to untransformed data. A sufficient number of samples around predicted maximal concentrations should have been taken to improve the accuracy of the t_{max} estimate. For parameters describing the elimination phase ($T_{1/2}$) only descriptive statistics should be given.

Methods for identifying and handling of possible outlier data should be specified in the protocol. Medical or pharmacokinetic explanations for such observations should be sought and discussed. As outliers may be indicative of product failure, post hoc deletion of outlier values is generally discouraged. An approach to dealing with data containing outliers is to apply distribution-free (non-parametric), statistical methods (*12*).

If the distribution of log-transformed data is not normal, non-parametric statistical methods can be considered. The justification of the intent to use non-parametric statistical methods should be included a priori in the protocol.

6.9 Acceptance ranges

Area under the curve-ratio

The 90% confidence interval for this measure of relative bioavailability should lie within a bioequivalence range of 0.80–1.25. If the therapeutic range is particularly narrow, the acceptance range may need to be reduced based on clinical justification. A larger acceptance range may be acceptable in exceptional cases if justified clinically.

C_{max}-ratio

In general the acceptance limit 0.80–1.25 should be applied to the C_{max}-ratio. However, this measure of relative bioavailability is inherently more variable than, for example, the AUC-ratio, and in certain cases a wider acceptance range (e.g. 0.75–1.33) may be acceptable. The range used must be defined prospectively and should be justified, taking into account safety and efficacy considerations. In exceptional cases, a simple requirement for the point estimate to fall within bioequivalence limits of 0.80–1.25 may be acceptable with appropriate justification in terms of safety and efficacy.

t_{max}-difference

Statistical evaluation of t_{max} makes sense only if there is a clinically relevant claim for rapid onset of action or concerns about adverse effects. The non-parametric 90% confidence interval for this measure of relative bioavailability should lie within a clinically relevant range.

For other pharmacokinetic parameters the same considerations as outlined above apply.

6.10 Reporting of results

The report of a bioequivalence study should give the complete documentation of its protocol, conduct and evaluation complying with good clinical practice rules (*4*). The relevant ICH guideline (*13*) can be used in the preparation of the study report. The responsible investigator(s) should sign their respective sections of the report. Names and affiliations of the responsible investigator(s), site of the study and period of its execution should be stated.

The names and batch numbers of the pharmaceutical products used in the study as well as the composition(s) of the tests product(s) should be given. Results of in vitro dissolution tests should be provided. In addition the ap-

plicant should submit a signed statement confirming that the test product is identical to the pharmaceutical product which is submitted for registration.

The bioanalytical validation report (see section 6.7) should be attached. The bioanalytical report should include the data on calibrations and quality control samples. A representative number of chromatograms or other raw data should be included covering the whole calibration range, quality control samples and specimens from the clinical trial.

All results should be presented clearly. All concentrations measured in each subject and the sampling time should be tabulated for each formulation. Tabulated results showing API concentration analyses according to analytical run (including runs excluded from further calculations, including all calibration standards and quality control samples from the respective run) should also be presented. The tabulated results should present the date of run, subject, study period, product administered (multisource or comparator) and time elapsed between drug application and blood sampling in a clear format. The procedure for calculating the parameters used (e.g. AUC) from the raw data should be stated. Any deletion of data should be justified. If results are calculated using pharmacokinetic models, the model and the computing procedure used should be justified. Individual blood concentration/time curves should be plotted on a linear/linear and log/linear scale. All individual data and results should be given, including information on those subjects who dropped out. The drop-outs and/or withdrawn subjects should be reported and accounted for.

Results of all measured and calculated pharmacokinetic parameters should be tabulated for each subject–formulation combination together with descriptive statistics. The statistical report should be sufficiently detailed to enable the statistical analyses to be repeated if necessary. If the statistical methods applied deviate from those specified in the trial protocol, the reasons for the deviations should be stated.

6.11 Special considerations

6.11.1 *Fixed-dose combination products*

If the pharmacokinetic bioequivalence of fixed-dose combination (FDC) products is assessed by in vivo studies the study design should follow the same general principles as described in previous sections. The multisource FDC product should be compared with the pharmaceutically equivalent comparator FDC product. In certain cases (e.g. when no comparator FDC product is available on the market) separate products administered in free combination can be used as a comparator (*3*). Sampling times should be chosen to enable the pharmacokinetic parameters of all APIs to be adequately assessed. The bioanalytical method should be validated on respect

to all compounds measured. Statistical analyses should be performed with pharmacokinetic data collected on all active ingredients; the 90% confidence intervals of test/comparator ratio of all active ingredients should be within acceptance limits.

6.11.2 *Clinically important variations in bioavailability*

Innovators should make all efforts to provide formulations with good bioavailability characteristics. If a better formulation is developed over time by the innovator, this should then serve as the comparator product. A new formulation with a bioavailability outside the acceptance range for an existing pharmaceutical product is not interchangeable by definition. Adjusting the strength to compensate with regard to sub- or suprabioavailability in comparison with the comparator product is beyond the scope of this document, as the prerequisite for pharmaceutical equivalence is not fullfilled.

6.11.3 *"Highly variable drugs"*

A "highly variable drug" has been defined as an API with a within-subject variability of ≥ 30% in terms of the ANOVA-CV (*14*). Moreover "highly variable drugs" are generally safe drugs with shallow dose–response curves. Proving the bioequivalence of medicinal products containing "highly variable drugs" is problematic because the higher the ANOVA-CV, the wider the 90% confidence interval. Thus large numbers of subjects must be enrolled in studies involving highly variable drugs to achieve adequate statistical power. The following approaches to this problem are currently being applied in different drug regulatory jurisdictions.

- Some regulatory authorities permit the use of broadened bioequivalence limits provided there is adequate justification (*15*) for example, the regulatory agency could broaden the bioequivalence limits from 0.8–1.25 to 0.75–1.33 taking into consideration the therapeutic category of the drug.
- Some regulatory authorities permit the use of scaling to broaden the bioequivalence limits. In a two-period design, the limits are scaled to the residual standard deviation, or in a replicate design, to the within-subject standard deviation of the comparator formulation (*16–18*).
- Some regulatory authorities allow the following acceptance criteria: "Products are considered to be bioequivalent, if the 90% confidence interval of average ratios of AUC and C_{max} between test and reference products is within the acceptable range of 0.8–1.25 (*19*); if the confidence interval is not in the above range, test products are accepted as bioequivalent, if the following three conditions are satisfied:
  - — the total sample size of the initial bioequivalence study is not less than 20 (n = 10/group) or pooled sample size of the initial and add-on subject studies is not less than 30;

— the ratio of geometric least squares means of AUC and C_{max} between the multisource and comparator product are between 0.9 and 1.11; and
— dissolution rates of test and reference products are evaluated to be equivalent under all dissolution testing conditions (*19*).

This rule cannot be applied to slowly dissolving products from which less than 80% of a drug dissolves within the final testing time (2 hr in pH 1.2 medium and 6 hr in others) under any conditions of the dissolution tests described (*19*).

- Some regulatory authorities do not allow for any adjustments (*20*).

The regulatory authority of the country should adopt one of these approaches prospectively to regulate the market authorization of highly variable pharmaceutical products.

6.11.4 *Application of truncated area under the curve in bioequivalence determination*

In bioavailability studies it is generally recommended that plasma concentrations should be followed for at least three half-lives post-dose. Potent drugs found at low concentrations in plasma usually require sophisticated and expensive equipment to enable the API to be measured in the terminal portions of the plasma concentration versus time curve. When considering the bioequivalence of immediate-release formulations for systemic delivery, the most important portion of the plasma concentration versus time curve is until the absorption phase is complete. On the other hand, the disposition phase does not illustrate formulation differences between the multisource product and comparator product in the bioequivalence decision-making process (*21*, *22*). Gaureault examined the use of partial (truncated) AUC using Monte Carlo simulations and found a high degree of concordance between the bioequivalence decision based on the partial area truncated to four times t_{max} and the area extrapolated to infinity. The evidence suggests that for immediate-release formulations it is unnecessary to take blood samples beyond four times t_{max} (*23*). There are two important advantages to the use of truncated areas:

- more blood samples can be clustered around t_{max} to give greater precision in the estimation of both t_{max} and C_{max};
- high assay sensitivity to define the disposition phase is not required.

The applicability of the truncated AUC approach merits particular consideration in the following cases:

— where low concentrations occur in the terminal portion of the plasma concentration versus time curve, which may not be quantifiable by means of an adequately validated, sensitive analytical method; and
— for products of APIs with long half-lives.

7. Pharmacodynamic studies

Studies in healthy volunteers or patients using pharmacodynamic measurements may be used for establishing equivalence between two pharmaceutical products. Pharmacodynamic studies are not recommended for orally administered pharmaceutical products for systemic action when the API is absorbed into the systemic circulation and a pharmacokinetic approach can be used to assess systemic exposure and establish bioequivalence. This is because variability in pharmacodynamic measures is always greater than that in pharmacokinetic measures. In addition pharmacodynamic measures are often subject to significant placebo effects which add to the variability and complicate experimental design. The result is that often huge numbers of patients would have to be enrolled in pharmacodynamic studies to achieve adequate statistical power. Pharmacodynamic bioequivalence studies may become necessary if quantitative analysis of the API and/or metabolite(s) in plasma or urine cannot be made with sufficient accuracy and sensitivity (see section 6.11.4 on truncated areas). Furthermore, pharmacodynamic bioequivalence studies in humans are required if measurements of API concentrations cannot be used as surrogate end-points for the demonstration of efficacy and safety of the particular pharmaceutical product. In certain treatment categories, such as pharmaceutical products designed to act locally, there is no realistic alternative to performing pharmacodynamic bioequivalence studies. Pharmacodynamic bioequivalence studies may be therefore appropriate for pharmaceutical products administered topically and for inhalation dosage forms.

If pharmacodynamic studies are to be used they must be performed as rigorously as bioequivalence studies, and the principles of GCP must be followed *(4)*.

The following requirements must be recognized when planning, conducting and assessing the results of a study intended to demonstrate equivalence by measuring pharmacodynamic drug responses.

- The response measured should be a pharmacological or therapeutic effect which is relevant to the claims of efficacy and/or safety.
- The methodology must be validated for precision, accuracy, reproducibility and specificity.
- Neither the test product nor the comparator product should produce a maximal response in the course of the study, since it may be impossible to detect differences between formulations given in doses which give maximum or near-maximum effects. Investigation of dose–response relationships may be a necessary part of the design.
- The response should be measured quantitatively, preferably under double-blind conditions, and be recordable by an instrument that produces and records the results of repeated measurements to provide a record

of the pharmacodynamic events, which are substitutes for measurements of plasma concentrations. Where such measurements are not possible, recordings on visual analogue scales may be used. Where the data are limited to qualitative (categorized) measurements appropriate special statistical analysis will be required.

- Participants should be screened prior to the study to exclude non-responders. The criteria by which responders are distinguished from non-responders must be stated in the protocol.
- In instances where an important placebo effect can occur, comparison between pharmaceutical products can only be made by a priori consideration of the potential placebo effect in the study design. This may be achieved by adding a third phase with placebo treatment in the design of the study.
- The underlying pathology and natural history of the condition must be considered in the study design. There should be knowledge of the reproducibility of baseline conditions.
- A cross-over design can be used. Where this is not appropriate a parallel group study design should be chosen.

The selection basis for the multisource and comparator products should be the same as described in section 6.5.

In studies in which continuous variables can be recorded, the time-course of the intensity of the drug action can be described in the same way as in a study in which plasma concentrations are measured, and parameters can be derived which describe the area under the effect–time curve, the maximum response and the time at which the maximum response occurred.

The statistical considerations for the assessment of the outcome of the study are in principle the same as those outlined for the analysis of pharmacokinetic bioequivalence studies. However, a correction for the potential non-linearity of the relationship between the dose and the area under the effect–time curve should be performed on the basis of the outcome of the dose-ranging study. However, it should be noted that the acceptance range as applied for bioequivalence assessment may not be appropriate and should be justified on a case-by-case basis and defined in the protocol.

8. Clinical trials

In some instances (see example (e) in section 5.1, "In vivo studies") plasma concentration time–profile data are not suitable for assessing equivalence between two formulations. Although in some cases pharmacodynamic bioequivalence studies can be an appropriate tool for establishing equivalence, in others, this type of study cannot be performed because of a lack of meaningful pharmacodynamic parameters which can be measured; a comparative clinical trial then has to be performed to demonstrate equivalence between

two formulations. In cases when equivalence can be assessed by a pharmacokinetic bioequivalence study, this is preferred, because the analogous clinical trial would be less sensitive. Huge numbers of subjects are required to achieve adequate statistical power. For example, it has been calculated that 8600 patients would be required to give adequate statistical power to detect a 20% improvement in response to the study drug compared with placebo (*24*). Similarly it was calculated that 2600 myocardial infarct patients would be required to show a 16% reduction in risk. A comparison of two formulations of the same API based on such end-points would require even greater numbers of subjects (*25*).

If a clinical bioequivalence study is considered as being undertaken to prove equivalence, the same statistical principles apply as for the pharmacokinetic bioequivalence studies. The number of patients to be included in the study will depend on the variability of the target parameters and the acceptance range, and is usually much higher than the number of subjects needed in pharmacokinetic bioequivalence studies.

The methodology for establishing equivalence between pharmaceutical products by means of a clinical trial in patients with a therapeutic end-point has not yet evolved as extensively as for pharmacokinetic bioequivalence trials. However, some important items which need to be defined in the protocol can be identified.

- The target parameters that usually represent relevant clinical end-points from which the onset, if applicable and relevant, and intensity of the response are to be derived.
- The size of the acceptance range has to be defined case by case, taking into consideration the specific clinical conditions. These include, among others, the natural course of the disease, the efficacy of available treatments and the chosen target parameter. In contrast to pharmacokinetic bioequivalence studies (where a conventional acceptance range is applied) the size of the acceptance range in clinical trials should be set individually according to the therapeutic class and indication(s).
- The presently used statistical method is the confidence interval approach. The main concern is to rule out the possibility that the test product is inferior to the comparator pharmaceutical product by more than the specified amount. Hence a one-sided confidence interval (for efficacy and/or safety) may be appropriate. The confidence intervals can be derived from either parametric or nonparametric methods.
- Where appropriate a placebo leg should be included in the design.
- In some cases it is relevant to include safety end-points in the final comparative assessments.
- The selection basis for the multisource and comparator products should be the same as described in section 6.5.

9. In vitro testing

Over the past three decades, dissolution testing has evolved into a powerful tool for characterizing the quality of oral pharmaceutical products. The dissolution test, at first exclusively a quality control test, is now emerging as a surrogate equivalence test for certain categories of orally administered pharmaceutical products. For these products (typically solid oral dosage forms containing APIs with suitable properties) a comparative in vitro dissolution profile similarity can be used to document equivalence of a multisource with a comparator product (see section 6.5 for selection of comparator products).

It should be noted, that although the dissolution tests recommended in *The International Pharmacopoeia* (*26*) for quality control have been designed to be compatible with the biowaiver dissolution tests, they may not fulfil all the requirements for evaluating equivalence of multisource products with comparator products. Dissolution tests for quality control purposes in other pharmacopoeia do not generally correspond to the test conditions required for evaluating bioequivalence of multisource products and should not be applied for this purpose.

9.1 In vitro testing and the Biopharmaceutics Classification System

9.1.1 *Biopharmaceutics Classification System*

The Biopharmaceutics Classification System (BCS) is based on aqueous solubility and intestinal permeability of the drug substance. It classifies the API into one of four classes:

— Class 1: high solubility, high permeability
— Class 2: low solubility, high permeability
— Class 3: high solubility, low permeability
— Class 4: low solubility, low permeability

Combining the dissolution of the pharmaceutical product with these two properties of the API, takes the three major factors that govern the rate and extent of drug absorption from immediate-release solid dosage forms into account (*27*). On the basis of their dissolution properties, immediate-release dosage forms can be categorized as having "very rapid", "rapid", or "not rapid" dissolution characteristics.

On the basis of solubility and permeability of the API, and dissolution characteristics of the dosage form, the BCS approach provides an opportunity to waive in vivo pharmacokinetic bioequivalence testing for certain categories of immediate-release drug products (*28*). Oral drug products *not* eligible for a so-called "biowaiver" based on the BCS approach are described under section 5.1 (a).

9.1.1.1 *High solubility*

An API is considered highly soluble when the highest dose recommended by WHO (if the API appears on the *WHO Model List of Essential Medicines*) or highest dose strength available on the market as a oral solid dosage form (if the API does not appear on the *WHO Model List of Essential Medicines*) is soluble in 250 ml or less of aqueous media over the pH range of 1.2–6.8. The pH-solubility profile of the API should be determined at 37 ± 1 °C in aqueous media. A minimum of three replicate determinations of solubility at each pH condition is recommended. Initial recommendations in the BCS Guidance (*28*) suggested that the solubility should be measured over a pH range of 1.2–7.5. But successive scientific discussions and publications suggest that a pH range of 1.2–6.8 is more appropriate (*29*).

9.1.1.2 *High permeability*

An API is considered highly permeable when the extent of absorption in humans is 85% or more based on a mass balance determination or in comparison with an intravenous comparator dose. The initial recommendation in the BCS Guidance (*28*) suggested an absorption value of ≥ 90% as a prerequisite for classification as highly permeable. However, successive scientific discussions and scientific publications have suggested relaxing the criterion to 85% absorption for classifying an API as highly permeable (*29*). An acceptable alternative test method for permeability determination of the API could be in vivo intestinal perfusion in humans (i).

When this method is used for permeation studies, suitability of the methodology should be demonstrated, including determination of permeability relative to that of a reference compound whose fraction of dose absorbed has been documented to be at least 85%, as well as use of a negative control.

Supportive data can be provided by the following additional test methods:

(ii) in vivo or in situ intestinal perfusion using animal models; or
(iii) in vitro permeation across a monolayer of cultured epithelial cells (e.g. Caco-2) using a method validated using APIs with known permeabilities,

although data from neither method (ii) nor (iii) would be considered acceptable on a stand-alone basis. In these experiments high permeability is assessed with respect to the high permeability of a series of reference compounds with documented permeabilities and fraction absorbed values, including some for which fraction of dose absorbed is at least 85% (*29*).

9.1.2 *Determination of dissolution characteristics of multisource products in consideration of a biowaiver based on the Biopharmaceutics Classification System*

For exemption from an in vivo pharmacokinetic bioequivalence study, an immediate-release multisource product should exhibit very rapid or rapid

in vitro dissolution characteristics (see below), depending on the BCS properties of the API. In vitro data should also demonstrate the similarity of dissolution profiles between the test and comparator products.

9.1.2.1 *Very rapidly dissolving*

A multisource product is considered to be very rapidly dissolving when no less than 85% of the labelled amount of the drug substance dissolves in 15 minutes using a paddle apparatus at 75 rpm or a basket apparatus at 100 rpm in a volume of 900 ml or less in each of the following media:

— pH 1.2 HCl solution;
— a pH 4.5 acetate buffer; and
— a pH 6.8 phosphate buffer.

(See also section 9.2, dissolution profile comparison.)

9.1.2.2 *Rapidly dissolving*

A multisource product is considered to be rapidly dissolving when no less than 85% of the labelled amount of the drug substance dissolves in 30 minutes using a paddle apparatus at 75 rpm or a basket apparatus at 100 rpm in a volume of 900 ml or less in each of the following media:

— pH 1.2 HCl solution;
— a pH 4.5 acetate buffer; and
— a pH 6.8 phosphate buffer.

9.2 Qualification for a biowaiver based on the Biopharmaceutics Classification System

A biowaiver based on the BCS considers:

(a) the solubility and permeability of the API (see section 9.1);
(b) the similarity of the dissolution profiles of the multisource and comparator products in pH 1.2, 4.5 and 6.8 media (see below);
(c) the excipients used in the formulation (see below); and
(d) the risks of an incorrect biowaiver decision in terms of the therapeutic index of, and clinical indications for, the API (see section 5.1 for cases where an in vivo study would be required to demonstrate bioequivalence).

Only when there is an acceptable benefit–risk balance in terms of public health and risk to the individual patient should bioequivalence testing according to the guidelines given in this section be permitted.

Risk reduction and assessment of excipients

The risk of reaching an inadequate decision that the multisource product is equivalent to the comparator product can be reduced by correct classification of the API and by following the recommendations for dissolution

testing and comparison of the dissolution profiles. In all cases it should be further demonstrated that the excipients included in the formulation of the multisource product are well-established for use in products containing that API, and that the excipients used will not lead to differences between the comparator and multisource product with respect to processes affecting absorption (e.g. by effects on gastrointestinal motility or interactions with transport processes), or which might lead to interactions that alter the pharmacokinetics of the API.

Evidence that each excipient present in the multisource product is well established and does not affect gastrointestinal motility or other processes affecting absorption, can be documented using the following information:

i) the excipient is present in the comparator product, or the excipient is present in a number of other products which contain the same API as the multisource drug product and which have marketing authorizations in countries participating in the International Committee on Harmonisation (ICH) or associated countries; and
ii) the excipient is present in the multisource product in an amount similar to that in the comparator, or the excipient is present in the multisource drug product in an amount typically used for that type of dosage form.

Information on the composition of drug products with marketing authorization is available on the web sites of some national drug regulatory authorities. Examples of excipients known to have caused bioinequivalence that would not have been predicted by dissolution testing include surfactants, mannitol and sorbitol.

As a general rule, the closer the composition of the multisource product to that of the comparator product with regard to excipients, the lower the risk of an inappropriate decision on equivalence using a biowaiver based on the BCS.

Sub- and suprabioavailable products

A further consideration is the potential risk to public health and to the individual patient, should an inappropriate decision with respect to bioequivalence be reached. Essentially there are two possible negative outcomes.

The first arises when the multisource product is sub-bioavailable. In this case substitution of the comparator with the multisource product could lead to reduced therapeutic efficacy. APIs which must reach a certain concentration to be effective (e.g. antibiotics) are most susceptible to problems of sub-bioavailability.

The second negative outcome arises when the multisource product is suprabioavailable. In this case substitution of the comparator with the multisource product could lead to toxicity. APIs which exhibit toxic effects at concentrations close to the therapeutic range are most susceptible to problems of

suprabioavailability. For these reasons, both the indication and therapeutic index are important considerations in determining whether the biowaiver based on BCS can be applied or not.

Dissolution profile comparison

Approval of multisource formulations using comparative in vitro dissolution studies should be based on the generation of comparative dissolution profiles rather than a single-point dissolution test. When comparing the multisource and comparator products, dissolution profiles can be compared using a similarity factor (f_2). This is a model-independent mathematical approach for comparing the dissolution profiles of two products. The dissolution profile of the two products (multisource (test) and comparator (reference) or two strengths from a given manufacturer) should be made under the same test conditions. The dissolution profile of the multisource and comparator products should be measured under the same test conditions using an apparatus that conforms to the specifications in *The International Pharmacopoeia* using either the paddle method at 75 rpm or the basket method at 100 rpm at pH 1.2, 4.5 and 6.8 (*International Pharmacopoeia* buffers are recommended; alternative compendial buffers with same pH and buffer capacity are also acceptable) at 37 °C.

Samples should be collected at a sufficient number of intervals to characterize the dissolution profile of the drug product completely, e.g. at 10, 15, 20, 30, 45 and 60 minutes. A minimum of 12 dosage units of each product (multisource and comparator) should be evaluated (*30*, *31*).

The dissolution profiles of the multisource and comparator products can be compared using a similarity factor (f_2). Data with less than 20% variance at the first time-point and less than 10% variance at subsequent time-points can be used for the f_2 calculation, noting that a maximum of one time-point should be considered after 85% dissolution of the comparator product has been reached. A minimum of three time-points (zero excluded) is required for the calculation of f_2. An f_2 value of 50 or greater (50–100) reflects sameness or equivalence of the two curves and thus equivalence of the in vitro performance of the two products. The similarity factor f_2 is to be computed using the equation:

$$f_2 = 50 \cdot \log \{[1 + (1/n)\Sigma_{t=1}^{n} (R_t - T_t)^2]^{-0.5} \cdot 100\}$$

where R_t and T_t are the cumulative percentage of the drug dissolved at each of the selected *n* time-points of the comparator (reference) and multisource (test) product respectively (*30*, *31*).

If the comparator and multisource products are very rapidly dissolving, i.e. at least 85% dissolution in 15 minutes or less, in all three media, using the recommended test method, a profile comparison is not necessary.

Other appropriate statistical methods can also be used for comparison of dissolution profiles, provided that the same criterion is used for acceptance (maximum 10% difference between the profiles).

9.2.1 *Dissolution criteria for biowaivers based on the Biopharmaceutics Classification System according to the properties of active pharmaceutical ingredients*

The major application of BCS is to provide criteria for biowaiver of multisource products. Classification of APIs on the *WHO Model List of Essential Medicines* according to the WHO criteria described in this document are available (*32*). Further, a series of individual biowaiver monographs has been initiated (*33*). To date the BCS Guidance of the United States Department of Health and Human Services, Food and Drug Administration of the USA (HHS-FDA) recommends the biowaiver only for drug products containing Class 1 drugs (*28*). These biowaiver criteria have been described as very conservative. Discussions at scientific workshops after the guidance became available and in subsequent publications recommended that biowaiver can, in principle, be extended to:

- BCS Class 3 drug products, if the multisource and comparator product are very rapidly dissolving (no less than 85% in 15 minutes at pH 1.2, 4.5 and 6.8); and
- BCS Class 2 weak acids if the API has a dose:solubility ratio of 250 ml or less at pH 6.8 and the multisource product is rapidly dissolving (no less than 85% in pH 6.8 in 30 minutes) and its dissolution profile is similar to that of the comparator product at pH 1.2, 4.5 and 6.8 under the dissolution test conditions described in section 9.2.

On the basis of the above concept, WHO has collated a draft proposal to waive in vivo bioequivalence requirements for the *WHO Model List of Essential Medicines* immediate-release, solid oral dosage forms (*32*).

In summary, biowaivers for solid oral dosage forms based on BCS can be considered under the following conditions.

1. Dosage forms of APIs which are highly soluble, highly permeable (BCS Class 1), and are rapidly dissolving are eligible for a biowaiver based on the BCS provided:

    (i) the dosage form is *rapidly dissolving* (as defined in section 9.1.2.2) and the dissolution profile of the multisource product is similar to that of the comparator product at pH 1.2, pH 4.5 and pH 6.8 buffer using the paddle method at 75 rpm or the basket method at 100 rpm (as described in section 9.2) and meets the criteria of dissolution profile similarity, $f_2 \geq 50$ (or equivalent statistical criterion);

(ii) if both the comparator and the multisource dosage forms are *very rapidly dissolving* (as defined in section 9.1.2.1) the two products are deemed equivalent and a profile comparison is not necessary.

2. Dosage forms of APIs which are highly soluble and have low permeability (BCS Class 3) are eligible for biowaivers provided all the criteria (a–d) listed in section 9.2 are met and the risk–benefit is additionally addressed in terms of extent, site and mechanism of absorption.

In general, the risks of reaching an inappropriate biowaiver decision need to be more critically evaluated when the extent of absorption is lower (especially if $f_{abs} < 50\%$), if the sites of absorption are restricted to the proximal regions in the gastrointestinal tract and/or if the mechanism of absorption is subject to induction/competition. If any of these cases apply, the excipients used will also need to be scrutinized carefully in terms of both qualitative and quantitative composition – the greater the deviation from the comparator composition, the greater the risk of an inappropriate biowaiver decision.

If it is deemed that the risk of reaching an inappropriate biowaiver decision and its associated risks to public health and for individual patients is acceptable, the multisource product is eligible for a biowaiver based on BCS when both the comparator and the multisource dosage forms are *very rapidly dissolving* (85% dissolution in 15 minutes as described in section 9.1.2.1).

3. Dosage forms of APIs with high solubility at pH 6.8 but not at pH 1.2 or 4.5 and with high permeability (by definition, some but not all BCS Class 2 compounds with weak acidic properties) are eligible for a biowaiver based on BCS provided that criteria (b), (c) and (d) described in section 9.2. are met, that the API has high permeability (i.e. the fraction absorbed is 85% or greater) and a dose:solubility ratio of 250 ml or less at pH 6.8, and that the multisource product:

   (i) is *rapidly dissolving* (85% in 30 minutes or less) in pH 6.8 buffer using the test procedure conforming to section 9.2; *and*
   (ii) the multisource product exhibits similar dissolution profiles, as determined with the f_2 value or equivalent statistical evaluation, to those of the comparator product at the three pH values (pH 1.2, 4.5 and 6.8).

For multisource products containing Class 2 APIs with dose:solubility ratios of 250 ml or less at pH 6.8, the excipients should additionally be critically evaluated in terms of type and amounts, e.g. of surfactants, in the formulation. Further, if the C_{max} is critical to the therapeutic efficacy of the API, the risk of reaching an inappropriate biowaiver decision and its associated risks to public health and for individual patients may be deemed unacceptable.

9.3 Biowaivers based on dose-proportionality of formulations

Under certain conditions, approval of different strengths of a multisource product can be considered on the basis of dissolution profiles if the formulations have proportionally similar compositions.

9.3.1 *Proportionally similar formulations*

For the purpose of this guidance proportionally similar formulations can be defined in two ways, based on the strength of dosage forms.

(i) All active and inactive ingredients are exactly in the same proportions in the different strengths (e.g. a tablet of 50 mg strength has all the active and inactive ingredients exactly half that of a tablet of 100 mg strength, and twice that of a tablet of 25 mg strength).

(ii) For a high potency API, where the amount of the API in the dosage form is relatively low (up to 10 mg per dosage unit), the total weight of the dosage form remains nearly the same for all strengths (within ± 10% of the total weight), the same inactive ingredients are used for all strengths, and the change in strength is obtained by altering essentially only the amount of the API(s).

9.3.2 *Qualification for biowaiver based on dose-proportionality of formulations*

A prerequisite for qualification for a biowaiver based on dose-proportionality of formulations is that the multisource product at one strength has been shown in in vivo studies to be bioequivalent to the corresponding strength of the comparator product. The second requirement is that the further strengths of the multisource product are proportionally similar in formulation to that of the strength studied. When both of these criteria are met and the dissolution profiles of the further dosage strengths are shown to be similar to that of the strength studied on a percentage released against time basis, the biowaiver procedure can be considered for the further strengths.

As in the case of biowaivers based on the BCS, a biowaiver based on dose-proportionality of formulations should be considered only when there is an acceptable benefit–risk balance in terms of public health and risk to the individual patient, as discussed in section 9.2.

9.3.3 *Dissolution profile comparison for biowaivers based on dose-proportionality of formulations*

As for biowaivers based on the BCS, a model independent mathematical approach (e.g. f_2 test) can be used for comparing the dissolution profiles of two products. The dissolution profile of the two products (multisource

(test) and comparator (reference)) should be measured under the same test conditions.

The dissolution sampling times for both multisource and comparator product profiles should be the same:

— for example for immediate-release products 10, 15, 20, 30, 45 and 60 minutes;
— for example for 12 hour extended-release products 1, 2, 4, 6 and 8 hours; and
— for example for 24 hour extended-release products 1, 2, 4, 6, 8 and 16 hours.

Only one time-point should be considered after 85% dissolution from the comparator product. An f_2 value of 50 or greater (50–100) reflects equivalence (less than 10% difference) of the two curves, and thus equivalence of in vitro performance of the two products. To allow the use of the mean data, the coefficient of variation should not be more than 20% at the earliest time-point (e.g. 10 minutes in the case of the example given for immediate-release products), and should not be more than 10% at other time-points.

9.3.3.1 *Immediate-release tablets*

Different strengths of a multisource formulation, when the pharmaceutical products are manufactured by the same manufacturer at the same manufacturing site, where:

(i) all strengths are proportionally similar in formulation (see definition above);
(ii) an appropriate equivalence study has been performed on at least one of the strengths of the formulation (usually the highest strength, unless a lower strength is chosen for reasons of safety); and
(iii) the dissolution profiles for the different strengths are similar.

As for the biowaiver based on BCS, if both strengths release 85% or more of the label amount of the API in 15 minutes, using all three dissolution media as recommended in section 9.2, the profile comparison with an f_2 test is unnecessary.

9.3.3.2 *Delayed-release tablets and capsules*

For delayed-release tablets, when the multisource product is in the same dosage form, but in a different strength, and is proportionally similar in its active and inactive ingredients and has the same delayed-release mechanism, a lower strength can be granted a biowaiver if it exhibits similar dissolution profile, $f_2 > 50$, in the recommended test condition for delayed-release product, i.e. dissolution test in acid medium (pH 1.2) for 2 hours followed by dissolution in pH 6.8.

For delayed-release capsules, where different strengths have been achieved solely by means of adjusting the number of beads containing the API, similarity in the dissolution profile of the new (lower) strength to that of the approved strength ($f_2 > 50$) under the test conditions recommended for delayed-release products (see above) is sufficient for a biowaiver.

9.3.3.3 *Extended-release beaded capsules*

For extended-release beaded capsules, where different strengths have been achieved solely by means of adjusting the number of beads containing the API, dissolution profile comparison ($f_2 \geq 50$) under one recommended test condition is sufficient for a biowaiver based on dose-proportionality of formulation.

9.3.3.4 *Extended-release tablets*

For extended-release tablets, when the multisource product is in the same dosage form, but in a different strength, is proportionally similar in its active and inactive ingredients and has the same drug-release mechanism, a lower strength can be granted a biowaiver if it exhibits similar dissolution profiles, $f_2 \geq 50$, in three different pH buffers (between pH 1.2 and 7.5) by the recommended test method.

9.4 Biowaivers for scale-up and post-approval changes

Although these guidelines comment primarily on registration requirements for multisource pharmaceutical products, it should be noted that under certain conditions, following minor formulation or manufacturing changes after drug approval, in vitro dissolution testing may also be suitable to confirm similarity of product quality and performance characteristics.

Acknowledgements

The World Health Organization acknowledges with thanks the input of the following: International Pharmaceutical Federation/World Health Organization/Biopharmaceutics Classification System (FIP/WHO/BCS) Task Force members: Kamal K. Midha, Vinod P. Shah, Gordon Amidon, Dirk Barends, Jennifer Dressman, John Hubbard, Hans Junginger, Rabi Patnaik, James Polli and Salomon Stavchansky.

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WHO Technical Report Series, No. 937, 2006

Annex 8

Proposal to waive in vivo bioequivalence requirements for *WHO Model List of Essential Medicines* immediate-release, solid oral dosage forms

Introduction

This proposal is closely linked to the *Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability* (WHO Technical Report Series, No. 937, Annex 7). It aims to give national authorities sufficient background information on the various orally administered active pharmaceutical ingredients (APIs) on the *WHO Model List of Essential Medicines* (EML), also taking into account local usage of the API, to enable them to make an informed decision as to whether generic formulations should be subjected to in vivo bioequivalence (BE) studies or whether a biowaiver can be granted. In light of scientific work and discussion in the last decade, some of the criteria used to evaluate the API in terms of potential for a biowaiver have been revised to allow a broadened scope of application. The result is that many APIs on the EML can now be considered for the biowaiver procedure, subject to the usage and risks in the national setting.

1. Background

1.1 Initiatives to allow biowaivers based on the Biopharmaceutics Classification System

In 1995 the American Department of Health and Human Services, US Food and Drug Administration (HHS-FDA) instigated the Biopharmaceutics

Classification System (BCS), with the aim of granting so-called biowaivers for scale-up and post-approval changes (SUPAC) (www.fda.gov/cder/guidance/cmc5.pdf). A biowaiver means that in vivo bioavailability and/or bioequivalence studies may be waived (i.e. not considered necessary for product approval). Instead of conducting expensive and time-consuming in vivo studies, a dissolution test could be adopted as the surrogate basis for the decision as to whether two pharmaceutical products are equivalent. At that time the biowaiver was only considered for SUPAC to pharmaceutical products.

More recently, the application of the biowaiver concept has been extended to approval of certain orally administered generic products (www.fda.gov/cder/guidance/3618fnl.htm).

Within the context of the documents cited above, only APIs with high solubility and high permeability and which are formulated in solid, immediate-release (IR) oral formulations can be approved on the basis of the biowaiver procedure. A major advantage of the biowaiver procedure is the simplification of the product approval process and the reduction of the time required, thus reducing the cost of bringing new products to market.

1.2 What is the Biopharmaceutics Classification System?

The Biopharmaceutics Classification System (BCS) was proposed in 1995 by Amidon et al.[1] It is a scientific framework which divides APIs into four groups, according to their solubility and permeability properties.

1.3 Classification of active pharmaceutical ingredients according to the Biopharmaceutics Classification System

According to the HHS-FDA definitions in the documents cited above, the four possible categories for an API according to the BCS are:

- BCS class I: "high" solubility – "high" permeability
- BCS class II: "low" solubility – "high" permeability
- BCS class III: "high" solubility – "low" permeability
- BCS class IV: "low" solubility – "low" permeability.

Depending on the classification, the oral availability of the API may be expected to range from being heavily dependent on the formulation and manufacturing method (e.g. Class II APIs: poorly soluble yet highly permeable) to being mostly dependent on the API permeability properties (e.g. Class III APIs: highly soluble yet poorly permeable).

[1] Amidon GL, Lennemas H, Shah VP, Crison JR. A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability. *Pharmaceutics Research*, 1995, 12:413–420.

1.4 How is high or low solubility currently defined by the Department of Health and Human Services, US Food and Drug Administration?

The aqueous solubility of a drug substance is considered as high according to the HHS-FDA BCS criteria when:

- the ratio of the *highest orally administered dose (in mg) to the solubility (mg/ml) is 250 ml or lower*.
  — This criterion is met over the pH range 1–7.5 at 37 °C.

According to HHS-FDA guidances, the determination of the equilibrium solubility should be carried out with the shake-flask method (other methods such as acid or base titration are permitted when their ability to predict the equilibrium solubility is justified). The experiments should be carried out at a temperature of 37 ± 1°C. Further, a sufficient number of pH conditions should be chosen to cover the pH range of 1–7.5 and each determination should be carried out at least in triplicate. The buffer solutions given in the *United States Pharmacopeia* (USP) are appropriate for the tests, but other buffers are also allowed for these experiments. The pH value of each buffer solution should be checked before and after each experiment. Degradation of the API due to pH or buffer composition should be reported together with other stability data.

The reason for the 250-ml cut-off criterion for the dose:solubility ratio is that in pharmacokinetic bioequivalence studies, the API formulation is to be ingested with a large glass of water (8 ounces corresponds to about 250 ml). If the highest orally administered dose can be completely dissolved in this amount of water, independent of the physiological pH value (hence the determination over the pH range 1–7.5), solubility problems are not expected to hinder the uptake of the API in the small intestine.

The other important parameter for the BCS is the intestinal permeability of the API.

1.5 How is high or low permeability currently defined by the Department of Health and Human Services, US Food and Drug Administration?

According to HHS-FDA a drug is considered highly permeable, when *90 % or more of the orally administered dose is absorbed in the small intestine*.

Permeability can be assessed by pharmacokinetic studies (for example, mass balance studies), or intestinal permeability methods, e.g. intestinal perfusion in humans, animal models, Caco 2 cell lines or other suitable, validated cell lines. In vivo or in situ animal models or in vitro models (cell lines) are only considered appropriate by HHS-FDA for passively transported drugs. It should be noted that all of these measurements assess the fraction absorbed (as opposed to the bioavailability, which can be reduced substantially by first-pass metabolism).

HHS-FDA suggests use of two different methods for determining the permeability classification if results with one method are inconclusive.

1.6 Which pharmaceutical formulations can currently be considered for a biowaiver according to the Department of Health and Human Services, US Food and Drug Administration?

To be considered bioequivalent according to the HHS-FDA biowaiver procedure, a pharmaceutical product:

- should contain a Class I API;
- should be rapidly dissolving, meaning it should release at least 85% of its content in 30 minutes in three different media (pH 1.2, pH 4.5 and pH 6.8, composition see "Multisource document")[1] in a paddle (50 rpm) or basket (100 rpm) apparatus at 37 °C and a volume of 900 ml;
- should not contain excipients which could influence the absorption of the API;
- should not contain an API with a narrow therapeutic index; and
- should not be designed to be absorbed from the oral cavity.

The reasoning for the above-mentioned dissolution restrictions is that when a highly soluble, highly permeable API dissolves rapidly, it behaves like a solution in the gastrointestinal tract. If this is the case, the pharmaceutical composition of the product is insignificant, provided that excipients which influence the uptake across the gut wall are excluded from the formulation. The API is not prone to precipitation after its dissolution due to its good solubility under all pH conditions likely to be found in the upper gastrointestinal tract. The high permeability ensures the complete uptake (> 90%) of the API during its passage through the small intestine. The rapid dissolution of the product guarantees that the API is available long enough for the uptake in the small intestine (the passage time in the small intestine is approximately four hours) and negates any slight differences between the formulations.

Pharmaceutical products containing an API with a narrow therapeutic index should always be tested with in vivo methods, because the risk to the patient resulting from a possible incorrect bioequivalence decision using the biowaiver procedure is considered too high with these kinds of APIs.

As the BCS is only applicable to APIs which are absorbed from the small intestine; drugs absorbed from other sites (e.g. from the oral cavity) are not eligible for a biowaiver.

It is clear that the HHS-FDA requirements for the classification of APIs and eligibility criteria for the biowaiver are very strict. During the last decade,

[1] *Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability* (WHO Technical Report Series, No. 937, Annex 7).

several publications and continuing scientific discussions have suggested that the original HHS-FDA criteria for application of the biowaiver procedure could be relaxed without substantially increasing the risk to public health or to the individual patient. On the basis of these publications and dialogue, WHO has proposed revised BCS criteria and additional considerations for the eligibility of a pharmaceutical product for the biowaiver procedure in the "Multisource document".[1]

2. WHO revisions to the criteria for BCS classification

WHO revisions to the BCS criteria are as follows:

- **WHO high-solubility definition**
  When an API shows a dose:solubility ratio of 250 ml or lower at 37 °C over a **pH range of 1.2–6.8**, it can be classified as "highly soluble". The decrease in pH from 7.5 in the FDA guidances to 6.8 reflects the need to dissolve the drug before it reaches the mid-jejunum to ensure absorption from the gastrointestinal tract.
- Furthermore, the dose that is to be used for the calculation is the **highest dose indicated in the Model List of Essential Medicines (EML)**. In some countries, products may be available at doses exceeding the highest dose on the *EML*. In such cases, the classification given in the tables at the end of this Annex may no longer be appropriate and the dose:solubility ratio and the permeability will have to be reassessed at the product dose.
- **WHO permeability definition**
  When an API is absorbed to an extent of 85% or more, it is considered to be "highly permeable". The permeability criterion was relaxed from 90% in the FDA guidance to 85% in the WHO "Multisource document". Some examples of APIs now included in BCS Class I that were previously considered to be in Class III are paracetamol, acetylsalicylic acid, allopurinol, lamivudine and promethazine.

Application of these revised criteria has changed the classification of some APIs in the list. Thus, the classifications in the tables attached to this document *supersede those in previous publications*. As new APIs appear on the EML, it will be necessary to classify them according to the revised BCS; so it is therefore anticipated that the tables will be revised regularly. In addition, some APIs have not yet been sufficiently characterized to assign them a BCS classification. As the tables evolve, it is anticipated that more concrete information will be generated for these APIs as well.

[1] *Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability* (WHO Technical Report Series, No. 937, Annex 7).

The potential impact of the revised guidelines on registration requirements to establish interchangeability is that many of the medicines on the EML could become eligible for approval based on in vitro bioequivalence testing in accordance with the dissolution tests prescribed in Section 9 of the "Multisource document".[1]

3. WHO extensions to the scope of application of the biowaiver

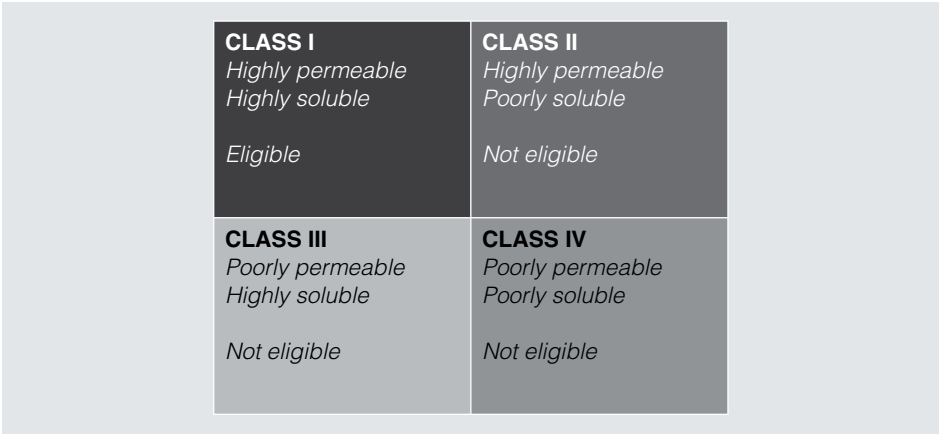
In the "Multisource document",[1] the WHO has broadened the scope of application of the biowaiver in three directions:

(1) The criteria for classification as a Class I API have been relaxed with respect to both the dose:solubility ratio and permeability requirements.
(2) The new requirements allow pharmaceutical products containing Class III APIs to be considered for a biowaiver, under application of more stringent dissolution criteria.
(3) The document further allows pharmaceutical products containing BCS Class II APIs that are weak acids which have a dose:solubility ratio of 250 ml or less at pH 6.8 to be eligible for the biowaiver procedure, provided that they dissolve rapidly at pH 6.8 and similarly to the comparator product at pH 1.2 and 4.5.

Diagrams depicting the products eligible for the biowaiver procedure under the HHS-FDA guidance and those eligible according to the WHO "Multisource document" are presented in Fig. 1.

Figure 1.
Eligibility for the biowaiver procedure based on solubility and permeability characteristics of the active pharmaceutical ingredient

a. according to HHS-FDA



[1] *Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability* (WHO Technical Report Series, No. 937, Annex 7).

b. according to WHO

4. WHO additional criteria for application of the biowaiver procedure

For all APIs on the EML, it is imperative to consider not only the physical, chemical and absorption properties of the API when evaluating them for biowaiver, but (as outlined in the "Multisource document")[1] to perform a benefit–risk analysis in view of the products' usage at the national level. As an example, in some countries amoxicillin is used primarily for the treatment of ambulatory patients with mild-to-moderate infections of the upper respiratory tract, urinary tract and other sites. In other countries, amoxicillin might also be used to treat severe or even life-threatening infections, in which case the risk to the patient of arriving at the wrong bioequivalence decision would be far greater.

Thus, the eligibility criteria according to WHO are:

(1) The **BCS classification** (according to the revised criteria) of the API.
(2) **Risk assessment:** only if the risk of an incorrect biowaiver decision and an evaluation of the consequences (of an incorrect, biowaiver-based equivalence decision) in terms of public health and risks to individual patients is outweighed by the potential benefits accrued from the biowaiver approach may the biowaiver procedure be applied.
(3) **Dissolution requirements** for the pharmaceutical product:

— *very rapidly dissolving* (release of > 85% of the labelled amount of drug in 15 minutes) in standard media at pH 1.2, 4.5 and 6.8, at a rotational speed of 75 rpm in the paddle apparatus or 100 rpm in

[1] *Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability* (WHO Technical Report Series, No. 937, Annex 7).

the basket apparatus (applies to pharmaceutical products containing Class III APIs);

— *rapidly dissolving* (release of > 85% of the labelled amount of drug in 30 minutes) in standard media at pH 1.2, 4.5 and 6.8, at a rotational speed of 75 rpm in the paddle apparatus or 100 rpm in the basket apparatus (applies to pharmaceutical products containing Class I APIs and/or Class II APIs which are weak acids and meet the 250 ml dose:solubility requirement at pH 6.8).

(4) **Considerations relating to excipients**

The national authority should be aware that some excipients can influence motility and/or permeability in the gastrointestinal tract. Therefore, the excipients used in the multisource product formulation should be scrutinized.

In this regard, the national authority can draw on the experience relating to formulations which have been approved on the basis of human bioequivalence studies in their own or in other jurisdictions.

If the multisource product under consideration contains excipients that have been used before in similar amounts in other formulations of the same API, it can be reasonably concluded that these excipients will have no unexpected consequences for the bioavailability of the product. If, however, the formulation contains different excipients, or amounts of the same excipients that are very different from usual, the national authority may choose to declare the biowaiver procedure inapplicable.

A list of usual and acceptable excipients can be found at the following web site: www.fda.gov/cder/iig/iigfaqWEB.htm; formulations of some products can be found on the web sites of some national drug regulatory authorities.

5. Explanation of the tables

The decision of a national authority to allow a biowaiver based on the BCS should take into consideration the solubility and permeability characteristics as well as the therapeutic use and therapeutic index of the API, its pharmacokinetic properties, the similarity of the dissolution profiles of the multisource and the comparator products in standard buffers with a pH of 1.2, pH 4.5 and pH 6.8 at 37 °C. Data related to the excipients composition in the multisource product are also required. A systematic approach to the biowaiver decision has been established by the International Pharmaceutical Federation (FIP) and published in the *Journal of Pharmaceutical Sciences* (http://www3.interscience.wiley.com/cgi-bin/jhome/68503813). The relevant documents can also be downloaded from the FIP web site at: http://www.fip.org/. These monographs provide detailed information which should be taken into account whenever available in the biowaiver consideration.

5.1 Which active pharmaceutical ingredients are included in the tables?

The substances listed in the 14th *WHO Model List of Essential Medicines* (EML) of March 2005 have been evaluated and classified according to the revised criteria given above.

5.2 Where do the data come from?

The solubility and permeability values were found in the publicly available literature, such as Martindale's, the Merck Index and scientific journals.

Please note that the doses used for the calculation of the dose:solubility ratio are those stated in the EML.

The indications given in the tables are reproduced directly from the EML. If the EML specifies the dosage form (e.g. sublingual tablet) this is indicated under "comments".

5.3 "Worst case" approach to the Biopharmaceutics Classification System

The drugs listed in the EML were classified according to the criteria explained above. Where no clear classification could be made, the "worst case" was assumed. For example if a substance is highly soluble, but absolute bioavailability data were not available, the test conditions for BCS Class III substances have been proposed. The same procedure was adopted for fixed combinations, for example amoxicillin and clavulanic acid, the testing procedure was always fixed according to the "worst" BCS classification, in this example clavulanic acid (BCS Class III/1), because amoxicillin is a BCS Class I drug. This combination would therefore be tested according to BCS Class III requirements.

The results of the revised classification can be found in Tables 1–3.

5.4 Why are there three Tables?

Table 1 lists all APIs on the EML that are administered orally, with the exception of the APIs listed as complementary. Table 2 summarizes the APIs listed as complementary in the EML and Table 3 lists the APIs for which no classification had previously been assigned, or that had been introduced with the 14th EML (March 2005), together with a more detailed explanation of their classification.

5.5 Risk assessment

To minimize the risks of an incorrect biowaiver decision in terms of public health and risks to individual patients, the therapeutic indications of the API, known pharmacokinetic variations, food effects, etc. should be evaluated based on local clinical experience, taking into account the indications

for which the API is prescribed in that country as well as specific pharmacokinetic population variations (for example CYP polymorphisms). Known potential risks are listed under "potential risks" in the tables. The absence of an entry under "potential risks" should not, however, be misconstrued as meaning that there are no risks associated with the use of the medicine.

6. Biowaiver testing procedure according to WHO

Depending on the BCS classification of the API, based on solubility and permeability characteristics listed in the accompanying tables, the testing procedure is defined in section 9.2.1 of the "Multisource document"[1]:

6.1 For pharmaceutical products containing Biopharmaceutics Classification System Class I (highly soluble, highly permeable) APIs

For *rapidly dissolving* (as defined above) pharmaceutical products containing **BCS Class I** APIs, more than 85% dissolution of the labelled amount is required within 30 minutes in standard media at pH 1.2, 4.5 and 6.8 using the paddle apparatus at 75 rpm or the basket apparatus at 100 rpm. The dissolution profiles of the comparator and the multisource products should be compared by an $f_2 > 50$ or an equivalent statistical criterion.

If within 15 minutes more than 85% of the API are released from the comparator and the multisource formulation under the above-mentioned conditions the products will be considered *very rapidly dissolving*. In this case the products are deemed to be equivalent and a profile comparison is not required.

6.2 For pharmaceutical products containing Biopharmaceutics Classification System Class III (highly soluble, low permeability) APIs

A biowaiver can be considered only if both the multisource and the comparator product are *very rapidly dissolving*. Eighty-five per cent or more dissolution of the labelled amount of the API should be achieved within 15 minutes in standard media at pH 1.2, 4.5 and 6.8 using the paddle apparatus at 75 rpm or the basket apparatus at 100 rpm.

Generally, the risks of an inappropriate biowaiver decision should be more critically reviewed (e.g. site-specific absorption, induction/competition at the absorption site, excipient composition and therapeutic risks) for products containing BCS Class III APIs than for BCS Class I drugs.

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[1] *Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability* (WHO Technical Report Series, No. 937, Annex 7).

6.3 For pharmaceutical products containing APIs with high solubility at pH 6.8 but not at pH 1.2 or 4.5 and with high permeability (by definition, BCS Class II compounds with weak acidic properties)

These are eligible for a biowaiver provided that the multisource product:

- is *rapidly dissolving,* i.e. 85% or more dissolution of the labelled amount of the API should be achieved within 30 minutes in standard media at pH 6.8 using the paddle apparatus at 75 rpm or the basket apparatus at 100 rpm; ***and***
- the multisource product exhibits similar dissolution profiles, as determined with the f_2 value or equivalent statistical evaluation, to those of the comparator product in buffers at all three pH values (pH 1.2, 4.5 and 6.8).

For multisource products containing BCS Class II APIs with dose:solubility ratios of 250 ml or less, at pH 6.8, the excipients should also be critically evaluated in terms of type and amounts of surfactants in the formulation.

Further details of eligibility for the biowaiver and appropriate test procedures can be found in sections 5 and 9 of the "Multisource document".[1]

[1] *Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability* (WHO Technical Report Series, No. 937, Annex 7).

Table 1
Substances on the *WHO Model List of Essential Medicines* (EML)

Medicine[a]	Highest oral strength according to WHO Essential Medicines List[a]	Solubility[b]	Permeability[c]	BCS class[d]	Dissolution test (for biowaiver)[e]	Potential risks[f]	Indication(s) according to WHO Essential Medicines List[a]	Comments and special dosage form indications[a]
abacavir	200 mg	high	low	3	9.2.1.2		antiretroviral	
acetazolamide	250 mg	low	low (?)	4/2	Not eligible for biowaiver		antiglaucoma medicine	unknown whether poor BA is due to poor solubility *or* poor solubility and poor permeability
acetylsalicylic acid	500 mg	high	high	1	9.2.1.1		NSAID, antimigraine medicine	
acetylsalicylic acid	100 mg	high	high	1	9.2.1.1		antithrombotic medicine	
aciclovir	200 mg	high	low	3	9.2.1.2		antiherpes medicines	
albendazole	400 mg	low	low (?)	4/2	Not eligible for biowaiver		anthelminthic	chewable tablet; unknown whether poor BA is due to poor solubility *or* poor solubility and poor permeability
allopurinol	100 mg	high	high	1	9.2.1.1		gout	
aluminium hydroxide	500 mg			NR	NA		antacid	used for local effect

NSAID, Non-steroidal anti-inflammatory drug; BA, bioavailability.

amiloride hydrochloride	5 mg	high	high	1	9.2.1.1		diuretic	
amitriptyline hydrochloride	25 mg (*1*)	high	high	1	9.2.1.1		psychotherapeutic medicine	
amlodipine	5 mg	high	high	1	9.2.1.1		antihypertensive medicine	
amodiaquine (base)	200 mg	high	borderline BA > 75%	3/1	9.2.1.2	CYP2C8 polymorphism, increased risk for agranulocytosis and liver toxicity	antimalarial	extent of first-pass metabolism uncertain
amoxicillin (a) + clavulanic acid (c)	(a) 500 mg + (c) 125 mg	(a) high + (c) high	(a) high + (c) borderline absorption >73% (radioactive excretion)	(a) 1 + (c) 3/1	9.2.1.2		antibacterial	combination should be tested according to clavulanic acid requirements
amoxicillin anhydrous	500 mg	high	high	1	9.2.1.1		antibacterial	
artemether (a) + lumefantrine (l)	(a) 20 mg + (l) 120 mg	(a and l) unknown	low (a and l)	(a) 4/3 + (l) 4/3	Not eligible for biowaiver		antimalarial	
ascorbic acid	50 mg	high	high	1	9.2.1.1		vitamin	
atenolol	100 mg	high	low	3	9.2.1.2		antianginal, antihypertensive, antiarrhythmic medicine and used in heart failure	

BA, bioavailability.

Medicine[a]	Highest oral strength according to WHO Essential Medicines List[a]	Solubility[b]	Permeability[c]	BCS class[d]	Dissolution test (for biowaiver)[e]	Potential risks[f]	Indication(s) according to WHO Essential Medicines List[a]	Comments and special dosage form indications[a]
azithromycin	500 mg	low	low (?)	4/2	Not eligible for biowaiver		antibacterial	unknown whether poor BA is due to poor solubility *or* poor solubility and poor permeability
benznidazole	100 mg	high	low	3	9.2.1.2		American trypanosomiasis	
biperiden hydrochloride	2 mg	high	insufficient literature	3/1	9.2.1.2		antiparkinson medicine	
carbamazepine	200 mg	low (neutral)	high	2	Not eligible for biowaiver		antiepileptic, psychotherapeutic medicine	scored tablet
cefixime	400 mg	low	low (?)	4/2	Not eligible for biowaiver		antibacterial	unknown whether poor BA is due to poor solubility *or* poor solubility and poor permeability
chloramphenicol	250 mg	high	low	3	9.2.1.2	narrow therapeutic index	antibacterial	
chloroquine phosphate or sulfate	150 mg	high	high	1	9.2.1.1		DMARD, antimalarial	

BA, bioavailability; DMRD, disease modifying antirheumatic drug.

chlorphenamine hydrogen maleate	4 mg	high	BA 25-59%, first pass	3/1	9.2.1.2	CYP2D6 polymorphism	antiallergic	extent of first-pass metabolism uncertain
chlorpromazine hydrochloride	100 mg	high	low	3	9.2.1.2		psychotherapeutic medicine	
ciprofloxacin hydrochloride	250 mg	high	BA 70–82%, possible first pass, high in Caco-2 cells	3/1	9.2.1.2		antibacterial	extent of first-pass metabolism uncertain
clofazimine	100 mg	insufficient literature	low	4/3	Not eligible for biowaiver at present		antileprosy medicine	
clomifene citrate	50 mg	high	insufficient literature	3/1	9.2.1.2		ovulation inducer	
clomipramine hydrochloride	25 mg	high	66% excreted in the urine, the remainder being eliminated in the faeces	3/1	9.2.1.2		psychotherapeutic medicine	lack of absolute bioavailability data
cloxacillin (as sodium salt)	1000 mg	high	low	3	9.2.1.2		antibacterial	
codeine phosphate	30 mg	high	low	3	9.2.1.2	risk of abuse	opioid analgesic, diarrhoea in adults	
dapsone	100 mg	low (weak base)	high	2	Not eligible for biowaiver	G6PD deficiency	antileprosy medicine	
diazepam	5 mg	high	high	1	9.2.1.1		psychotherapeutic medicine	scored tablet

BA, Bioavailability; G6PD, glucose-6-phosphate dehydrogenase.

Medicine[a]	Highest oral strength according to WHO Essential Medicines List[a]	Solubility[b]	Permeability[c]	BCS class[d]	Dissolution test (for biowaiver)[e]	Potential risks[f]	Indication(s) according to WHO Essential Medicines List[a]	Comments and special dosage form indications[a]
didanosine	200 mg	high	low	3	9.2.1.2		antiretroviral	buffered chewable, dispersible tablet
didanosine	400 mg	high	low	3	see comment		antiretroviral	unbuffered enteric coated capsule → not eligible for biowaiver in this dosage form[i]
digoxin	250 µg	high	high	1	9.2.1.1		antiarrhythmic and used in heart failure	
diloxanide furoate	500 mg	low (*2*)	low (?)	4/2	Not eligible for biowaiver		antiprotozoal	unknown whether poor BA is due to poor solubility *or* poor solubility and poor permeability
doxycycline hydrochloride	100 mg	high	high	1	9.2.1.1		antibacterial	
efavirenz	200 mg	low (*1*)	low (?)	4/2	Not eligible for biowaiver		antiretroviral	unknown whether poor BA is due to poor solubility *or* poor solubility and poor permeability
enalapril	2.5 mg	high	low	3	9.2.1.2		antihypertensive medicine	

BA, Bioavailability.

ergocalciferol	1.25 mg (50 000 IU)	high	low	3	9.2.1.2		vitamin	
erythromycin stearate + ethylsuccinate	250 mg	low	low	4	Not eligible for biowaiver		antibacterial	
ethambutol hydrochloride	400 mg	high	low	3	9.2.1.2	risk of dose-related ototoxicity	antituberculosis medicine	
ethinylestradiol	50 µg	high	borderline, BA 40–50%, first pass	3/1	9.2.1.2		estrogen	extent of first-pass metabolism uncertain
ethinylestradiol (e) + levonorgestrel (l)	30 µg + 150 µg	high	(e) borderline, BA 40–50%, first pass + (l) high	3/1 + 1	9.2.1.2		hormonal contraceptive	extent of first-pass metabolism uncertain; combination should be tested according to ethinylestradiol requirements
ethinylestradiol (e) + norethisterone (n)	35 µg + 1 mg	high	(e) borderline, BA 40–50%, first pass + (n) high	3/1 + 1	9.2.1.2		hormonal contraceptive	extent of first-pass metabolism uncertain; combination should be tested according to ethinylestradiol requirements
ferrous salt	equivalalent to 60 mg iron	high (see footnote)	low	3	9.2.1.2		antianaemia medicine	commonly used salts: see footnote

BA, Bioavailability; GI, gastrointestinal.

Medicine[a]	Highest oral strength according to WHO Essential Medicines List[a]	Solubility[b]	Permeability[c]	BCS class[d]	Dissolution test (for biowaiver)[e]	Potential risks[f]	Indication(s) according to WHO Essential Medicines List[a]	Comments and special dosage form indications[a]
ferrous salt (fs) + folic acid (fa)	equivalent to 60 mg iron + 400 µg folic acid	(fs) high + (fa) high	(fs) low + (fa) low (urinary recovery 28.5%) (*2*)	3 + 3/1	9.2.1.2		antianaemia medicine (during pregnancy)	lack of absolute bioavailability data; commonly used salts: see footnote; combination should be tested according to ferrous salt requirements
fluconazole	50 mg	high	high	1	9.2.1.1		antifungal	
folic acid	5 mg	high	low (?)	3/1	9.2.1.2		antianaemia medicine	lack of absolute bioavailability data
furosemide	40 mg	low	low (?)	4/2	Not eligible for biowaiver	highly variable BA	medicine used in heart failure, diuretic	unknown whether poor BA is due to poor solubility *or* poor solubility and poor permeability
glibenclamide	5 mg	low	low (?)	4/2	Not eligible for biowaiver		antidiabetic agent	unknown whether poor BA is due to poor solubility *or* poor solubility and poor permeability

NSAID, Non-steroidal anti-inflammatory drugs; GI, gastrointestinal.

glyceryl trinitrate	500 µg	high	sublingual application, permeability in the oral cavity more important than GI permeability	3/1	NA[h]	local absorption	antianginal medicine	sublingual application
griseofulvin	250 mg	low (neutral)	high	2	Not eligible for biowaiver		antifungal	
haloperidol	2 mg	borderline < 0.01 mg/ml[2]	low	4/3	Not eligible for biowaiver		psychotherapeutic medicine	
hydralazine hydrochloride	50 mg	high	low	3	9.2.1.2		antihypertensive medicine	
hydrochlorothiazide	25 mg	high	low	3	9.2.1.2		antihypertensive medicine, diuretic and used in heart failure	scored tablet
ibuprofen	400 mg	low, weak acid (pK_a 4.4, 5.2)	high	2	9.2.1.3		NSAID, antimigraine medicine	
indinavir sulfate	400 mg	low	low (?)	4/2	Not eligible for biowaiver	CYP 450 3A4, food effect (–)	antiretroviral	unknown whether poor BA is due to poor solubility *or* poor solubility and poor permeability

D:S, Dose:solubility ratio; BA, bioavailability.

Medicine[a]	Highest oral strength according to WHO Essential Medicines List[a]	Solubility[b]	Permeability[c]	BCS class[d]	Dissolution test (for biowaiver)[e]	Potential risks[f]	Indication(s) according to WHO Essential Medicines List[a]	Comments and special dosage form indications[a]
iopanoic acid	500 mg	low, weak acid (pK_a 4.8) (*2*)	high	2	Not eligible for biowaiver		radiocontrast media	Insufficiently soluble in water (15 µg/ml) to be eligible for biowaiver
isoniazid	300 mg	high	borderline	3/1	9.2.1.2		antituberculosis medicine	
isoniazid (i) + ethambutol (e)	(i) 150 mg + (e) 400 mg	(i) high + (e) high	(i) borderline + (e) low	(i) 3/1 + (e) 3	See footnote[g]	ocular toxicity	antituberculosis medicine	
isosorbide dinitrate	5 mg	high	sublingual application, permeability in the oral cavity more important than GI permeability	3/1	NA[h]		antianginal medicine	sublingual
ivermectin	6 mg	practically insoluble in water[3] D:S > 6000 ml	low (?)	4/2	Not eligible for biowaiver		antifilarial	scored tablet; unknown whether poor BA is due to poor solubility *or* poor solubility and poor permeability
lamivudine	150 mg	high	high	1	9.2.1.1		antiretroviral	

BA, bioavailability; GI, gastrointestinal; D:S, Dose: solubility ratio.

levamisole hydrochloride	150 mg	high	borderline	3/1	9.2.1.2		anthelminthic	
levodopa (l) + carbidopa (c)	(l) 250 mg + (c) 25 mg	(l) high + (c) high	(l) high + (c) insufficient data (BA_{humans} 58%, BA_{dogs} 88%)	(l) 1 + (c) 3/1	9.2.1.2	narrow therapeutic index	antiparkinson medicine	extent of human first-pass metabolism uncertain; combination should be tested according to carbidopa requirements
levonorgestrel	30 µg	high	high	1	9.2.1.1		hormonal contraceptive	
levonorgestrel	750 µg × 2 (pack of two)	high	high	1	9.2.1.1		hormonal contraceptive	
levothyroxine sodium salt	100 µg	high	low	3	9.2.1.2	narrow therapeutic index	thyroid hormone	
lithium carbonate	300 mg	high	high	1	9.2.1.1	narrow therapeutic index	psychotherapeutic medicine	
lopinavir (l) + ritonavir (r)	(l) 133.3 mg + (r) 33.3 mg	(l) low + (r) low	(l) low (insufficient data) (?) + (r) low (?)	(l) 4/2 + (r) 4/2	Not eligible for biowaiver		antiretroviral	unknown whether poor BA is due to poor solubility *or* poor solubility <u>and</u> poor permeability

NSAID, Non-steroidal anti-inflammatory drugs.

Medicine[a]	Highest oral strength according to WHO Essential Medicines List[a]	Solubility[b]	Permeability[c]	BCS class[d]	Dissolution test (for biowaiver)[e]	Potential risks[f]	Indication(s) according to WHO Essential Medicines List[a]	Comments and special dosage form indications[a]
mebendazole	500 mg	low	low (?)	4/2	NA		anthelminthic	chewable tablet; anthelminthics usually applied orally for action in GI tract: solubility more important than permeability, but unknown whether poor BA is due to poor solubility *or* poor solubility and poor permeability
mefloquine hydrochloride	250 mg	low[2]	low (?)	4/2	Not eligible for biowaiver		antimalarial	unknown whether poor BA is due to poor solubility *or* poor solubility and poor permeability
DL-methionine	250 mg	high	high	1	9.2.1.1		antidote	
metformin hydrochloride	500 mg	high	low	3	9.2.1.2		antidiabetic agent	
methyldopa	250 mg	high	low	3	9.2.1.2		antihypertensive medicine	
metoclopramide hydrochloride	10 mg	high	low	3	9.2.1.2		antiemetic	

metronidazole	500 mg	high	high	1	9.2.1.1		antiprotozoal, antibacterial	
morphine sulfate	10 mg	high	insufficient data (BA ~ 30% but extensive first pass)	3/1	9.2.1.2	risk of abuse	opioid analgesic	extent of first pass metabolism uncertain
nelfinavir mesilate	250 mg	low	low (?)	4	Not eligible for biowaiver	CYP 450 3A4, food effect (+)	antiretroviral	unknown whether poor BA is due to poor solubility *or* poor solubility and poor permeability
neostigmine bromide	15 mg	high	low	3	9.2.1.2		muscle relaxant	
nevirapine	200 mg	low (weak base)	high	2	Not eligible for biowaiver		antiretroviral	
niclosamide	500 mg	low	low (?)	4/2	NA		anthelminthic	chewable tablet; anthelminthics usually applied orally for action in GI tract: solubility more important than permeability
nicotinamide	50 mg	high	high	1	9.2.1.1		vitamin	
nifedipine	10 mg	low, weak acid, solubility at pH7 0.0056 mg/ml[2]	high	2	Not eligible for biowaiver		antioxytocic	

BA, bioavailability; GI, gastrointestinal.

Medicine[a]	Highest oral strength according to WHO Essential Medicines List[a]	Solubility[b]	Permeability[c]	BCS class[d]	Dissolution test (for biowaiver)[e]	Potential risks[f]	Indication(s) according to WHO Essential Medicines List[a]	Comments and special dosage form indications[a]
nifurtimox	250 mg	high	low	3	9.2.1.2		American trypanosomiasis	
nitrofurantoin	100 mg	low, weak acid, solubility at pH 7.0 0.374 mg/ml (pK_a 7.2 (25 °C)) (*2*)	high	2	Not eligible for biowaiver		antibacterial	Not soluble enough at pH 6.8 to be eligible for biowaiver
norethisterone	5 mg	high	high	1	9.2.1.1		progestogen	
nystatin	500 000 IU	–	–	NR	NA		antifungal	local effect
paracetamol	500 mg	high	high	1	9.2.1.1		NSAID, antimigraine medicine	
penicillamine	250 mg	high	low	3	9.2.1.2		antidote	
phenobarbital	100 mg	high	high	1	9.2.1.1	narrow therapeutic index	antiepileptic	
phenoxymethyl penicillin (as potassium salt)	250 mg	high	high	1	9.2.1.1		antibacterial	
phenytoin sodium salt	100 mg	low, weak acid, sol. at pH 6.8 1.7 mg/ml (*4*) pK_a 8.3 (25 °C)) (*2*)	high	2	9.2.1.3	narrow therapeutic index, non-linear pharmacokinetics	antiepileptic	

potassium iodide	60 mg	high	high	1	9.2.1.1		thyroid hormones and antithyroid medicines	
praziquantel	600 mg	low (neutral)	high	2	Not eligible for biowaiver		anthelminthic, antischistosomal, antitrematode	
prednisolone	25 mg	high	high	1	9.2.1.1		antiallergic	
primaquine diphosphate	15 mg	high	high	1	9.2.1.1		antimalarial	
proguanil hydrochloride	100 mg	high	high	1	9.2.1.1		antimalarial	
promethazine hydrochloride	25 mg	high	high	1	9.2.1.1	CYP2D6 polymorphism	antiemetic	
propranolol hydrochloride	40 mg	high	high	1	9.2.1.1		antimigraine medicine	
propylthiouracil	50 mg	high	high	1	9.2.1.1		antithyroid medicine	
pyrantel embonate	250 mg	low	low (?)	4/2	NA		anthelminthic	chewable tablet; anthelminthics usually applied orally for action in GI tract: solubility more important than permeability
pyrazinamide	400 mg	high	borderline	3/1	9.2.1.2	Liver toxicity	antituberculosis medicine	
pyridoxine hydrochloride	25 mg	high	high	1	9.2.1.1		vitamin	

NSAID, Non-steroidal anti-inflammatory drugs.

Medicine[a]	Highest oral strength according to WHO Essential Medicines List[a]	Solubility[b]	Permeability[c]	BCS class[d]	Dissolution test (for biowaiver)[e]	Potential risks[f]	Indication(s) according to WHO Essential Medicines List[a]	Comments and special dosage form indications[a]
pyrimethamine	25 mg	borderline; < 0.1 mg/ml[3]	low	4/3	Not eligible for biowaiver		anti-pneumocystosis and antitoxoplasmosis medicine	
quinine bisulfate or sulfate	300 mg	high	high	1	9.2.1.1		antimalarial	
ranitidine hydrochloride	150 mg	high	low	3	9.2.1.2		antiulcer medicine	
retinol palmitate	110 mg (200 000 IU)	low (*3*)	low (?)	4/2	Not eligible for biowaiver		vitamin	unknown whether poor BA is due to poor solubility *or* poor solubility and poor permeability
riboflavin	5 mg	high	high	1	9.2.1.1		vitamin	
rifampicin	300 mg	low (amphiphilic) (pK_a 1.7, 7.9) (*1*)	high	2	Not eligible for biowaiver		antileprosy and antituberculosis medicine	
rifampicin (r) + isoniazid (i)	(r) 300 mg + (i) 150 mg	(r) low + (i) high	(r) high + (i) borderline	(r) 2 + (i) 3/1	See footnote[g]		antituberculosis medicine	
rifampicin (r) + isoniazid (i) + pyrazinamide (p)	(r) 150 mg + (i) 150 mg + (p) 500 mg	(r) low + (i) high + (p) high	(r) high + (i) borderline + (p) borderline	(r) 2 + (i) 3/1 + (p) 3/1	See footnote[g]		antituberculosis medicine	

BA, bioavailability.

rifampicin (r) + isoniazid (i) + pyrazinamide (p) + ethambutol (e)	(r) 150 mg + (i) 75 mg + (p) 400 mg + (e) 275 mg	(r) low + (i) high + (p) high + (e) high	(r) high + (i) borderline + (p) borderline + (e) low	(r) 2 + (i) 3/1 + (p) 3/1 + (e) 3	See footnote[g]		antituberculosis medicine	
ritonavir	100 mg	low	low (?)	4/2	Not eligible for biowaiver	CYP 450 3A4	antiretroviral	unknown whether poor BA is due to poor solubility *or* poor solubility and poor permeability
salbutamol sulfate	4 mg	high	high	1	9.2.1.1		antiasthmatic and medicine for COPD	
saquinavir	200 mg	low	low (?)	4/2	Not eligible for biowaiver	CYP 450 3A4, food effect (+)	antiretroviral	unknown whether poor BA is due to poor solubility *or* poor solubility and poor permeability
senna	7.5 mg (sennoside)	–	–	NR	NA		laxative	local effect
spironolactone	25 mg	borderline	low	4/3	Not eligible for biowaiver		diuretic	
stavudine	40 mg	high	high	1	9.2.1.1		antiretroviral	
sulfamethoxazole (s) + trimethoprim (t)	(s) 400 mg + (t) 80 mg	(s) low (amphiphil) + (t) low (weak base)	(s) high + (t) high	(s) 2 + (t) 2	Not eligible for biowaiver	G6PD deficiency	antibacterial	

G6PD, Glucose-6-phosphate dehydrogenase; BA, bioavailability; COPD: Chronic Obstructive Pulmonary Disease.

Medicine[a]	Highest oral strength according to WHO Essential Medicines List[a]	Solubility[b]	Permeability[c]	BCS class[d]	Dissolution test (for biowaiver)[e]	Potential risks[f]	Indication(s) according to WHO Essential Medicines List[a]	Comments and special dosage form indications[a]
sulfasalazine	500 mg	low	low	4	NR		gastrointestinal, anti-inflammatory medicine	used for local action in the gastrointestinal tract
thiamine hydrochloride	50 mg	high	low	3	9.2.1.2		vitamin	
triclabendazole	250 mg	insufficient literature	low	4/3	Not eligible for biowaiver		antischistosomal, antitrematode	
trimethoprim	200 mg	low (weak base)	high	2	Not eligible for biowaiver		antibacterial	
valproic acid sodium salt	500 mg	high	high	1	see comment		antiepileptic, psychotherapeutic medicine	enteric-coated tablet → not eligible for biowaiver in this dosage form[l]
verapamil hydrochloride	80 mg	low (weak base)	high	2	Not eligible for biowaiver		antianginal and antiarrhythmic medicine	
warfarin sodium salt	5 mg	high (soluble 1 in less than 1 of water) (*1*)	high	1	9.2.1.1	narrow therapeutic index	medicines affecting coagulation	
zidovudine	300 mg	high	high	1	9.2.1.1		antiretroviral	
zinc sulfate	10 mg (per unit dosage form)	high	low	3	9.2.1.2		diarrhoea in children	

[a] *14th WHO Model List of Essential Medicines*, March 2005; available at: http://whqlibdoc.who.int/hq/2005/a87017_eng.pdf.
[b] Solubility based on the lowest solubility in the pH range from 1 to 6.8 at 37 °C. "Low" indicates a dose[a] :solubility ratio > 250 ml for at least one pH value in this range.
[c] Permeability based on fraction of the dose absorbed after oral dosing in humans, except where otherwise indicated. "Low" indicates that less than 85% of the oral dose was absorbed at the highest oral strength listed in the EML.
[d] The acceptance criteria that have been adapted by WHO are explained in Section 2 ("WHO revisions to the criteria for BCS classification").
[e] WHO "Multisource document": *Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability* (WHO Technical Report Series, No. 937, Annex 7).
[f] Known potential risks are indicated where appropriate. Where no information is given, this often indicates lack of availability of data and should not be construed as meaning that there are no risks associated with use of the compound. Assessment of risks should be made by the individual national authority based on local conditions of use.
[g] The possibility of biowaiving fixed-dose combinations of antituberculosis drugs is still under consideration because of their specific stability, toxicity and interaction issues.
[h] Medicine is applied sublingually, major site of absorption is from the oral cavity.
[i] Dosage form not designed for immediate release.

NR, not relevant: locally acting, no significant systemic absorption.
NA, not applicable, includes: locally acting, systemic absorption from the oral cavity or dosage form not designed for immediate release.

Compounds introduced to the EML since March 2005 or for which no classification had been previously reported.

1. *Clarke's analysis of drugs and poisons*. 3rd ed. London, Pharmaceutical Press, Royal Pharmaceutical Society of Great Britain, 2004.
2. Brittain K, Florey HG. *Analytical profiles of drug substances and excipients*. Oxford University Press.
3. Sweetman S. *Martindale: the complete drug reference*, 34th ed. London, Pharmaceutical Press, 2004.
4. Stippler E. [Dissertation]. Biorelevant Dissolution Test Methods to Assess Bioequivalence of Drug Products. Germany, Johann-Wolfgang von Goethe University Frankfurt, 2004.
5. *Merck index*. New Jersey, USA, Merck Publishers, 2004.

Ferrous salts:
Commonly used iron salts:[3]
- ferrous ascorbate (anhydrous)
- ferrous aspartate (tetrahydrate)
- ferrous chloride (tetrahydrate)
- ferrous fumarate (anhydrous)
- ferrous gluconate (dihydrate)
- ferrous glycine sulfate
- ferrous orotate
- ferrous succinate (anhydrous)
- ferrous sulfate (dried)
- ferrous sulfate (heptahydrate)

Solubility of ferrous salts:
- lowest solubility of all commonly used iron salts: ferrous succinate anhydrous, sparingly soluble in water[5] (dose:solubility ratio 6ml)

Table 2

Active pharmaceutical ingredients on the complementary list of the *WHO Model List of Essential Medicines* (EML)

Medicine[a]	Highest oral strength according to WHO Essential Medicines List[a]	Solubility[b]	Permeability[c]	BCS class[d]	Dissolution test (for biowaiver)[e]	Potential risks[f]	Indication(s) according to WHO Essential Medicines List[a,g]	Comments and special dosage form indications[a]
artesunate	50 mg	low	borderline (BA_{abs} 82–88%) but dependent on severity of disease (*1, 2*)	4/2	Not eligible for biowaiver	extent of absorption depends on severity of disease	antimalarial	
azathioprine sodium salt	50 mg	low	low (?)	4/2	Not eligible for biowaiver	immunosuppressive, TDM recommended	immunosuppressive, DMARD	unknown whether poor BA is due to poor solubility *or* poor solubility and poor permeability
calcium folinate	15 mg	high	high	1	9.2.1.1		anticytotoxic medicine	
chlorambucil	2 mg	high	insufficient literature (BA after repeated dosage > 70% but urinary analytical profile i.v. similar to p.o.) (*3, 4*)	3/1	9.2.1.2	myelosuppression (leukopenia) = dose-limiting toxicity	cytotoxic medicine[g]	
cyclosporine	25 mg	low	low	4/3	Not eligible for biowaiver	immunosuppressive, TDM recommended	immunosuppressive	

TDM: Therapeutic Drug Monitoring; DMARD, disease modifying antirheumatic drug; BA, bioavailability; i.v., intravenous; p.o. per orale.

clindamycin	150 mg	high	high	1	9.2.1.1		antibacterial	
cyclophosphamide	25 mg	high	high	1	9.2.1.1	myelosuppression (leukopenia) = dose-limiting toxicity, accelerated metabolism leading to reduced oral BA after repeated treatment cycles	cytotoxic medicine[g]	
cycloserine	250 mg	high	insufficient literature (urinary recovery 65% (*5*), 70–90% of the dose is absorbed (*6*))	3/1	9.2.1.3	serum levels > 30 µg/ml associated with CNS toxicity	antituberculosis medicine	
diethylcarbamazine dihydrogen citrate	100 mg	high	high	1	9.2.1.2	myelosuppression (leukopenia) = dose-limiting toxicity, accelerated metabolism leading to reduced oral BA after repeated treatment cycles	antifilarial	

BA, Bioavailability; CNS, central nervous system; GI gastrointestinal.

Medicine[a]	Highest oral strength according to WHO Essential Medicines List[a]	Solubility[b]	Permeability[c]	BCS class[d]	Dissolution test (for biowaiver)[e]	Potential risks[f]	Indication(s) according to WHO Essential Medicines List[a,g]	Comments and special dosage form indications[a]
doxycycline hydrochloride	100 mg	high	high	1	9.2.1.1		antimalarial	
ethionamide	250 mg	high	insufficient literature ("readily absorbed from the GI tract") (*7*)	3/1	9.2.1.2		antituberculosis medicine	
ethosuximide	250 mg	high	insufficient literature	3/1	9.2.1.2		antiepileptic	
etoposide	100 mg	low	low (?)	4/2	Not eligible for biowaiver	myelosuppression (leukopenia) = dose-limiting toxicity, accelerated metabolism leading to reduced oral BA after repeated treatment cycles	cytotoxic medicine[g]	unknown whether poor BA is due to poor solubility *or* poor solubility and poor permeability
flucytosine	250 mg[3]	high	borderline (BA_{abs} 76–89%) (*8, 9*)	3/1	9.2.1.2		antifungal	

BA, Bioavailability; DMARD, disease modifying antirheumatic drug.

levamisole hydrochloride	50 mg	high	no human data available	3/1	9.2.1.2		cytotoxic medicine[g]	
levofloxacin	500 mg	high	high	1	9.2.1.1		antituberculosis medicine	
mefloquine hydrochloride	250 mg	low	insufficient literature ("well absorbed") (*7*)	4/2	Not eligible for biowaiver	pharmacokinetics of mefloquine may be altered by malaria infection (*7*)	antimalarial	
mercaptopurine	50 mg	low	low (?)	4/2	Not eligible for biowaiver		cytotoxic medicine[g]	unknown whether poor BA is due to poor solubility *or* poor solubility and poor permeability
methotrexate sodium salt	2.5 mg	high	low	3	9.2.1.2	severity of adverse effects depends on dose and indication	cytotoxic medicine[g], DMARD	
mifepristone – misoprostol	200 mg	no literature data available	low	4/3	Not eligible for biowaiver at present		oxytocic	
ofloxacin	400 mg	high	high	1	9.2.1.1		antituberculosis medicine	
oxamniquine	250 mg	low	insufficient literature (urinary recovery as single acid 70%) (*7*)	4/2	Not eligible for biowaiver		antischistosomal, antitrematode	

BA, Bioavailability; DMARD, disease modifying antirheumatic drug.

Medicine[a]	Highest oral strength according to WHO Essential Medicines List[a]	Solubility[b]	Permeability[c]	BCS class[d]	Dissolution test (for biowaiver)[e]	Potential risks[f]	Indication(s) according to WHO Essential Medicines List[a,g]	Comments and special dosage form indications[a]
p-aminosalicylic acid	500 mg	low	borderline (80% urinary recovery (*7*)	4/2	Not eligible for biowaiver		antituberculosis medicine	
penicillamine	250 mg	high	low	3	9.2.1.2		DMARD	
pentamine	300 mg	high	no literature data	3/1	9.2.1.2		anti-pneumocystosis and anti-toxoplasmosis medicine	
prednisolone	25 mg	high	high	1	9.2.1.1		hormone/ antihormone	
procarbazine hydrochloride	50 mg	high	insufficient literature (urinary recovery 70%, 24 h) (*5*)	3/1	9.2.1.2	myelosuppression (leukopenia) = dose-limiting toxicity	cytotoxic medicine[g]	
pyridostigmine bromide	60 mg	high	low	3	9.2.1.2		muscle relaxant	
quinidine sulfate	200 mg	high	insufficient literature (BA 70% but first pass) (*5*)	3/1	9.2.1.2		antiarrhythmic	
sulfadiazine	500 mg	borderline	low	4/3	Not eligible for biowaiver		antibacterial	

BA, Bioavailability; DMARD, disease modifying antirheumatic drug.

sulfadoxine (s) + pyrimeth-amine (p)	(s) 500 mg + (p) 25 mg	(s) high + (p) border-line (< 0.1 mg/ml (*7*)	(s) insufficient data + (p) low	(s) 3/1+ (p) 4/3	Not eligible for biowaiver		antimalarial	
sulfasalazine	500 mg	low	low	4	NR		DMARD	Used for local action in the gastro-intestinal tract
tamoxifen citrate	20 mg	high	high	1	9.2.1.1		antihormone	

[a] *14th WHO Model List of Essential Medicines*, Geneva, World Health Organization, March 2005; available at: http://whqlibdoc.who.int/hq/2005/a87017_eng.pdf.

[b] Solubility based on the lowest solubility in the pH range from 1 to 6.8 at 37 °C. "Low" indicates a dose[a] :solubility ratio > 250ml for at least one pH value in this range.

[c] Permeability based on fraction of the dose absorbed after oral dosing in humans, except where otherwise indicated. "Low" indicates that less than 85% of the oral dose was absorbed at the highest oral strength in the EML.[a]

[d] The original Biopharmaceutics Classification System (BCS)is available at: http://www.fda.gov/cder/guidance/3618fnl.pdf .

Note: the acceptance criteria have been adapted according to WHO requirements as explained in Section 2 of this Annex.

[e] See WHO "Multisource document": *Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability* (WHO Technical Report Series, No. 937, Annex 7).

[f] Known potential risks are indicated where appropriate. Where no information is given, this may indicate lack of availability of relevant data and should not be construed as meaning that there are no risks associated with use of the compound. Assessment of risks should be made by the national authority based on local conditions of use.

[g] Cytotoxic medicines: the risks associated with applying the biowaiver procedure should be very carefully scrutinized by the national regulatory authority.

NR not relevant: locally acting, no significant systemic absorption.

Compounds introduced to the EML since March 2005 or for which no classification had been previously reported.

1. Newton P et al. Antimalarial bioavailability and disposition of artesunate in acute falciparum malaria. *Antimicrobial Agents and Chemotherapy*, 2000, 44:972-977.
2. Newton PN et al. Comparison of oral artesunate and dihydroartemisinin antimalarial bioavailabilities in acute falciparum malaria. *Antimicrobial Agents and Chemotherapy*, 2002, 46:1125-1127.
3. McLean A et al. Pharmacokinetics and metabolism of chlorambucil in patients with malignant disease. *Cancer Treatment Reviews,* 1979, 6, Suppl:33-42.
4. Silvennoinen R et al. Pharmacokinetics of chlorambucil in patients with chronic lymphocytic leukaemia: comparison of different days, cycles and doses. *Pharmacology & Toxicology,* 2000, 87:223-228.
5. *Clarke's Analysis of Drugs and Poisons*. 3rd ed. London, Pharmaceutical Press, 2004.
6. Brittain HG, Florey K. *Analytical Profiles of Drug Substances and Excipients*. ed. Oxford University Press.
7. Sweetman S. *Martindale: The complete drug reference*. 34 ed. London, Pharmaceutical Press, 2004.
8. Vermes A et al. Population pharmacokinetics of flucytosine: comparison and validation of three models using STS, NPEM, and NONMEM. *Therapeutic Drug Monitoring*, 2000, 22:676-687.
9. Vermes A, Guchelaar HJ, Dankert J. Flucytosine: a review of its pharmacology, clinical indications, pharmacokinetics, toxicity and drug interactions. *Journal of Antimicrobial Chemotherapy*, 2000, 46:171-179.

Table 3

Compounds introduced to the *WHO Model List of Essential Medicines* since March 2005 for which no certain classification had been previously reported (these compounds also appear in Table 1 and Table 2)

Medicine[a]	Highest oral strength according to WHO Essential Medicines List[a]	Solubility[b]	Permeability[c]	BCS class[d]	Dissolution test (for biowaiver)[e]	Potential risks[f]	Indication(s) according to WHO Essential Medicines List (EML)[a]	Comments and special dosage form indications[a]
amlodipine	5 mg	slightly soluble (*1*), D:S 5 ml	BA_{abs} 60–65%, excretion of drug metabolites in urine 90–95% (*2*)	1	9.2.1.1		antihypertensive medicine	BA_{abs} < 85% ascribed to first-pass metabolism
amodiaquine (base)	200 mg	45 mg/ml[2], D:S 4.4 ml	BA > 75% (*3*)	3/1	9.2.1.2	CYP2C8 polymorphism, increased risk for agranulocytosis and hepatotoxicity (*4*)	antimalarial	
amoxicillin + clavulanic acid	500 mg + 125 mg	freely soluble in water (*1*), D:S 1.25 ml	absorption > 73% (*5*)	1 + 3/1	9.2.1.2		antibacterial	tests based on clavulanic acid classification
artesunate	50 mg	very slightly soluble (*6*), D:S 500 ml; (weak acid, pK_a ~ 6.4)	BA_{abs} 82% (*1*), BA_{abs} 88% (*7*), BA_{abs} 61% (*8*)	4/2	Not eligible for biowaiver		antimalarial	permeability depends on severity of disease

D:S, Dose: solubility; BA, Bioavailability.

azithromycin	500 mg	practically insoluble in water (*1*) < 0.01mg/ml, D:S 50 000 ml	BA_{abs} 16% (*9*); BA 37% (*10, 11*);	4/2	Not eligible for biowaiver		antibacterial	unknown whether poor BA is due to poor solubility *or* poor solubility and poor permeability
calcium folinate	15 mg	sparingly soluble in water (Ph. Eur. 5.2); very soluble (USP 28); D:S 15 ml and 0.015 ml, respectively	BA_{abs} 92% 25 mg (*12, 13*); BA_{abs} 73.4% (15 mg) (*14*); fully absorbed; AUC and $t_{1/2}$ similar after i.v. & p.o (*15*)	1	9.2.1.1		anticytotoxic medicine	
levodopa (l) + carbidopa (c)	(l) 250 mg + (c) 25 mg	(l) high + (c) soluble 1 in 500 of water, freely soluble in 3 M HCl (*1*)	(l) high + (c) BA 58% (16); BA_{abs} 88% (dogs) (*17*)	(l) 1 + (c) 3/1	9.2.1.2	narrow therapeutic index	antiparkinson medicine	tests based on carbidopa classification
cefixime	400 mg	slightly soluble (*2*), D:S 400 ml	22–54% (*2*)	4	Not eligible for biowaiver		antibacterial	

D:S, Dose: solubility; BA: Bioavailability; Ph.Eur., *European Pharmacopoeia*; USP, *United States Pharmacopoeia*; AUC, area under the curve; i.v., intravenous.

Medicine[a]	Highest oral strength according to WHO Essential Medicines List[a]	Solubility[b]	Permeability[c]	BCS class[d]	Dissolution test (for biowaiver)[e]	Potential risks[f]	Indication(s) according to WHO Essential Medicines List (EML)[a]	Comments and special dosage form indications[a]
chlorambucil	2 mg	"practically insoluble in water" (*1*), but D:S ~ 20 ml	i.v. vs. p.o. similar analytical profile in urine = high degree of absorption (*18*), BA_{abs} > 70% after repeated oral dosage (*19, 20*)	3/1	9.2.1.2	myelosuppression (leukopenia) = dose-limiting toxicity; accelerated metabolism leading to reduced oral BA after repeated treatment cycles (*21, 22*)	cytotoxic medicine[g]	
clindamycin	150 mg	500 mg/ml[2], D:S 0.3 ml	about 90% of the dose absorbed (*1*)	1	9.2.1.1	diarrhoea/ nausea	antibacterial	
cylcoserine	250 mg	soluble 100 mg/ml[2], D:S 2.5 ml	65% urinary excretion (*2*), 70–90% of a p.o. dose absorbed (*23*)	3/1	9.2.1.2	serum levels > 30 µg/ml associated with CNS toxicity	antituberculosis medicine	

i.v., intravenous; p.o., per orale; BA: Bioavailability; D:S, Dose: solubility.

enalapril	2.5 mg	sparingly soluble in water (*1*), D:S 0.25 ml; dissolves in dilute solutions of alkali hydroxides (*1*)	absorption p.o. 69%, urinary recovery 77%, BA 38%, first pass 10% (*24*); p.o. children, urinary recovery ~ absorption 50% (*25*)	3	9.2.1.2		antihypertensive medicine	
ethionamide	250 mg	slightly soluble in water at 25° C (*2*) D:S < 250 ml	readily absorbed from the gastrointestinal tract, extensively metabolized, probably in the liver, less than 1% of a dose appears in the urine as unchanged drug (*1*)	3/1	9.2.1.2		antituberculosis medicine	

D:S, Dose: solubility; BA: Bioavailability; p.o., per orale.

Medicine[a]	Highest oral strength according to WHO Essential Medicines List[a]	Solubility[b]	Permeability[c]	BCS class[d]	Dissolution test (for biowaiver)[e]	Potential risks[f]	Indication(s) according to WHO Essential Medicines List (EML)[a]	Comments and special dosage form indications[a]
etoposide	100 mg	practically insoluble in water (*2*), D:S 1000 ml	excretion 30–50% unchanged in the urine, 20% as metabolites = 50–70% (*2*), absorption 48–57% (*23*), 60% absorption in children (*26*)	4/2	Not eligible for biowaiver	myelosuppression (leukopenia) = dose-limiting toxicity; great variability in absorption (all references)	cytotoxic medicine[g]	unknown whether poor BA is due to poor solubility *or* poor solubility and poor permeability
ferrous salt	equivalent to 60 mg iron	high (see footnote, Table 1)	low	3	9.2.1.2		antianaemia medicine	applies to commonly used salts
ferrous salt (fs) + folic acid (fa)	equivalent to 60 mg iron + 400 µg folic acid	(fs) high (see footnote) + very slightly soluble in water (*2*), D:S 2.5ml; 0,0016 mg/ml (25 °C) water (*23*), D:S 250 ml	(fs) low + (fa) low (urinary recovery 28% (*23*))	(fs) 3 + (fa) 3/1	9.2.1.2		antianaemia medicine (during pregnancy)	combination should be tested according to requirements for BCS Class III compounds; applies to commonly used iron salts

D:S, Dose: solubility; BA: Bioavailability.

flucytosine	250 mg	soluble 15 mg/ml (*2*), D:S 17 ml; 14.2 mg/ml (*23*); D:S 17.6 ml	BA_{abs} 76–89% (*27, 28*)	3/1	9.2.1.2		antifungal	
levofloxacin	500 mg	high (30–300 mg/ml) (*29*) D:S 16.7 ml	high (oral vs i.v. 100% BA; Caco-2 permeability high) (*29*)	1	9.2.1.1	for main side-effects refer to (*30*)	antituberculosis medicine	
mebendazole	500 mg	practically insoluble in water (both monohydrate and anhydrous (*2*)), D:S > 50 000 ml	BA_{abs} 2% (*31*); urinary recovery 2% of orally administered dose (*32*)	4/2	NA		anthelminthic	Chewable tablet, anthelminthics usually administered orally for action in GI tract: solubility more important than permeability – but unknown whether poor BA is due to poor solubility *or* poor solubility and poor permeability
medroxy-progesterone acetate	5 mg	practically insoluble in water (*2*), 1 g in >10 000 ml, < 0.1 mg/ml, D:S < 50 ml	in rats + dogs BA 27% first-pass metabolism, self-induced metabolism; 16% and very variable (*2*)	3/1	9.2.1.2		progestogen	extent of first-pass metabolism in humans uncertain

D:S, Dose: solubility; BA: Bioavailability; i.v., intravenous.

Medicine[a]	Highest oral strength according to WHO Essential Medicines List[a]	Solubility[b]	Permeability[c]	BCS class[d]	Dissolution test (for biowaiver)[e]	Potential risks[f]	Indication(s) according to WHO Essential Medicines List (EML)[a]	Comments and special dosage form indications[a]
mercaptopurine	50 mg	low (insoluble in water; pK_a 7.7/ 11.0, < 0.1 mg/ml)[2], D:S > 500 ml (*2*)	BA_{oral} von aza 47%, first pass, 50% in urine (2)	4/2	Not eligible for biowaiver	antimetabolite, TDM suggested by Lennard (*1*)	cytotoxic medicine[g]	unknown whether poor BA is due to poor solubility *or* poor solubility and poor permeability
mifepristone – misoprostol	200 mg	no information available	BA 70%; also reported 40% after 100 mg oral dose (*2*)	4/3	Not eligible for biowaiver at present		oxytocic	insufficient information available
niclosamide	500 mg	5–8mg/l (20 °C) (*33*), D:S 77 000 ml	2–25% of a dose of 2 g radiolabelled drug recovered in the urine, rest in faeces (*33*)	4/2	NA		anthelminthic	chewable tablet, anthelminthics usually applied orally for action in GI tract: solubility more important than permeability
ofloxacin	400 mg	high (30–300 mg/ml) (*29*), D:S 13 ml	dose proportional 100% BA (*29*)	1	9.2.1.1	for main side- effects refer to (*30*)	antituberculosis medicine	

D:S, Dose: solubility; BA: Bioavailability; TDM, therapeutic drug monitoring; GI, gastrointestinal.

oxamniquine	250 mg	low (1 in 3300 at 27 °C, 0.3 mg/ml) (*23*), D:S 825 ml	"readily absorbed", urinary excretion 70% as single acid (*1*)	4/3	Not eligible for biowaiver	no significant toxic effects on liver, kidney or heart, dose 15 mg/kg (*1*)	antischistosomal, antitrematode	
p-aminosalicylic acid	500 mg	low (1 g in 600 ml, 1.66 mg/ml) (*23*); D:S 301 ml, weak acid, pK_a not found in literature	borderline, 80% excretion in urine (*1*)	4/2	Not eligible for biowaiver at present		antituberculosis medicine	borderline in both solubility and permeability – solubility profile needs to be better characterized
pentamine	300 mg	high (1 in 10 → 100 mg/ml)[2], D:S 3 ml	no information available	3/1	9.2.1.2		anti-pneumocystosis and antitoxoplasmosis medicine	
potassium iodide	60 mg	very soluble in water, D:S < 0.06 ml	BA 96.4% (*35*); urinary recovery 89%, faeces 11% (*36*)	1	9.2.1.1		thyroid hormones and antithyroid medicines	
procarbazine hydrochloride	50 mg	high (200 mg/ml) (*23*), D:S 0.25 ml	readily absorbed, 70% dose excreted in urine after 24h (*2*)	3/1	9.2.1.2	tumour inhibitor, haematologic (*2*)	cytotoxic medicine[g]	

D:S, Dose: solubility; BA: Bioavailability.

Medicine[a]	Highest oral strength according to WHO Essential Medicines List[a]	Solubility[b]	Permeability[c]	BCS class[d]	Dissolution test (for biowaiver)[e]	Potential risks[f]	Indication(s) according to WHO Essential Medicines List (EML)[a]	Comments and special dosage form indications[a]
pyrantel embonate	250 mg	low (practically insoluble in water, 1 g in >10 000 ml[2], < 0.1 mg/ml), D:S > 2500 ml	16% BA_{oral} (palmoate), 41% oral BA (citrate) (*37*)	4/2	NA		anthelminthic	chewable tablet, anthelminthics usually applied orally for action in GI tract:solubility more important than permeability
quinidine sulfate	200 mg	high (10 mg/ml) (*23*), D:S 20 ml	rapidly absorbed BA 70%; permeability varies widely, first pass (*2*)	3/1	9.2.1.2	narrow therapeutic index	antiarrhythmic	
ranitidine hydrochloride	150 mg	high (freely soluble in water (*2*) > 1000 mg/ml), D:S 0.15 ml	50% BA, first pass (*2, 38*)	3/1	9.2.1.2		antiulcer medicine	
sulfadoxine	25 mg	very slightly soluble in water (*2*), D:S < 250 ml	readily absorbed after oral administration (*2*)	3/1	9.2.1.2		antimalarial	

D:S, Dose: solubility; BA: Bioavailability; GI, gastrointestinal.

tamoxifen citrate	20 mg	high (very slightly soluble in water (*1*), 0.1 mg/ml -1 mg/ml), D:S 200 ml	BA_{abs} ~ 100% (*39*)	1	9.2.1.1	endometrial cancer, uterine sarcoma (*1*)	antihormone	
zinc sulfate	10 mg (per unit dosage form)	high (very soluble in water) (*1*), D:S 0.01, same solubility for all hydrates of the sulfate	11 % absorbed, with meal versus percentage of i.v. dose absorbed 20–30%	3	9.2.1.2		diarrhoea in children	

D:S, Dose:solubility; BA, bioavailability; i.v., intravenous.

[a] *14th WHO Model List of Essential Medicines*, Geneva, World Health Organization, March 2005; available at: http://whqlibdoc.who.int/hq/2005/a87017_eng.pdf.

[b] Solubility based on the lowest solubility in the pH range from 1 to 6.8 at 37 °C. "Low" indicates a dose[a] :solubility ratio > 250ml for at least one pH value in this range.

[c] Permeability based on fraction of the dose absorbed after oral dosing in humans, except where otherwise indicated. "Low" indicates that less than 85% of the oral dose was absorbed at the highest oral strength in the EML.[a]

[d] The original Biopharmaceutics Classification System (BCS) is available at: http://www.fda.gov/cder/guidance/3618fnl.pdf.

Note: the acceptance criteria have been adapted according to WHO requirements as explained in Section 2 of this Annex.

[e] See WHO "Multisource document": *Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability* (WHO Technical Report Series, No. 937, Annex 7).

[f] Known potential risks are indicated where appropriate. Where no information is given, this may indicate lack of availability of relevant data and should not be construed as meaning that there are no risks associated with use of the compound. Assessment of risks should be made by the national authority based on local conditions of use.

[g] Cytotoxic medicines: the risks associated with applying the biowaiver procedure should be very carefully scrutinized by the national regulatory authority.

NR not relevant: locally acting, no significant systemic absorption.

NA not applicable, locally acting.

Ferrous salts: (see footnote to Table 1).

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WHO Technical Report Series, No. 937, 2006

Annex 9

Additional guidance for organizations performing in vivo bioequivalence studies

Introduction

Multisource pharmaceutical products need to conform to the same standards of quality, efficacy and safety as required of the originator's (comparator) product. Specifically, the multisource product should be therapeutically equivalent and interchangeable with the comparator product. Testing the bioequivalence between a product and a suitable comparator (pharmaceutically equivalent or a pharmaceutical alternative) in a pharmacokinetic study with a limited number of subjects is one way of demonstrating therapeutic equivalence without having to perform a clinical trial involving many patients. In such a pharmacokinetic study any statement about the safety and efficacy of the test product will be a prediction based on measurement of systemic concentrations, assuming that essentially similar plasma concentrations of the drug will result in essentially similar concentrations at the site of action, and thus an essentially similar therapeutic outcome. The bioequivalence study thus provides indirect evidence of the efficacy and safety of a multisource drug product. Often this will be the only evidence that the product is safe and efficacious. It is therefore crucial that the bioequivalence study is performed in an appropriate manner. Several guidance documents stress the importance of on-site inspections to verify compliance with standards of good clinical practice (GCP) (*1*, *2*).

The WHO prequalification project was started in 2001 to assure that medicinal products supplied for procurement meet WHO norms and standards with respect to quality, safety and efficacy (http://www.who.int/medicines/). Specifically it is a requirement that the submitted product dossier with all its necessary contents is assessed and found acceptable, and that the manufacturing sites of both the finished pharmaceutical product and of the active pharmaceutical ingredient (API), are inspected and found to comply with WHO good manufacturing practices (GMP). Because products submitted to the prequalification project are usually multisource ("generic") products, therapeutic equivalence is generally demonstrated by performing a bioequivalence study, for example in a contract resource organization (CRO). For prequalification of such a product it is vital that, in addition to the above-mentioned requirements, the CRO used by the sponsor to undertake the bioequivalence studies complies with WHO GCP and considers relevant elements from WHO good laboratory practice (GLP) and good practices for quality control laboratories to ensure integrity and traceability of data. Those involved in the conduct and analysis of bioequivalence studies on products to be submitted for prequalification therefore need to ensure that they comply with the above-mentioned WHO norms and standards to be prepared for any inspections by WHO.

1. Scope

The objective of this document is to provide guidance to organizations involved in the conduct and analysis of in vivo bioequivalence studies.

Bioequivalence studies should be performed in compliance with the general regulatory requirements and recommendations on good practices as specified in the WHO bioequivalence guidelines (*3*), good clinical practices (*1*) and good laboratory practices (*4*) guidelines.

The text below lists general recommendations for organizations (including CROs and laboratories) conducting bioequivalence studies and analysis of clinical trial samples. Recommendations for facilities and equipment are listed in the respective paragraphs. Recommended documents and records are listed in Appendix 1.

This document provides information on:

— organization and management;
— study protocols;
— clinical phase of a study;
— bioanalytical phase of a study;
— pharmacokinetic and statistical analysis; and
— study report.

The present guidelines target organizations conducting bioequivalence studies and highlight certain important aspects of the activities of such organizations. This document does not replace the above-mentioned GCP or GLP or good practices for quality control laboratories guidelines, which are more complete. It is, therefore, not a stand-alone document. For further guidance, see the guidelines for GCP for trials on pharmaceutical products (*1*).

2. Glossary[1]

The definitions given below apply to the terms used in this guidance. They may have different meanings in other contexts.

adverse event

Any untoward medical occurrence in a clinical trial subject administered a pharmaceutical product; it does not necessarily have a causal relationship with the treatment.

audit of a trial

A systematic examination, carried out independently of those directly involved in the trial, to determine whether the conduct of a trial complies with the agreed protocol and whether the data reported are consistent with the records on site, e.g. whether data reported or recorded in the case-report forms (CRFs) are consonant with those found in hospital files and other original records.

[1] Reproduced from *Guidelines for WHO good clinical practice (GCP) for trials on pharmaceutical products*. Geneva, World Health Organization, 1995 (WHO Technical Report Series, No. 850):97–137.

bioequivalence test

A test that determines the equivalence between the multisource product and the comparator product using in vivo and/or in vitro approaches.

case-report form (CRF)

A document that is used to record data on each trial subject during the course of the trial, as defined by the protocol. The data should be collected by procedures which guarantee preservation, retention and retrieval of information and allow easy access for verification, audit and inspection.

comparator product

A pharmaceutical or other product (which may be a placebo) used as a reference in a clinical trial.

contract

A document, dated and signed by the investigator, institution and sponsor, that sets out any agreements on financial matters and delegation/distribution of responsibilities. The protocol may also serve as a contract when it contains such information and is signed.

contract research organization

A scientific organization (commercial, academic or other) to which a sponsor may transfer some of its tasks and obligations. Any such transfer should be defined in writing.

ethics committee

An independent body (a review board or a committee, institutional, regional or national), constituted of medical professionals and non-medical members, whose responsibility is to verify that the safety, integrity and human rights of the subjects participating in a particular trial are protected and to consider the general ethics of the trial, thereby providing public reassurance. Ethics committees should be constituted and operated so that their tasks can be executed free from bias and from any influence of those who are conducting the trial.

final report

A comprehensive description of the trial after its completion including a description of experimental methods (including statistical methods) and materials, a presentation and evaluation of the results, statistical analysis and a critical, ethical, statistical and clinical appraisal.

good clinical practice (GCP)

A standard for clinical studies which encompasses the design, conduct, monitoring, termination, audit, analysis, reporting and documentation of the studies

and which ensures that the studies are scientifically and ethically sound and that the clinical properties of the pharmaceutical product (diagnostic, therapeutic or prophylactic) under investigation are properly documented.

good laboratory practice (GLP)

A quality system concerned with the organizational process and the conditions under which nonclinical health and environmental safety studies are planned, performed, monitored, recorded, archived and reported.

informed consent

A subject's voluntary confirmation of willingness to participate in a particular trial, and the documentation thereof. This consent should be sought only after all appropriate information has been given about the trial including an explanation of its status as research, its objectives, potential benefits, risks and inconveniences, alternative treatment that may be available, and of the subject's rights and responsibilities in accordance with the current revision of the Declaration of Helsinki.

inspection

An officially-conducted examination (i.e. review of the conduct of the trial, including quality assurance, personnel involved, any delegation of authority and audit) by relevant authorities at the site of investigation and/or at the site of the sponsor in order to verify adherence to GCP and GLP as set out in this document.

investigational labelling

Labelling developed specifically for products involved in a clinical trial.

investigational product (synonym: study product)

Any pharmaceutical product (see definition) or placebo being tested or used as a reference in a clinical trial.

investigator

A person responsible for the trial and for the rights, health and welfare of the subjects in the trial. The investigator should have qualifications and competence in accordance with local laws and regulations as evidenced by an up-to-date curriculum vitae and other credentials. Decisions relating to, and the provision of, medical or dental care must always be the responsibility of a clinically competent person legally allowed to practise medicine or dentistry.

monitor

A person appointed by, and responsible to, the sponsor or CRO for the monitoring and reporting of progress of the trial and for verification of data.

pharmaceutical product

Any substance or combination of substances which has a therapeutic, prophylactic or diagnostic use, or is intended to modify physiological functions, and is presented in a dosage form suitable for administration to humans.

principal investigator

The investigator serving as coordinator for certain kinds of clinical trials, e.g. multicentre trials.

protocol

A document which states the background, rationale and objectives of the trial and describes its design, methodology and organization, including statistical considerations, and the conditions under which it is to be performed and managed. The protocol should be dated and signed by the investigator, the institution involved and the sponsor. It can also function as a contract.

quality assurance relating to clinical trials

Systems and quality control procedures that are established to ensure that the trial is performed and the data are generated in compliance with GCP and GLP. These include procedures to be followed which apply to ethical and professional conduct, standard operating procedures (SOPs), reporting, and professional qualifications or skills of personnel.

raw data

All records or certified copies of original observations, clinical findings or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Such material includes laboratory notes, memoranda, calculations and documents, as well as all records of data from automated instruments or exact, verified copies, e.g. in the form of photocopies or microfiches. Raw data can also include photographic negatives, microfilm, magnetic media (e.g. computer diskettes) and optical media (CD-ROMs).

serious adverse event

An event that is associated with death, admission to hospital, prolongation of a hospital stay, persistent or significant disability or incapacity, or is otherwise life-threatening in connection with a clinical trial.

sponsor

An individual, a company, an institution or an organization which takes responsibility for the initiation, management and/or financing of a clinical trial. When an investigator initiates and takes full responsibility for a trial, the investigator then also assumes the role of the sponsor.

standard operating procedures (SOPs)

Standard, detailed, written instructions for the management of clinical trials. They provide a general framework enabling the efficient implementation and performance of all the functions and activities for a particular trial as described in this document.

study director

According to the Organisation for Economic Co-operation and Development (OECD) Principles of good laboratory practice: the individual responsible for the overall conduct of the nonclinical health and environmental safety study. In a bioequivalence trial, the individual responsible for the conduct of the bioanalytical part of the study.

study product: see investigational product

trial subject

An individual who participates in a clinical trial, either as a recipient of the pharmaceutical product under investigation or as a control. The individual may be:

— a healthy person who volunteers to participate in a trial;
— a person with a condition unrelated to the use of the investigational product;
— a person (usually a patient) whose condition is relevant to the use of the investigational product.

validation

Action of proving and documenting, in accordance with the principles of GCP and GLP, that any procedure, process, equipment (including the software or hardware used), material, activity or system actually and consistently leads to the expected results.

verification (validation) of data

The procedures carried out to ensure that the data contained in the final report match original observations. These procedures may apply to raw data, data in case-report forms (in hard copy or electronic form), computer printouts and statistical analysis and tables.

3. Organization and management

Note: the acronym "CRO" is used throughout this document to refer not only to a contract research organization (CRO), but also to any *organization involved in the conduct or analysis of in vivo bioequivalence studies*. As defined in the International Conference on Harmonisation (ICH) Tripartite Harmonised Guidelines, Guidelines for Good Clinical Practice (*5*), a "CRO" is a person or an organization (commercial, academic or other) contracted by the sponsor to perform one or more of a sponsor's trial-related duties and functions.

3.1 Where national requirements exist as to the legal status of a CRO these have to be complied with. This also applies to research units which are a subsidiary of the manufacturer.

3.2 The CRO should have an organizational chart that lists the key positions and the names of responsible people. The organizational chart should be authorized (signed and dated).

3.3 There should be job descriptions for all personnel, including a description of the responsibilities of key personnel.

3.4 There should be a list of sample signatures of authorized personnel.

4. Computer systems

Note: computer systems should be qualified (hardware and software) *(6)*.

Qualification is the planning, carrying out and recording of tests on equipment and systems, which form part of the validated process, to demonstrate that it will perform as intended.

As many of the data for bioequivalence studies are transferred electronically between organizations involved in the studies, compatible software is essential.

Hardware

4.1 There should be a sufficient number of computers to enable personnel to perform data entry and data handling, required calculations and compilation of reports.

4.2 Computers should have sufficient capacity and memory for the intended use.

4.3 There should be controlled access to the trial-related information entered and stored in computers. The method of access control should be specified (e.g. password protection) and a list of people who have access to the database should be maintained.

Software

4.4 The software programs selected should be suitable for the intended use.

4.5 Software programs used, frequency of virus testing, storage of data and the making, archiving and keeping of back-ups should be specified in writing.

4.6 The programs used should be able to provide the required quality and management information, reliably and accurately. Necessary programmes for data management include word processing, data entry, databases, graph-

ics, pharmacokinetics and statistical programmes. Self-designed software programs must be suitable for the intended use.

Data management

4.7 Data entry includes transfer of the data from source data forms, case-report forms (CRF) and analytical data to the computerized system for pharmacokinetic and statistical analysis and reporting.

4.8 Data-entry procedures should be designed to prevent errors. The data-entry process should be specified in the standard operating procedure (SOP).

4.9 Double-entry of the data should be performed. Data validation methodology (proofreading, double-data entry, electronic logical control) should be specified in writing.

4.10 Changes to data entered in the database should be made by authorized persons only. Changes should be specified and documented.

5. Archive facilities

Note: the CRO should have sufficient and appropriately secure storage space, which should be fireproof, for archiving of trial-related documentation and product samples.

5.1 An SOP should be in place for archiving.

5.2 Access to archive storage areas should be controlled and restricted to authorized personnel.

5.3 The length of period for which study documentation including raw data is kept in the archive should be defined in the SOP and may vary depending on country requirements.

5.4 Product samples should be retained for a specified period in compliance with local requirements or international recommendations as appropriate and should be defined in the SOP.

6. Premises

6.1 Clinical trials must be carried out under conditions which ensure adequate safety for the subjects. The site selected should be appropriate to the stage of development of the product and the potential risk involved.

6.2 The CRO should have sufficient space to accommodate the personnel and activities required to perform the studies.

6.3 The trial site must have adequate facilities, including laboratories. The facilities used for the clinical phase of the study, including areas listed in

paragraph 6.4 should be well organized to allow the activities to be carried out in a logical order. Also, entry to the facility should be restricted and controlled.

6.4 The premises for the various laboratories should be designed to suit the operations to be carried out in them. Sufficient space should be available to avoid mix-ups, contamination and cross-contamination. There should be adequate and suitable storage space for samples, standards, instruments, equipment, solvents, reagents and records. There should be an alarm system and an adequate system to monitor the temperature of the critical stage and storage areas. If there is an automatic alarm system, it has to be tested regularly to ensure its functionality. Daily temperature records should be kept and all the alarm checks should be documented.

6.5 There should be access to telephone, e-mail and facsimile facilities to ensure good communication. The CRO should have the necessary office equipment (e.g. printer and copier) to perform the required activities.

7. Clinical phase

Note: as in vivo bioequivalence trials are considered as clinical trials, specifically as a phase I study, the general requirements and recommendations of GCP apply to all bioequivalence trials. Clinical trials must be carried out under conditions which ensure adequate safety of the subjects. The clinical phase of the study can be performed in the premises of a CRO or in suitable premises in a hospital.

7.1 A CRO should have rooms meeting the requirements listed in the sections below.

7.2 There should be sufficient space to accommodate the study subjects.

7.3 Where appropriate, beds should be available for the volunteers. The necessity for beds and facilities for overnight stays depends on the type of trial and the drug under investigation and should be specified in the trial protocol.

7.4 Facilities for changing and storing clothes and for washing and toilet purposes should be easily accessible and appropriate for the number of users.

7.5 The study site should have the following facilities which should be separate areas where appropriate:

— rooms (areas) for volunteer registration and screening;
— room (area) for volunteers (recreation area);
— ancillary areas for the volunteers;
— restricted-access area for pharmaceutical operations (e.g.storage, repacking, dispensing, documentation) (see also section 13);
— rooms (areas) for dosing and administration of the drug(s) under investigation and sample collection;

— room (area) for sample processing (e.g. plasma separation) and storage (freezer);
— access to controlled storage areas for study materials, medication and documentation including CRFs;
— rooms (areas) in which to prepare standardized meals and a dining hall;
— availability of emergency or first-aid equipment and appropriate rescue medication for use in emergencies.
— adequate facilities for the proper care of subjects who require emergency or other medical care; and
— archiving facilities.

8. Clinical laboratory

8.1 A suitable qualified clinical laboratory should be used for analysing samples.

8.2 Haematological tests, urine analysis and other tests should be performed during the clinical trial as specified in the study protocol.

8.3 The CRO should be supplied with information about analytical methods used in the laboratory, a dated list of laboratory normal ranges and accreditation certificate of the laboratory, if available.

8.4 A current and signed curriculum vitae of the responsible analyst should be available in the laboratory information file.

8.5 Individual reports should be established by the laboratory for each subject and should be included in the CRFs. Source or raw data for all tests performed should be archived by the laboratory.

9. Personnel

9.1 There should be a sufficient number of qualified and appropriately trained personnel for the activities performed. The number of members of staff required depends on the number and complexity of the trials performed by the CRO. At all stages during the trial, including at night, there should be a sufficient number of appropriately qualified and trained personnel to ensure that the rights, safety and well-being of the subjects are maintained, and to take care of the subjects in emergency situations.

9.2 The conduct and analysis of the in vivo bioequivalence studies should be done by the following key persons with appropriate responsibilities:

9.2.1 medical/scientific director
9.2.2 principal investigator/investigator and co-investigators
9.2.3 study director
9.2.4 quality assurance manager

9.2.5 technical manager
9.2.6 quality control manager.

9.3 One person could perform more than one of the above-mentioned functions; however, the person responsible for quality assurance should be independent and report to the head of the organization only.

9.4 Contract workers may be employed to perform certain activities.

9.5 Current curriculum vitae and training records should be kept for full-time and contract workers.

9.6 The personnel responsible for the planning and conduct of the study should have appropriate qualifications and sufficient knowledge and experience in the relevant field.

9.7 Records of training and assessment of knowledge of GCP and GLP should be maintained.

10. Quality assurance

10.1 The CRO should have an appropriate quality assurance (QA) system.

10.2 The QA system and the person(s) responsible for QA should operate independently of those involved in the conduct or monitoring of the trial.

10.3 The QA unit should be responsible for:

— verifying all activities undertaken during the study;
— ensuring that the QA systems, including SOPs of the CRO, are followed, reviewed and updated;
— checking all the study data for reliability and traceability;
— planning and performing self-inspections (internal audits) at regular and defined intervals in accordance with an SOP, and following up on any corrective action as required;
— ensuring that contract facilities, such as analytical laboratories, adhere to good practices for quality control laboratories. This would include auditing of such facilities, and following up on any corrective action as required;
— verifying that the trial report accurately and completely reflects the data of the study.

10.4 The CRO should allow the sponsor to monitor the studies and to perform audits of the clinical and analytical study and the sites.

10.5 The laboratory should have a QA unit which should be independent from the person(s) responsible for analytical work and which should ensure that the analytical method in use is validated and current.

11. Ethics

11.1 Independent ethics committee

Trials must be approved by an independent ethics committee (IEC) (or equivalent) before a study is conducted, according to the enforced legislation (*7*). This committee must be independent from the promoter, the investigator and of the CRO. The discussions, recommendations and decisions of the IEC meetings should be documented in detailed minutes of the meeting. The IEC should be given sufficient time for reviewing protocols, informed consent forms (ICFs) and related documentation.

11.2 Informed consent

- Information for study participants should be given in a language and on a level of complexity appropriate and understandable to the subject, both orally and in writing.
- Informed consent must always be given by the subject and documented in writing before the start of any trial-related activities, in accordance with GCP.
- The information must make clear that participation is voluntary and that the subject has the right to withdraw from the study on his or her own initiative at any time, without having to give a reason (compensation should be paid pro rata temporis). If subjects who withdraw from the study offer their reasons for doing so, those reasons should be included in the study records.
- The subject must have access to information about insurance, and other procedures for compensation or treatment should he or she be injured or disabled as a result of participating in the trial.

12. Monitoring

Note: monitoring is an essential part of the clinical trial.

12.1 The monitor should be qualified (see section 8, Personnel). The main responsibility of the monitor for a bioequivalence trial is to ensure that the study is conducted in accordance with the protocol, GCP, GLP and applicable ethical and regulatory requirements. This includes provision of guidance on correct procedures for completion of CRFs and verification of the accuracy of data obtained.

12.2 In exceptional cases, the sponsor can delegate the monitoring function to the CRO. In such cases the CRO should be able to arrange for the monitoring of the trial according to regulatory requirements.

12.3 The frequency of monitoring visits should be agreed to between the CRO and the sponsor. However, a pre- and post-study visit as well as a

monitoring visit during the conduct of the trial are usually performed. The monitor should prepare a written report after each site visit.

12.4 The CRO should have a written set of SOPs concerning the visit procedures, extent of source data verification, drug accountability and adherence to the protocol.

12.5 Separate SOPs (with checklists for the monitor) for the initiation visit, routine monitoring visits and a closing visit are recommended.

13. Investigators

13.1 The principal investigator should have the overall responsibility for the clinical conduct of the study, including clinical aspects of study design, administration of the products under investigation, contacts with local authorities and the ethics committee, and for signing the protocol and the final study report.

13.2 The investigator(s) should have appropriate qualifications, be suitably trained and have experience in the conduct of bioequivalence studies (the legal status of persons authorized to act as investigators differs between countries), and at least one investigator must be legally allowed to practice medicine.

13.3 The medically qualified investigator should be responsible for the integrity, health and welfare of the subjects during the trial, and the accurate documentation of all trial-related clinical data.

13.4 The CRO is responsible for selecting investigator(s). In cases where the investigators are not permanent employees of the CRO, external investigators should be contracted and adequately trained.

14. Receiving, storage and handling of investigational drug products

14.1 CROs should document all the information concerning the receipt, storage, handling and accountability of investigational and comparator products at all stages of the trial. CROs must keep records of the shipment, delivery, receipt, storage (including storage conditions), dispensing, administration, reconciliation, return and/or destruction of any remaining investigational pharmaceutical products. Details of the drug product used should include dosage form and strength, lot number, expiry date and other coding that identifies the specific characteristics of the product tested. Samples of the product in the original container should be retained for possible confirmatory testing in the future.

14.2 A suitable location within the CRO, a local pharmacy or hospital pharmacy, should assume responsibility for storage, delivery, return and

record-keeping of the investigational drug and, when appropriate, comparator product(s).

14.3 Drug products should be stored under appropriate conditions as specified in the official drug information provided by the sponsor.

14.4 All study medication should be kept in a securely locked area accessible only to authorized persons.

14.5 The randomization and dispensing, including the labelling of drug products, should be done in accordance with GMP, good dispensing practices and an SOP and appropriate records should be maintained. Measures taken to ensure that the randomization list is followed and to avoid possible mistakes should be documented. Such measures include line clearance, separation of operations for the test and reference products, control of operations by a second person and reconciliation at the end of these operations. Reference can be made to GMP guidelines for additional guidance.

14.6 Drug reconciliation should be verified by a second responsible person such as the study monitor.

14.7 The investigator should follow the protocol requirements, randomization scheme and where required, use blinding. The investigator should ensure that the investigational product use is documented in such a way as to ensure correct dosage. This documentation should confirm that each subject did receive the product dispensed for him or her and state the identity, including the dosage, of the product received.

15. Case-report forms

15.1 CRFs should be used to record data on each subject during the course of the trial.

15.2 The CRO should have a procedure for designing CRFs, if the sponsor requests it to do so. Use of a standardized format is recommended; this should be adapted for each study protocol in accordance with the requirements for the particular study.

15.3 The required data to be collected on each volunteer should be specified in the trial protocol. A sample CRF should be appended to the protocol.

15.4 CRFs should be used to guarantee preservation, retention and retrieval of information on volunteers. CRFs should reflect the actual results obtained during the study and allow easy access for verification, audit and inspection of the data.

15.5 Appropriate procedures should be established and followed to document the investigator's certification of the accuracy of CRFs. Any errors

or omissions should be clarified with the investigator, corrected, dated and signed and explained on the CRF.

15.6 A subject file should be kept for each subject to record his or her participation in successive trials and to record any information that could be useful for subsequent trials.

16. Volunteers – recruitment methods

Note: the organization or institution performing bioequivalence studies should ideally have a pool of healthy volunteers who have been medically tested and selected in advance. Recruitment of volunteers undertaken immediately before the study is often done in a hurry and may compromise adherence to the selection criteria, especially for safety.

16.1 Informed consent of potential subjects should be obtained for any screening procedures required to determine eligibility for the study, in addition to informed consent for participation in the research portion of the study.

16.2 Criteria for selection of subjects (inclusion and exclusion criteria) and recruitment procedures should be described in the clinical trial protocol.

17. Dietary considerations

17.1 Fasting and meals should be adequately controlled during the study days, as food intake can significantly affect the absorption of drugs. Standardized meals, snacks and drinks should be planned and provided to study subjects in accordance with the clinical trial protocol.

17.2 Records should be maintained of the timing and duration of meals, and amount of food and fluids consumed.

18. Safety, adverse events and reporting of adverse events

18.1 Appropriate study planning includes adequate evaluation of any risk to the subjects. The study should be planned, organized, performed and monitored so that the safety profile will be acceptable to all concerned, including to the volunteers.

18.2 First-aid emergency equipment and appropriate rescue medication should be available at the study site and adequate facilities for the proper care of subjects who require emergency or other medical care.

18.3 The investigator(s) should be responsible for medical decisions in case of adverse events and for notifying the relevant health authorities, the sponsor and, when applicable, the ethics committee, without delay. In the

case of serious adverse events, appropriate timelines for reporting them should be respected as governed by national regulations.

18.4 The CRO should have the appropriate forms for the registration and reporting of adverse events, which should be provided to the investigator. The forms can be part of the CRF. If required, the relevant sponsor's forms may be used.

19. Sample collection, storage and handling of biological material

19.1 The specification of the samples (serum, plasma or urine), sampling method, volume and number of samples should be stated in the clinical trial protocol and the information provided to the volunteer. In the case of plasma samples the anticoagulant to be used should be specified in the protocol.

19.2 There should be documented procedures for the collection, preparation, transport and storage of samples.

19.3 Actual sampling times and deviations from the pre-specified sampling times should be recorded.

19.4 Labelling of collected samples should be clear to ensure correct identification and traceability of each sample.

19.5 The conditions for the storage of samples depend on the drug under investigation. However, all storage conditions (e.g. temperature in the freezer) should be specified in the study protocol, controlled, monitored and recorded throughout the storage period and during transportation. Procedures should be in place to ensure sample integrity in case of system failures.

19.6 Records of the storage and retrieval of samples should be maintained.

19.7 It is recommended that duplicate or back-up samples be kept, and that they be stored and shipped separately.

19.8 Local requirements for the handling and destruction or disposal of biological materials should be followed.

20. Bioanalytical data (laboratory phase)

Note: the analysis of drug concentrations may be performed by the same CRO which conducted the clinical study, or may be contracted to another laboratory or CRO.

20.1 Although most GLP guidelines apply formally only to nonclinical safety studies, general principles of GLP should also be followed in the analysis of biological samples from clinical trials.

20.2 Analysis should be performed in a laboratory with established quality assurance systems.

20.3 Premises and equipment

20.3.1 The laboratory should have sufficient space and infrastructure to perform the required analysis. Separate areas for specified activities should be provided to prevent possible contamination and mix-ups of samples during preparation and analysis.

20.3.2 Utilities such as water, air, gas and electricity should be adequate, stable and uninterrupted.

20.3.3 Analytical equipment and instruments should be appropriately calibrated, qualified and maintained, and methods used should be described and validated.

20.3.4 There should be SOPs for the operation, use, calibration and preventive maintenance of equipment. Records should be maintained.

20.3.5 Items of equipment used during the course of the trial should be identified to allow verification that they have been appropriately qualified and calibrated and to ensure traceability.

20.4 Validation requirements for the analytical method should be described in the protocol. There should be separate SOPs for analytical method validation.

20.5 Data to support the stability of the samples under the stated conditions and period of storage should be provided in the trial report.

20.6 Chemicals, reagents, solvents and solutions should be labelled to indicate identity, purity concentration (if appropriate), expiry date and specific storage instructions. Information concerning source, preparation date and stability should be available.

20.7 Each analytical run should include calibration and quality control samples. Acceptance criteria should be defined in SOPs.

20.8 Where chromatographic methods are used, there should be SOPs for chromatographic acceptance criteria and chromatogram integration. All chromatograms in a run (calibration samples, quality control (QC) samples and subject samples) should be integrated consistently. Manual reintegration of chromatograms should be performed only by trained personnel. A paper or electronic audit trail of manual integrations should be kept.

20.9 Criteria for reporting the results of reassayed samples should be defined in an SOP. The trial report should include a list of reassayed samples

with the reason for the repeat, all the values obtained and the value ultimately selected to be reported.

20.10 To avoid bias in the evaluation of the actual precision and accuracy of the bioanalytical method, the results of all QC samples assayed within accepted analytical runs should be reported and taken into consideration in the descriptive statistical analysis. Exclusion of values should be considered only in the case of a documented analytical problem (e.g. chromatographic interference) and the reason for the exclusion should be reported. This applies to both the pre-study validation of the method and the study phase itself.

21. Documentation

21.1 All original analytical raw data (e.g. calculations, chromatograms, etc.) should be documented in a manner that will ensure traceability with respect to the sample number, equipment used, date and time of analysis and the name(s) of the technician(s). In the case of raw data presented as paper chromatograms, these should be printed at an appropriate scale, allowing the visual verification of the peak shape and integration.

21.2 Each data point should be traceable to a specific sample, and information given should include, e.g. sample number, time of collection of the sample, time of centrifugation (if applicable), time when the sample was placed in the freezer (if applicable) and time of sample analysis, to enable the investigators to determine whether any aberrant results might have been due to sample mishandling.

21.3 The laboratory should have suitable coding techniques and methods to perform blinded analysis when relevant.

22. Pharmacokinetic and statistical calculations

22.1 Calculations should be made by qualified persons. See section 8 (Personnel).

22.2 The calculation methods should be specified in the study protocol and data analysis should conform to the protocol requirements.

22.3 For information on the use of computerized systems, see section 3, Computer systems (*6*).

23. Study report

23.1 The study report should reflect all of the study procedures and results in an accurate manner.

23.2 The study report should be well-written and presented. All deviations from the protocol in the performance of the study should be reported.

23.3 There should be no discrepancies between the results stated in the report and the original (raw) data.

23.4 The report should comply with regulatory requirements as applicable, and be presented in a standard format. The report should cover at least the items listed in the International Conference on Harmonisation (ICH) guideline (*8*).

23.5 The study report should include a report on the bioanalytical part of the trial, including a description of the bioanalytical method used and the validation report of this method.

23.6 The procedure for approval of the study report by the investigator and sponsor should be specified.

23.7 The report should be approved (signed and dated) by the responsible persons.

23.8 The monitoring report and audit report should be made available before release of the final study report.

References

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4. *Good Laboratory Practice (GLP), Quality practices for regulated non-clinical research and development*. Geneva, UNDP/World Bank/WHO, Special Programme for Research and Training in Tropical Diseases (TDR), 2001.
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6. *The good automated manufacturing practice (GAMP) guide for validation of automated systems in pharmaceutical manufacture (GAMP4)*. ISPE – International Society for Pharmaceutical Engineering, December 2001.
7. *Operational guidelines for ethics committees that review biomedical research*. Geneva, World Health Organization, 2000 (TDR/PRD/ETHICS/2000.1).
8. International Conference on Harmonisation (ICH) guideline. *Topic E3. Structure and Content of Clinical Study Report*. Geneva, ICH Secretariat (IFPMA), 1995.

Appendix 1

Examples of the list of standard operating procedures at the contract research organization

Note: all documents at the CRO related to a bioequivalence/clinical trial should be controlled (version date, approved, etc.) documents. This control is easier if the documents are in the SOP format or are appended to SOPs. SOPs should be in place at least for all the critical and major operations in the bioequivalence/clinical trial.

No.	Name of SOP
1.	Conduct of bioequivalence (BE) study
2.	Archiving and retrieval of documents related to BE study
3.	Quality assurance of the BE study; audits of clinical and bioanalytical part of the study and the study report
4.	Study files
5.	Preparation and review of the protocol for the study
6.	Amendment to the protocol for the study
7.	Protocol deviations/violation recording and reporting
8.	Sponsor/CRO quality assurance agreement in conducting the BE study
9.	Study approval process by ethical committee
10.	Bioavailability (BA)/BE report
11.	Study report
12.	Written informed consent
13.	Obtaining written informed consent for screening from study volunteers
14.	Allotment of identification numbers to volunteers at various stages in BE study
15.	Investigator's brochure (IB)
16.	Case-report form (CRF)
17.	Preparation of CRF, review and completion
18.	Data collection and CRF completion
19.	Adverse/serious adverse event monitoring, recording and reporting
20.	Organization chart of the study
21.	Training of the personnel
22.	Responsibilities of the members of the research team
23.	Monitoring of the study by the sponsor
24.	Conduct of pre-study meeting
25.	Study start-up
26.	Subject management

No.	Name of SOP
27.	SOP on mobilization of individuals for registration into volunteer bank
28.	Eligibility criteria for registration and registration of individuals into volunteer bank
29.	Handling of subject withdrawal
30.	Allotment of identification numbers to volunteers at various stages in biostudy
31.	Screening of enrolled volunteers for the study
32.	Collection of urine samples of subjects for detection of drugs of abuse and transportation of samples to pathology laboratory
33.	Custodian duties
34.	Payments to research subjects for BA/BE studies
35.	Procedures for entry into and exit from clinical unit
36.	Handling of subject check-in and check-out
37.	Housekeeping at clinical unit
38.	Planning, preparation, evaluation and service of standardized meals for bio-studies.
39.	Distribution of meals to study subjects
40.	Operation and maintenance of nurse calling system
41.	Administration of oral solid dosage form of the drug to human subjects during BA/BE study.
42.	Cannulation of study subjects
43.	Collection of blood samples from study subjects
44.	System for number of bio-samples
45.	Recording of vital signs of subjects
46.	Operation and verification of fire alarm system
47.	Oxygen administration to subject from medical oxygen cylinder
48.	Emergency care of subjects during BA/BE study
49.	Availability of ambulance during BA/BE study
50.	Centrifugation and separation of blood samples
51.	Storage of plasma/serum samples
52.	Segregation of bio-samples
53.	Transfer of plasma/serum samples to bioanalytical laboratory
54.	Procedures for washing glassware
55.	Recording temperature and relative humidity of rooms
56.	Instruction on operation and maintenance procedures for all the equipment in the clinical unit
57.	Numbering the equipment and log books for use in the clinical unit
58.	Control of access to pharmacy
59.	Pharmacy area requirements
60.	Authorization related to drug storage, dispensing and retrieval from storage for BE study

No.	Name of SOP
61.	Study drug receipt, return and accountability documentation
62.	Study drug receipt and return procedures
63.	Storage of drugs in the pharmacy
64.	Line clearance before and after dispensing
65.	Documentation of line clearance and dispensing; packaging records and release of dispensed drugs
66.	Retention of samples of study drugs
67.	Disposal of archived study drugs
68.	Disposal of biological materials
69.	Procedures for bioanalytical laboratory (SOPs for the different equipment, analytical methods, reagent preparation)
70.	Out-of-specification (OOS) situation in the laboratory
71.	Acceptance criteria for analytical runs: acceptance of calibration curves, acceptance of the runs based on QC samples results
72.	Chromatographic acceptance criteria, chromatogram integration
73.	Sample reassay
74.	Pharmacokinetic data from bioanalytical data
75.	Statistics in the BE study

SELECTED WHO PUBLICATIONS OF RELATED INTEREST

The International Pharmacopoeia, third edition.
Volume 1: general methods of analysis. 1979 (223 pages)
Volume 2: quality specifications. 1981 (342 pages)
Volume 3: quality specifications. 1988 (407 pages)
Volume 4: tests, methods, and general requirements: quality specifications for pharmaceutical substances, excipients and dosage forms. 1994 (358 pages)
Volume 5: tests and general requirements for dosage forms. Quality specifications for pharmaceutical substances and dosage forms. 2003 (371 pages)

Basic tests for drugs: pharmaceutical substances, medicinal plant materials and dosage forms.
1998 (94 pages)

Basic tests for pharmaceutical dosage forms.
1991 (134 pages)

Quality Assurance of Pharmaceuticals: a compendium of guidelines and related materials.
Volume 1: 1997 (244 pages)
Volume 2: good manufacturing practices and inspection. 2004 (236 pages)

WHO Expert Committee on Specifications for Pharmaceutical Preparations.
Thirty-ninth report.
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2004 (available in CD-ROM format only)

The use of essential medicines
Report of the WHO Expert Committee (including the 13th Model List of Essential Medicines).
WHO Technical Report Series, No. 920, 2004 (133 pages)

WHO Expert Committee on Biological Standardization.
Fifty-fourth report.
WHO Technical Report Series, No. 927, 2005 (160 pages)

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This report presents the recommendations of an international group of experts convened by the World Health Organization to consider matters concerning the quality assurance of pharmaceuticals and specifications for drug substances and dosage forms.

The report is complemented by a number of annexes. These include: a list of available International Chemical Reference Substances and International Infrared Spectra; supplementary guidelines on good manufacturing practices for heating, ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms; updated supplementary guidelines on good manufacturing practices for the manufacture of herbal medicines; supplementary guidelines on good manufacturing practices for validation; good distribution practices for pharmaceutical products; a model quality assurance system for procurement agencies (recommendations for quality assurance systems focusing on prequalification of products and manufacturers, purchasing, storage and distribution of pharmaceutical products); multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability; a proposal to waive in vivo bioequivalence requirements for *WHO Model List of Essential Medicines* immediate-release, solid oral dosage forms; and additional guidance for organizations performing in vivo bioequivalence studies.

ISBN 92-4-120937-2