

WHO EXPERT COMMITTEE ON SPECIFICATIONS FOR PHARMACEUTICAL PREPARATIONS

Thirty-seventh Report



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WHO Expert Committee on Specifications for Pharmaceutical Preparations

Geneva, 22–26 October 2001

Members*

Professor I. Addae-Mensah, Vice-Chancellor, University of Ghana, Accra, Ghana
(*Chairperson*)

Ms K. Bremer, Director, Medicines, Norwegian Control Authority, Oslo, Norway
(*Co-Chairperson*)

Professor A.A. Haggag, Department of Biochemistry, College of Pharmacy, University of Tanta, Tanta, Egypt

Professor Jin Shaohong, Deputy Director, National Institute for the Control of Pharmaceutical and Biological Products, Beijing, China

Ms A. Poompanich, Senior Technical Advisor (Efficacy of Medicine), Department of Medical Sciences, Ministry of Public Health, WHO Collaborating Centre for Drug Quality Assurance, Nonthaburi, Thailand

Mr R.W. Tribe, Chief GMP Auditor, Conformity Assessment Branch, Therapeutic Goods Administration, Woden, ACT, Australia (*Rapporteur*)

Representatives of other organizations†

Council of Europe

Dr J.H.McB. Miller, Head of Division III (Laboratory), European Directorate for the Quality of Medicines, Council of Europe, Strasbourg, France

International Atomic Energy Agency (IAEA)

Dr H.V. Ruiz, Head, Industrial Applications and Chemistry Section, Vienna, Austria

International Federation of Pharmaceutical Manufacturers Associations (IFPMA)

Dr O. Morin, Director, Regulatory and Scientific Affairs, IFPMA, Geneva, Switzerland

International Pharmaceutical Excipients Council (IPEC)

Dr P. Rafidison, Chairperson, GMP/GDP Committee, IPEC Europe, Opio, France

United Nations Children's Fund (UNICEF)

Ms Thuy Huong Ha, Technical Services Centre, UNICEF Supply Division, Copenhagen, Denmark

World Self-Medication Industry (WSMI)

Dr J.A. Reinstein, Director-General, WSMI, London, England

* Unable to attend: Mrs A.B. Moraes da Silva, National School of Public Health (FIOCRUZ), Coordination of Technical Cooperation, Rio de Janeiro, Brazil.

† Unable to attend: European Chemical Industry Council (CEFIC), Brussels, Belgium; International Pharmaceutical Federation (FIP), The Hague, Netherlands; Pharmaceutical Inspection Convention (PIC), Geneva, Switzerland; United Nations Industrial Development Organization (UNIDO), Vienna, Austria; The World Bank, Washington, DC, USA; World Trade Organization (WTO), Geneva, Switzerland.

Secretariat*

- Dr R. Balocco-Mattavelli, Technical Officer, Quality Assurance and Safety: Medicines, Department of Essential Drugs and Medicines Policy, WHO, Geneva, Switzerland
- Dr M. Chisale, Regional Adviser, WHO Regional Office for Africa, Harare, Zimbabwe
- Ms F. Dansereau, Head, Inspection Unit, OCPC, Bureau of Compliance and Enforcement, Ottawa, Ontario, Canada (*Temporary Adviser*)
- Dr E. Ehrin, WHO Collaborating Centre for Chemical Reference Substances, Central Laboratory, Kungens Kurva, Sweden (*Temporary Adviser*)
- Dr E. Griffiths, Coordinator, Quality Assurance and Safety: Biologicals, Department of Vaccines and Biologicals, WHO, Geneva, Switzerland
- Dr S. Kopp, Scientist, Quality Assurance and Safety: Medicines, Department of Essential Drugs and Medicines Policy, WHO, Geneva, Switzerland (*Secretary*)
- Miss Y. Maruyama, Technical Officer, Traditional Medicine, Department of Essential Drugs and Medicines Policy, WHO, Geneva, Switzerland
- Dr K. Morimoto, Scientist, Quality Assurance and Safety: Medicines, Department of Essential Drugs and Medicines Policy, WHO, Geneva, Switzerland
- Dr P. Munderi, Technical Officer, Policy, Access and Rational Use, Department of Essential Drugs and Medicines Policy, WHO, Geneva, Switzerland
- Dr E. Njau, Pharmaceutical Consultant, Arusha, United Republic of Tanzania (*Temporary Adviser*)
- Dr C. Ondari, Technical Officer, Policy, Access and Rational Use, Department of Essential Drugs and Medicines Policy, WHO, Geneva, Switzerland
- Dr A.M. Padilla, Quality and Safety of Plasma Derivatives and Related Substances, Department of Blood Safety and Clinical Technology, WHO, Geneva, Switzerland
- Dr S. Phanouvong, Technical Officer, Policy, Access and Rational Use, Department of Essential Drugs and Medicines Policy, WHO, Geneva, Switzerland
- Dr L.F. Ponce D'León, Department of Pharmacy, Faculty of Science, National University of Colombia, Bogotá, Colombia (*Temporary Adviser*)
- Dr J.D. Quick, Director, Department of Essential Drugs and Medicines Policy, WHO, Geneva, Switzerland
- Dr L. Rãgo, Coordinator, Quality Assurance and Safety: Medicines, Department of Essential Drugs and Medicines Policy, WHO, Geneva, Switzerland
- Dr V. Reggi, Scientist, Quality Assurance and Safety: Medicines, Department of Essential Drugs and Medicines Policy, WHO, Geneva, Switzerland

* Unable to attend: Mr A. Kumar, Drugs Controller General, Directorate-General of Health Services, Nirman Bhawan, New Delhi, India (*Temporary Adviser*); Dr B. Santoso, Regional Adviser, WHO Regional Office for the Western Pacific, Manila, Philippines; Dr K. Weerasuriya, Regional Adviser, WHO Regional Office for South-East Asia, New Delhi, India.

- Dr S. Sur, Deputy Chief Inspector, State Inspectorate for Quality Control of Medicines, Ministry of Health, Kiev, Ukraine (*Temporary Adviser*)
- Dr Y. Suzuki, Executive Director, Health Technology and Pharmaceuticals, WHO, Geneva, Switzerland
- Dr K. Tamiya, Assistant Professional Officer, Quality Assurance and Safety: Medicines, Department of Essential Drugs and Medicines Policy, WHO, Geneva, Switzerland
- Dr P. Vanbel, Technical Officer, Quality Assurance and Safety: Medicines, Department of Essential Drugs and Medicines Policy, WHO, Geneva, Switzerland
- Mr A. van Zyl, Technical Officer, Quality Assurance and Safety: Medicines, Department of Essential Drugs and Medicines Policy, WHO, Geneva, Switzerland
- Dr B. Vareldzis, Department of HIV/AIDS/STI, WHO, Geneva, Switzerland
- Dr R.L. Williams, Executive Vice-President, The United States Pharmacopeia, Rockville, MD, USA (*Temporary Adviser*)
- Mr E. Wondemagegnehu, Scientist, Quality Assurance and Safety: Medicines, Department of Essential Drugs and Medicines Policy, WHO, Geneva, Switzerland
- Dr X. Zhang, Coordinator, Traditional Medicine, Department of Essential Drugs and Medicines Policy, WHO, Geneva, Switzerland

1. Introduction

The WHO Expert Committee on Specifications for Pharmaceutical Preparations met in Geneva from 22 to 26 October 2001. The meeting was opened on behalf of the Director-General by Dr Y. Suzuki, Executive Director, Health Technology and Pharmaceuticals, who said that, since the last meeting of the Committee, there has been more evidence of globalization and the harmonization of specifications for pharmaceutical preparations, especially for pharmaceuticals used in the treatment of HIV, tuberculosis and malaria. WHO was committed to helping to ensure the quality of pharmaceuticals and to treat these diseases.

Dr J.D. Quick, Director, Essential Drugs and Medicines Policy, briefed the Committee on the WHO strategy for medicines, which focuses on:

- ready access to essential medicines at affordable prices;
- quality and safety of such medicines;
- rational drug use;
- effective national drug policies.

It was intended that the information arising from the meeting would be readily available through the WHO web site and through the “Global Medicines Family”.

Dr L. Rågo, Coordinator, Quality Assurance and Safety: Medicines (QSM), informed the Committee about the wide range of activities undertaken by the QSM team. A substantial number of countries were now using the WHO good manufacturing practices (GMP) guide and there was greater cooperation with WHO collaborating centres.

2. General policy

2.1 Specifications for medicinal plant materials and for herbal products

The Committee was informed of the WHO strategy for traditional medicines, including medicinal herbal materials and products, and the following four major objectives in this area:

- policy;
- safety/efficacy/quality;
- access;
- rational use.

The Committee was informed of the WHO documents available for medicinal plant materials and herbal products, and that further

documents are planned. The Committee noted that various pharmacopoeias are working on similar monographs and would be willing to share their information with WHO.

The Committee commended the work undertaken by WHO in this area and urged that it should be continued.

2.2 Risk of transmitting animal spongiform encephalopathy agents via medicinal products

The Committee was asked to endorse a general text concerning the risk of transmitting animal spongiform encephalopathy agents via medicinal products. It was intended that this text would be included in relevant WHO publications such as *The International Pharmacopoeia*.

The Committee noted the report of a WHO consultation on medicinal and other products in relation to human and animal transmissible spongiform encephalopathies and considered a recommendation made during a consultation held in September 2001.

The Committee recommended that the text be adopted, but with one minor modification (Annex 1).

2.3 Stop TB programme

The Committee noted the work undertaken by this programme and supported the policy of developing quality specifications for priority drugs used to treat tuberculosis.

2.4 Roll Back Malaria programme

The Committee noted the work undertaken by this programme and the importance of ensuring rapid and long-lasting cures for individual malaria patients, as well as achieving an overall reduction in malaria morbidity.

2.5 HIV/AIDS programme

The Committee was informed of WHO's goal and strategy for access to drugs, and treatment of HIV patients in developing countries. The challenges to be met in achieving the goal and implementing the strategy were also outlined. The Committee learnt that, because of the use of more effective treatments, HIV infection had become a chronic illness rather than a fatal disease.

The Committee endorsed the need for this programme to learn from the positive and negative experiences in the quality assurance of drugs of the Stop TB programme.

2.6 Future of *The International Pharmacopoeia*

The Committee was informed of the new WHO strategy for a global step-wise approach to the quality control of pharmaceuticals, including basic tests, screening tests, and monographs in *The International Pharmacopoeia*. The development of new monographs for *The International Pharmacopoeia* would give priority to the needs of specific disease programmes and the essential drugs nominated under these programmes.

The Committee confirmed that *The International Pharmacopoeia* continued to fulfil a need in developing countries. While it contains monographs with stringent specifications, it also provides equally acceptable but less technically demanding alternative methods for specific substances and preparations wherever possible.

At an informal consultation held in Geneva on September 2001, the uniqueness of WHO's role in developing global standards was emphasized and the global and step-wise approach to the quality control of pharmaceuticals and the list of priorities given in this document were strongly supported.

The following recommendations were made by the Expert Committee:

- In the light of the increasing shift to more sophisticated methods and international proposals to introduce more stringent test limits, *The International Pharmacopoeia* and related activities should be strengthened and promoted.
- The approach recently adopted whereby alternative test specifications are included in new monographs for *The International Pharmacopoeia* should be maintained.
- The title of *The International Pharmacopoeia* should be maintained.

The Committee adopted the recommendations and the relevant document entitled "*The International Pharmacopoeia: revised concepts and future perspectives*" (Annex 2). The Committee also agreed that the survey of the use of *The International Pharmacopoeia* conducted 5 years ago should be repeated, and advocated that *The International Pharmacopoeia* should be promoted more effectively.

2.7 Pharmacopoeial Discussion Group (PDG)¹

The Committee was informed of the new collaboration between the Pharmacopoeial Discussion Group (PDG) and WHO. The

¹ Composed of representatives of the European, Japanese and United States pharmacopoeias, with WHO as an observer.

collaboration between WHO and PDG was very well received and was seen as providing a new platform for discussion and communication between pharmacopoeias.

The Committee adopted the following recommendations on WHO collaboration with the PDG made during a consultation held in Geneva in September 2001:

- The joint development of monographs using this forum should be encouraged so as to make the pharmacopoeial requirements for specific priority diseases such as HIV/AIDS, malaria and tuberculosis, available more quickly.
- Existing harmonized monographs, e.g. for excipients, should be included in *The International Pharmacopoeia* and WHO should contact the PDG for the “modus operandi”.

2.8 International Conference on Harmonisation (ICH)

The Committee was provided with a draft document titled “Some considerations on the impact of ICH in non-member countries” and the Committee was informed that this document and its recommendations would be brought to the attention of the Tenth International Conference of Drug Regulatory Authorities to be held in Hong Kong Special Administrative Region of China in 2002.

The Committee considered that, while ICH standards were important in specifying requirements for pharmaceutical manufacturers of new chemical entities, WHO had an important role in adopting and adapting ICH standards for developing countries. The Committee therefore endorsed the need for WHO to intensify its efforts to develop international standards on the approval of generic products in consultation with the generic industry, related organizations and national authorities. This would improve access to quality essential drugs.

The Committee endorsed the general principles of the document.

3. Quality control — specifications and tests

3.1 Thin-layer chromatography screening tests for antimalarials

The Committee noted and accepted the recommendations made during a consultation held in Geneva in September 2001 on thin-layer chromatography (TLC) screening tests for antimalarials while also noting that further experimental work was necessary.

3.2 Radiopharmaceuticals

The Committee was informed that *The International Pharmacopoeia* contained only general methods for the analysis of radiopharmaceuticals; there were no individual monographs for such products, mainly because they were not on the WHO Model List of Essential Drugs. The Committee discussed a proposal to either retain or delete the general methods for the analysis of radiopharmaceuticals, and/or to prepare specific monographs for them. The Committee recommended that the general methods of analysis should be deleted from *The International Pharmacopoeia* and that a separate publication on radiopharmaceuticals (independent of *The International Pharmacopoeia*) should be prepared in collaboration with the International Atomic Energy Agency (IAEA). It was also agreed that, at a future meeting of the Committee, it should be decided whether these newly developed monographs for radiopharmaceuticals should be kept separate from, or again included in, *The International Pharmacopoeia*.

3.3 Pharmacopoeial monographs on antiretrovirals

The Committee adopted the recommendations on the development of pharmacopoeial monographs on antiretrovirals made during a consultation held in Geneva in September 2001, but advocated that the Secretariat should review the list of substances and products in accordance with the new treatment pattern regimen. For a number of antiretrovirals, manufacturers' specifications are available. The Committee therefore recommended that WHO should seek information from additional manufacturers willing to collaborate. It was suggested that national authorities with experience in evaluating and testing new antiretrovirals should be asked for their support. This also applies to the possibility of obtaining samples.

The following recommendations were made by the Expert Committee:

- Since the development and validation of analytical methods and requirements (including screening tests and pharmacopoeial monographs) as well as the establishment of International Chemical Reference Substances will require a significant budget, the possibility of obtaining financial support should be investigated.
- The development of quality specifications for substances and pharmaceutical products including one active pharmaceutical ingredient should be given priority.
- The collaboration of the PDG should be sought in elaborating monographs on antiretrovirals.

3.4 **Thin-layer chromatography screening tests for antituberculosis drugs**

The Committee noted and accepted the recommendations on TLC screening tests for antituberculosis drugs made during a consultation held in Geneva, in September 2001. The document prepared during this consultation is ready for circulation to WHO collaborating centres for validation.

3.5 **Draft monograph on rifampicin, isoniazid, pyrazinamide and ethambutol hydrochloride tablets**

The Committee noted the collaboration between WHO and *The United States Pharmacopeia* in developing this monograph, received the monograph as a working document and approved the recommendations made during a WHO consultation held in Geneva in September 2001, which can be summarized as follows:

- Since the experimental validation of the methods, currently undertaken by WHO, shows that they need to be improved, further investigations should be carried out.
- Less technically demanding analytical procedures, as alternatives to high-performance liquid chromatography (HPLC) for identification and dissolution testing now being developed by WHO, should be described.
- Close cooperation between WHO and *The United States Pharmacopeia* aimed at improving the monograph should be continued.

4. **Quality control — international reference materials**

The reports of the WHO Collaborating Centre for Chemical Reference Substances for 1999 and 2000 were presented to the Committee.

The Committee noted that the prices of reference substances had not changed for the past 4 years, and that there would be a small increase in price in the near future. It was also noted that only substances that were related to the WHO Model List of Essential Drugs were supplied as reference substances.

The Committee adopted the reports and expressed its appreciation to the WHO Collaborating Centre for Chemical Reference Substances for its work.

Orders for 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 6040
Email: who.apl@apoteket.se

5. **Quality control — national laboratories**

5.1 **External quality assessment scheme**

The Committee noted that 12 national quality control laboratories had been involved in a external quality assessment scheme, with feedback being obtained from most of these laboratories. It also noted that a second phase involving 36 laboratories would soon commence.

This scheme contributes to the establishment of mutual confidence between users and laboratories, and is a very useful tool for assessing the analytical skills of participating laboratories.

The Committee adopted the following recommendations on the External Laboratory Assessment Scheme made during a consultation held in Geneva in September 2001:

- The same methodology (pharmacopoeia methods) should be used by all laboratories in the statistical evaluation of results.
- This initiative should be pursued provided that funds are available. In experimental studies, the methods given in *The International Pharmacopoeia* should continue to be used.
- If funds are not available, WHO should inform the laboratories about other existing schemes. In this context, WHO should ask for more information from other sources about existing schemes.

5.2 **Cost estimate of equipment for model quality control laboratories**

The Committee adopted the document providing information on the cost of equipment for model quality control laboratories (*Cost estimate of equipment for model quality control laboratories*. Working document QAS/01.42), but acknowledged that technical specifications needed to be included for each item of equipment since these could influence prices.

6. **Quality assurance — good manufacturing practices**

6.1 **Specific GMP guidelines for radiopharmaceutical products**

The Committee was informed of the collaboration between WHO and the IAEA in developing these specific GMP guidelines. The Committee was also informed that these guidelines are supplementary to the general requirements for GMP set out in WHO's GMP for pharmaceutical products (Annex 4).

The Committee adopted the guidelines, noting that several minor editorial changes were required (“Guidelines on Good Manufacturing Practices for radiopharmaceutical products”) (Annex 3).

6.2 **GMP guidelines for active pharmaceutical ingredients**

The Committee was informed of the background to the development of the ICH GMP guidelines for active pharmaceutical ingredients (APIs), including the earlier involvement of the Pharmaceutical Inspection Cooperation Scheme in initiating the preparation of this guide.

The Committee recognized the difficulty that countries would have in implementing the ICH GMP guide in a short period of time. The Committee was informed that, from a legal standpoint, WHO cannot simply take over any GMP document from another source. The Committee therefore considered that it would be best for the current WHO GMP for APIs to be revised to reflect current GMP requirements.

The Committee agreed that WHO should review the current WHO GMP for APIs, taking into account other published guidelines, including the ICH document, and also consider current practices. The Committee endorsed the step-wise approach to the implementation of GMP for APIs.

6.3 **WHO GMP: main principles for pharmaceutical products**

The Committee was informed of the main changes that had been made in revising these GMP guidelines, to incorporate texts and recommendations published separately, and to bring the guidelines into line with current GMP requirements, particularly in relation to validation, authorized persons, documentation and definitions. Consultations in December 2000 and August 2001 had been arranged to consider comments made by interested parties. During these consultations, all comments received were carefully examined.

The Committee discussed the difficulty of implementing cleaning validation in some countries and the apparent lack of guidelines on this subject to assist GMP inspectors. Examples of guidelines currently available were brought to the attention of the Committee. It was recommended that WHO should start work soon on the preparation of additional guidance documents for key areas of GMP such as validation and aerosol manufacture.

The Committee adopted the revised guidelines “Good Manufacturing Practices for pharmaceutical products: main principles” (Annex 4) and noted that they should be discussed at the next meeting of the Expert Committee to take account of any comments made in the interim.

6.4 **WHO basic training modules on GMP**

WHO has developed GMP training modules to promote GMP implementation in response to difficulties in achieving GMP compliance in developing countries. The modules are available on CD-ROM and via the WHO web site. The CD-ROMs have been distributed free of charge to all Member States and other relevant organizations. The Committee had the opportunity to view the contents of the training modules.

Pilot workshops for GMP inspectors and representatives of industry have been held in all WHO regions, and feedback from participants has so far been very positive.

The Committee commended WHO for taking this initiative and urged that the project on the strengthening of pharmaceutical manufacturing inspection should be continued and expanded.

7. **Quality assurance — inspection**

7.1 **Model certificate of GMP**

The Committee was informed of the purpose of this certificate and that they were specific to manufacturing sites and the product categories and manufacturing activities undertaken at these sites. This will help to resolve the difficulties raised during the 1999 International Conference of Drug Regulatory Authorities, where it was indicated that GMP certificates often differ in layout and type of information provided.

The Committee adopted the document “Model certificate of good manufacturing practices” (Annex 5).

7.2 **Guidance for GMP inspection report**

The Committee was informed that the document submitted at the present meeting was intended to replace that currently published under the title “Form and content of the inspector’s report” (1).

The Committee adopted the document “Guidance on good manufacturing practices (GMP): inspection report” (Annex 6).

8. **Quality assurance — distribution and trade-related**

8.1 **Good trade and distribution practices of pharmaceutical starting materials**

The Committee was informed that a number of incidents involving diethylene glycol had led to the preparation of guidelines for good trade and distribution practices of pharmaceutical starting materials and recommendations to Member States. This document is focussed on the repacking or relabelling of starting materials. The Committee was informed that the consultation process involving all interested parties had still not been completed. However, it endorsed the principles contained in the draft guidelines.

8.2 **WHO Scheme for the Certification of Pharmaceutical Starting Materials Moving in International Commerce: guidelines on implementation**

The Committee considered the draft document in which two model certificates were proposed: one for issue by national authorities and the other for completion by manufacturers of starting materials.

The Committee noted that the document and called for further comments; these should be sent to WHO by the end of 2001. WHO should seek ways of discussing the proposed model certificates with national drug regulatory authorities in international fora in order to obtain feedback on the operational aspects of their implementation in regulatory practice.

8.3 **WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce**

The Committee was briefed on the recommendations made at the International Conference of Drug Regulatory Authorities held in 1999 on the issue of certificates.

The Committee was informed that the paper advocated the preparation of electronic certificates on the web sites of regulatory authori-

ties. Some members of the Committee considered that this would be difficult for both exporting and importing countries.

The Committee noted the document and agreed that a small working group should be established to discuss and introduce any further improvements that would increase the credibility of the WHO Certification Scheme.

9. **Quality assurance — risk analysis**

9.1 **Risk analysis in quality control and impurities**

The Committee noted that, even though there was an increasing shift to more sophisticated methods and more stringent test limits internationally, no scientific data were available that demonstrated that the safety of patients was thereby increased. It was therefore recommended that specifications published to date in *The International Pharmacopoeia* should be maintained and the currently used approach retained. The monographs published in *The International Pharmacopoeia* can thus be retained — subject to the normal revision process — especially as the majority of monographs concern well known essential drugs proved to be safe over a long period of time.

For new monographs, it was important to define a level of impurities consistent with those in other official standards or pharmacopoeias. The fact that different pharmacopoeias may provide different specifications for varying impurities profiles for the same product must also be considered. If available, harmonized monographs should be preferred.

The recently adopted approach to include — in newly developed monographs — alternative test specifications should also be maintained. The policy is to introduce less technically demanding analytical procedures as alternatives when more sophisticated methods are described in the monograph (Annex 2).

9.2 **Application of hazard analysis and critical control point methodology for pharmaceuticals**

The Committee was briefed about the content of a document on the application of the hazard analysis and critical control point (HACCP) system to pharmaceuticals. It noted that the document provided general guidance on the use of HACCP to ensure the quality of pharmaceuticals, while recognizing that the details may vary depending on the circumstances. It was emphasized to the Committee that HACCP

does not replace GMP but focusses on the prevention of hazards. The Committee was also informed that HACCP should not be confused with validation.

The Committee adopted the document “Application of Hazard Analysis and Critical Point (HACCP) Methodology for Pharmaceuticals” subject to: (1) the addition of a statement or addendum on the use of HACCP in other industries; and (2) some minor editorial changes being made in relation to consistency in the use of terms (e.g. “pharmaceuticals”, “pharmaceutical finished products”, “finished products”) (Annex 7).

10. **Quality assurance — drug supply**

10.1 **Procedure for assessing the acceptability for purchase of pharmaceutical products**

The Committee was informed that WHO was in the process of developing a pre-qualification system for suppliers of pharmaceutical products. The purpose of this procedure was to verify that prequalified pharmaceutical products meet the specifications set by relevant agencies of the United Nations and the requirements recommended by WHO, including compliance with GMP. The need for inspection reports to be confidential and for competent inspectors to be selected was emphasized by members of the Committee.

The Committee adopted the relevant document “Procedure for assessing the acceptability, in principle, of pharmaceutical products for purchase by United Nations agencies” (Annex 8).

10.2 **Procedure for assessing the acceptability for purchase of pharmaceutical products for the treatment of HIV/AIDS**

The Committee was informed of WHO’s pilot project, in conjunction with the United Nations Children’s Fund (UNICEF), the Joint United Nations Programme on HIV/AIDS (UNAIDS), and the United Nations Population Fund (UNFPA), together with the support of the World Bank, to test the system for the pre-qualification of suppliers of drugs for the treatment of HIV/AIDS. This included: (1) evaluation of the dossier; (2) provision of samples for analysis; and (3) inspection of the manufacturing site. Only manufacturers of dosage forms would be subject to inspection under this programme (manufacturers of active pharmaceutical ingredients would not be inspected at this time but such inspections are not excluded in the future). The Committee was briefed on the number of quality defects found in

the course of this project, and recommended that every effort should be made to ensure budgetary support for its continuation.

11. **Quality assurance — storage**

11.1 **WHO guidelines for stability testing of pharmaceutical products containing well established drug substances in conventional dosage forms**

The Committee discussed and adopted the recommended modification of the storage conditions given in the “WHO guidelines for stability testing of pharmaceutical products containing well established drug substances in conventional dosage forms” to read 30°C ($\pm 2^\circ\text{C}$) and a relative humidity of 65% ($\pm 5\%$) for real-time stability studies for climatic zone IV (2). It was also agreed that, where special transportation and storage conditions were not in accordance with these criteria, additional study data justifying these conditions may need to be made available.

11.2 **Good storage practices**

The Committee was informed that the document on good storage practices was intended to serve as a methodological aid and to offer advice to those involved in the storage, transportation and distribution of pharmaceuticals.

The Committee considered various comments recently received and agreed to a number of amendments to the document.

The Committee adopted the document “Guide to good storage practices for pharmaceuticals”, as amended (Annex 9).

12. **International Nonproprietary Names (INNs) programme**

The Committee was informed of the workplan and progress of the programme on International Nonproprietary Names (INNs) and the challenges facing it in the future. The Committee was also informed that priority was being given to upgrading the database architecture and functionality.

The Committee noted that a small panel of experts had recently been established to advise on matters relating to compounds in the area of biologicals.

The Committee commended the close collaboration with the WHO Expert Committee on Biological Standardization. The Committee commended the INN programme for its good work.

13. **Miscellaneous**

13.1 **Proposal to the WHO Expert Committee by the Scientific Working Group on Bioequivalence of the International Pharmaceutical Federation (FIP)**

The Committee was informed of the joint work between WHO and the International Pharmaceutical Federation (FIP) on the development of a biopharmaceutical classification system (BCS) for assessing the reliability of in vitro dissolution testing as a surrogate for the in vivo bioequivalence testing of immediate-release (IR) solid dosage forms.

The Committee agreed that this work was particularly important for ethical reasons and that it reduced costs of analysis. It therefore endorsed WHO's participation in further work in this area.

13.2 **Dissolution tests for quality control**

The Committee agreed that work should be carried out to establish dissolution requirements, details of test conditions and acceptance criteria for inclusion in the relevant monographs of *The International Pharmacopoeia*.

13.3 **Electronic version of publications**

An early version of a new CD-ROM under development, containing a searchable version of *The International Pharmacopoeia* in English, French and Spanish, was demonstrated to the Committee. This would be made widely available when ready.

13.4 **Standardized reporting sheet**

The reporting of experimental results on the verification and validation of analytical methods and requirements, e.g. basic tests and specifications for pharmacopoeial monographs, has not yet been standardized. As a result, reports received from collaborating centres or experts vary widely.

The Committee recommended that a standardized reporting sheet should be used by collaborating centres and experts for reporting experimental results and data. This would lead to better traceability regarding the development and validation of quality specifications.

The Secretariat was asked to draft a standard report sheet which will be circulated for comments before it is introduced.

13.5 **Distribution of documents for procedural consultation process**

The Committee was informed that the Secretariat would be preparing a paper on the future procedures for the distribution of documents and the consultation process. Some suggestions made by the Committee included:

- use of email, wherever possible, for the distribution of documents;
- distribution of documents several weeks before the meeting to allow participants sufficient time to study them;
- posting draft documents on the WHO web site for greater transparency, the early drafts being password protected until they are ready to be made more widely available;
- marking as “Draft” any draft documents posted on the WHO web site.

The Committee was informed of the consultation process for WHO documents, as well as expected changes in this process whereby greater use would be made of the WHO web site to give draft documents wider exposure.

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and Control, Belgrade, Yugoslavia; Professor E. Doelker, University of Geneva, Geneva, Switzerland; Dr D.I. Ellsworth, Division of Manufacturing and Product Quality, Center for Drug Evaluation and Research, Food and Drug Administration, Rockville, MD, USA; Dr T. Eriksen, Sudaththa Liyanaarachchi, Avissawella, Sri Lanka; Mr S. Fairchild, European Agency for Evaluation of Medicinal Products, London, England; Dr C.J. Fallais, University of Liège and the Free University of Brussels, Brussels, Belgium; Dr A. Farina, Higher Institute of Health, Ministry of Health, Rome, Italy; Dr E. Fefer, International Affairs, US Pharmacopoeia, Rockville, MD, USA; Mrs S. Fuerst, The USAN Council Program, AMA, Chicago, IL, USA; Dr H. Fukuda, Society of Japanese Pharmacopoeia, Tokyo, Japan; Ms D. Gal, International Pharmaceutical Federation, The Hague; Netherlands; Mr S. Ghani, Division of Pharmaceutical Quality, Therapeutic Products Programme, Ottawa, Ontario, Canada; Ms E. Gomez Munoz, Quality Assurance and Regulatory Affairs, Baxter Laboratories, Cali, Colombia; Dr R. Gooch, Representative of the International Pharmaceutical Federation, Netherlands; Dr. T. Gosdschan, Intercantonal Office for the Control of Medicines, Division of Inspections, Bern, Switzerland; Mr P. Graaff, WHO Regional Office for the Eastern Mediterranean, Alexandria, Egypt; Dr O. Gross, Pharmaceutical Starting Materials Unit, Directorate of Inspection of Establishments, French Agency for Health Safety of Health Products, Saint-Denis, France; Professor A.A. Haggag, Department of Biochemistry, College of Pharmacy, University of Tanta, Tanta, Egypt; Dr S. Haghghi, Pharmaceutical and Microbiology Department, Institute Pasteur of Iran, Teheran, the Islamic Republic of Iran; Ms N. Haji Naim, Pharmaceutical Services, Ministry of Health, Jalan University, Petaling Jaya, Malaysia; Dr N.G. Hartman, The Ottawa Hospital, Division of Nuclear Medicine, Ottawa, Ontario, Canada; Dr P. Helboe, Pharmaceutical Affairs, Danish Medicines Agency, Brønshøj, Denmark; Dr E. Henriksen, Division of Manufacturing and Product Quality, Office of Compliance, FDA, Rockville, MD, USA; Mr H. Hofstetter, Intercantonal Office for the Control of Medicines, Bern, Switzerland; Professor J. Hoogmartens, Katholieke Universiteit Leuven, Leuven, Belgium; Dr J. Hoose, Agency for Work, Health and Social Office for Health, Health Department, Hamburg, Germany; Dr H. Ibrahim, DebioPharm SA, Lausanne, Switzerland; Professor R. Jachowicz, Department of Pharmaceutical Technology and Biopharmaceutics, Jagiellonian University, Cracow, Poland; Mr M. Jahnsson, Technical Coordination Unit—Inspections, The European Agency for the Evaluation of Medicinal Products, London, England; Professor Jin Shaohong, National Institute for the Control of Pharmaceutical and Biological Products, Ministry of Public Health, Beijing, China; Mrs G. Jiragobchaipong, Division of Drug Analysis, Department of Medical Sciences, Ministry of Public Health, Nonhaburi, Thailand; Dr A. Kakwemeire, National Drug Quality Control Laboratory, Uganda National Drug Authority, Kampala, Uganda; Dr K. Kawamura, Japan PDA, Tokyo, Japan; Mr M. Keller, Intercantonal Office for the Control of Medicines, Division of Inspections, Bern, Switzerland; Dr S. Kennedy, Technical Co-ordination, Inspection Sector, European Agency for the Evaluation of Medicinal Products, London, England; Professor S. Khomvili, Hoechst Marion Roussel Industry, Thailand; Ms K. Kikule, National Drug Authority, Kampala, Uganda; Dr Q.L. Kintanar, Bureau of Food and Drugs, Ministry of Health, Muntinlupa, Philippines; Dr P. Kokkinou, Pharmaceutical Services, Ministry of Health, Lefkosia, Cyprus; Professor M.A. Koupparis, Laboratory of Analytical Chemistry, Department of Chemistry, University of Athens, Athens, Greece; Dr R. Krause, International Federation of Pharmaceutical Manufacturers Associations, Geneva, Switzerland; Professor H.G. Kristensen, Royal Danish School of Pharmacy, Department of Pharmaceutics, Copenhagen, Denmark; Dr P.B. Kulkarni, Technical Services Division, Bhabha Atomic Research Centre, Mumbai, India; Mr R. Kuwana, Medicines Control Authority, Harare, Zimbabwe; Mr J. Lanet, Qualassur, Paris, France; Dr T. Lapnet Moustapha, National Drug Quality Control and Valuation Laboratory, Yaoundé, Cameroon; Mr P. Lefèvre, Medicines Agency, Saint Denis, France; Ms E. Leinonen, National Agency for Medicines, Helsinki,

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Annex 1

Recommendations on Risk of Transmitting Animal Spongiform Encephalopathy Agents via Medicinal Products

Products with risk of transmitting agents of animal spongiform encephalopathies are those derived from tissues or secretions of animals susceptible to transmissible spongiform encephalopathies other than by experimental challenge. This definition applies to all substances or preparations obtained from such animals and to all substances or preparations where products obtained from such animals are included as active substances or excipients or have been used during production, e.g. as raw or source materials, starting materials or reagents.

Materials of animal origin should be avoided whenever possible. However, if used, manufacturers should be aware of the risk and have a system in place to minimize it, especially since international trading patterns, often include the processing and re-export of products, so that their origin may not be traceable.

In order to minimize the risk of transmitting animal spongiform encephalopathy agents via medicinal products, manufacturers should follow the recommendations of the Joint Technical Consultation on Bovine Spongiform Encephalopathy, public health, animal health and trade, convened by the WHO, the Food and Agriculture Organization of the United Nations and the Office International des Epizooties 11–14 June 2001 in Paris.¹

¹ *Proceedings — Joint WHO/FAO/OIE Technical Consultation on BSE: public health, animal health and trade.* Paris: Office International des Epizooties, World Health Organization, Food and Agriculture Organization, World Organisation for Animal Health; 2002.

Annex 2

The International Pharmacopoeia: revised concepts and future perspectives

General Context and Overview

WHO Constitution and World Health Assembly

The quality of pharmaceuticals has been a concern of WHO since its inception. The setting of global standards is requested in Article 2 of the WHO constitution which cites as one of the Organization's functions that it should "develop, establish and promote international standards with respect to food, biological, pharmaceutical and similar products". The World Health Assembly has adopted many resolutions requesting the Organization to develop international standards, recommendations and instruments to assure the quality of medicines, whether produced and traded nationally or internationally. In addition, many national governments support the activities of WHO Collaborating Centres financially.

Expert Committee and activities related to The International Pharmacopoeia

In response to the World Health Assembly resolutions, the WHO Expert Committee on Specifications for Pharmaceutical Preparations, which was originally established to prepare *The International Pharmacopoeia*, has made numerous recommendations relevant to quality assurance and control.¹

The activities related to *The International Pharmacopoeia* are an essential element in overall quality control and assurance of pharmaceuticals contributing to the safety and efficacy of drugs. Compared to other pharmacopoeias, priority is given to drugs included in the WHO Model List of Essential Drugs and to drugs important for WHO health programmes which may not be included in other pharmacopoeias, e.g. new antimalarials. The quality control specifications published in *The International Pharmacopoeia* are developed independently via an international consultative procedure. The

¹ See, for example, *Quality assurance of pharmaceuticals: a compendium of guidelines and related materials. Vol. 1.* Geneva, World Health Organization, 1997; *Quality assurance of pharmaceuticals: a compendium of guidelines and related materials. Vol. 2. Good manufacturing practices and inspection.* Geneva, World Health Organization, 1999.

needs of developing countries are taken into account and, whenever possible, classical analytical procedures are used. The policy is to include robust alternative methods when more complex methods are suggested. This publication undoubtedly strengthens the scientific credibility of WHO.

Revised concepts and future perspectives

The first volume of the first edition of *The International Pharmacopoeia* was published in 1951 with the aim of harmonizing quality requirements for pharmaceutical substances worldwide. After 50 years of existence and in the light of the development of the three major pharmacopoeias, namely the *European Pharmacopoeia*, *Japanese Pharmacopoeia* and *United States Pharmacopoeia*, and their current involvement in the Pharmacopoeial Discussion Group¹, it would seem appropriate to propose revised concepts and future perspectives for *The International Pharmacopoeia*. A more global approach to the quality control of pharmaceuticals in direct relation to the needs of developing countries and with WHO's Disease Control Programmes, is therefore suggested, including not only essential drugs but also the development of new therapeutic agents and/or new drug combinations.

Targets and priorities

The ultimate goals remain unchanged, namely the promotion of good quality pharmaceutical products, and the development of quality control methods for detecting counterfeit drugs so as to assure the safety and efficacy of medical treatments worldwide. This is also essential in promoting successful programmes for the eradication or control of diseases and in avoiding the emergence of drug resistance.

The development of screening tests and pharmacopoeial monographs for therapeutic agents, including combination products, to treat tuberculosis, malaria and AIDS, is the top priority.

New WHO quality control strategy

Sequential and graduated approach (step-wise strategy)

The priority is the development of quality control methods at different levels depending on the analytical methods and expertise (instrumentation, trained personnel, etc.) which are available and/or applicable in the countries concerned. Each level of analysis is designed to meet specific objectives and therefore should be selected for its intended purpose.

¹ WHO was recently granted observer status in the Pharmacopoeial Discussion Group.

Basic tests. These are intended to provide simple and readily applicable methods of confirming the identity of active ingredients. They are especially useful when a fully equipped laboratory and/or analytical expertise are not available and when indicative and rapid control is needed. Basic tests therefore have a clearly defined but limited role and are valuable tools for primary testing and for the detection of counterfeit drugs, but cannot replace a full analysis. When the identity is in doubt, further testing should be performed. Basic tests should be promoted and further developed.

Screening tests. The WHO Expert Committee on Specifications for Pharmaceutical Preparations has endorsed on several occasions the usefulness of thin-layer chromatography (TLC) in screening the identity of drugs and detecting counterfeit drugs and gross degradation. The method may be used for qualitative purposes and requires the use of appropriate Chemical Reference Substances. The development and validation of robust experimental conditions for TLC, both for field and laboratory testing, especially in the context of WHO's disease control programmes (i.e. those on malaria, tuberculosis and AIDS), is the principal objective of the Department of Essential Drugs and Medicines Policy.

Screening tests cannot replace a full analysis. When the result indicates deficiencies in quality, a full pharmacopoeial analysis must therefore be performed.

Pharmacopoeial monographs. *The International Pharmacopoeia* provides international standards for the content, purity and quality of active ingredients, pharmaceutical products and excipients moving in international commerce. Each monograph must be interpreted in accordance with all the general requirements and testing methods, texts or notices pertaining to it. A product is not of pharmacopoeial quality unless it complies with all the requirements stated in the respective context. Moreover, the underlying principle of a pharmacopoeia is that pharmaceutical substances and products intended for medical use should be manufactured according to Good Manufacturing Practices since quality cannot be tested into a product.

The recently adopted approach to include — in newly developed monographs — alternative analytical procedures when more sophisticated methods are described in the monographs concerned should be maintained.

The development of monographs in the context of WHO's disease control programmes (i.e. those on malaria, tuberculosis and AIDS) is a priority.

Monographs in *The International Pharmacopoeia*, together with related general methods and notices have an added value as discussed above and can also be used as references in the development of national (local) quality standards as well as for the assessment of sections on quality control in registration dossiers.

Independence of WHO and independent worldwide validation

Independent worldwide validation of analytical methods is very important, particularly in the context of the use of generics traded and sourced internationally. The active assistance of numerous WHO collaborating centres worldwide is therefore essential in developing international requirements and must be encouraged. The validation of newly developed analytical methods, e.g. for antiretrovirals, should be performed too. The independence of WHO in this matter is unique and of fundamental importance.

International Chemical Reference Substances

The establishment of International Chemical Reference Substances is also an essential part of quality control. This major task is directly related to pharmacopoeial activities and is performed by the WHO Collaborating Centre for Chemical Reference Substances in Kungens Kurva, Sweden. This work should be fully supported to ensure the supply of International Chemical Reference Substances and thus the success of WHO programmes.

List of priorities

In the context of drug quality control priorities are as follows:

- Continuation of the development of international requirements for testing pharmaceuticals.
- Promotion of the global and step-wise approach in the quality control of pharmaceuticals.
- Increasing the availability of documents and information on WHO activities in quality control.
- Providing advice to WHO priority programmes on quality control matters.
- Strengthening collaboration with the Pharmacopoeial Discussion Group.
- Providing information to WHO Member States on the harmonization process and collaboration.
- Promotion of external assessment schemes to improve the performance and recognition of laboratories.
- Coordination of training courses for quality control laboratories on essential sophisticated techniques.

Annex 3

Guidelines on Good Manufacturing Practices for radiopharmaceutical products

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1. **Scope of these guidelines**

These guidelines are intended to complement those already available for pharmaceutical products (1,2) as well as those for sterile pharmaceutical products (3).

The regulatory procedures necessary to control radiopharmaceutical products are in large part determined by the sources of these products and the methods of manufacture. Manufacturing procedures within the scope of these guidelines include:

- The preparation of radiopharmaceuticals in hospital radiopharmacies.
- The preparation of radiopharmaceuticals in centralized radiopharmacies.
- The production of radiopharmaceuticals in nuclear centres and institutes or by industrial manufacturers.
- The preparation and production of radiopharmaceuticals in positron emission tomography (PET) centres.

Radiopharmaceuticals can be classified into four categories:

1. Ready-for-use radioactive products.
2. Radionuclide generators.

3. Non-radioactive components (“kits”) for the preparation of labelled compounds with a radioactive component (usually the eluate from a radionuclide generator).
4. Precursors used for radiolabelling other substances before administration (e.g. samples from patients).

Radiopharmaceutical products include inorganic compounds, organic compounds, peptides, proteins, monoclonal antibodies and fragments, and oligonucleotides labelled with radionuclides with half-lives from a few seconds to several days.

2. Principles

Radiopharmaceuticals must be manufactured in accordance with the basic principles of good manufacturing practices (GMP). The matters covered by these guidelines should therefore be considered as supplementary to the general requirements for GMP previously published (1,2) and relate specifically to the production and control of radiopharmaceuticals. In the preparation of these guidelines, due consideration was given to national or international radiation safety guidelines (4).

Because of their short half-lives, many radiopharmaceuticals are released and administered to patients shortly after their production, so that quality control may sometimes be retrospective. Strict adherence to GMP is therefore mandatory.

3. Personnel

3.1 The manufacturing establishment, whether a hospital radiopharmacy, centralized radiopharmacy, nuclear centre or institution, industrial manufacturer or PET centre, and its personnel should be under the control of a person who has a proven record of academic achievement together with a demonstrated level of practical expertise and experience in radiopharmacy and radiation hygiene. Supporting academic and technical personnel should have the necessary post-graduate or technical training and experience appropriate to their function.

3.2 Personnel required to work in radioactive, clean and aseptic areas should be selected with care, to ensure that they can be relied on to observe the appropriate codes of practice and are not subject to any disease or condition that could compromise the integrity of the product. Health checks on personnel should be requested before employment and periodically thereafter. Any changes in personal health status (e.g. in haematology) may require the temporary exclusion of the person from further radiation exposure.

3.3 Only the minimum number of personnel required should be present in clean and aseptic areas when work is in progress. Access to these areas should be restricted during the preparation of radiopharmaceuticals, kits or sterile set-ups. Inspection and control procedures should be conducted from outside these areas as far as possible.

3.4 During the working day, personnel may pass between radioactive and non-radioactive areas only if the safety rules of radiation control (health physics control) are respected.

3.5 The release of a batch may be approved only by a pharmacist or a person with academic qualifications officially registered as a suitably qualified person, and with appropriate experience in the manufacture of radiopharmaceuticals.

3.6 To ensure the safe manufacture of radiopharmaceuticals, personnel should be trained in GMP, the safe handling of radioactive materials and radiation safety procedures. They should also be required to take periodic courses and receive training to keep abreast of the latest developments in their fields.

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

3.8 All personnel engaged in production, maintenance and testing should follow the relevant guidelines for handling radioactive products and be monitored for possible contamination and/or irradiation exposure.

4. **Premises and equipment**

4.1 As a general principle, buildings must be located, designed, constructed, adapted and maintained to suit the operations to be carried out within them. Laboratories for the handling of radioactive materials must be specially designed to take into consideration aspects of radiation protection in addition to cleanliness and sterility. Interior surfaces (walls, floors and ceilings) should be smooth, impervious and free from cracks; they should not shed matter and should permit easy cleaning and decontamination. Drains should be avoided wherever possible and, unless essential, should be excluded from aseptic areas.

4.2 Specific disposal systems should be mandatory for radioactive effluents. These systems should be effectively and carefully maintained to prevent contamination and exposure of personnel to the radioactive waste both within and outside the facility.

4.3 Sinks should be excluded from aseptic areas. Any sink installed in other clean areas should be of suitable material and be regularly

sanitized. Adequate precautions should be taken to avoid contamination of the drainage system with radioactive effluents.

4.4 Lighting, heating, ventilation and, if necessary, air-conditioning should be designed to maintain a satisfactory temperature and relative humidity to ensure the comfort of personnel working in protective clothing. Buildings should be in a good state of repair. The condition of the buildings should be reviewed regularly and repairs carried out when and where necessary. Special care should be exercised to ensure that building repair or maintenance operations do not compromise products. Premises should provide sufficient space for the operations to be carried out, allowing an efficient flow of work and effective communication and supervision. All buildings and rooms should be clean, sanitary and free from radioactive contamination.

4.5 Ventilation of radiopharmaceutical production facilities should meet the requirement to prevent the contamination of products and the exposure of working personnel to radioactivity. Suitable pressure and airflow patterns should be maintained by appropriate isolation/enveloping methods. Air handling systems for both radioactive and non-radioactive areas should be fitted with alarms so that the working personnel in the laboratory are warned of any failure of these systems.

4.6 Dedicated facilities and equipment should be used for the manufacture of any radiopharmaceutical product derived from human blood or plasma. Autoclaves used in production areas for radiopharmaceuticals may be placed behind a lead shield to minimize the radiation exposure of the operators. Such autoclaves should be checked for contamination immediately after use to minimize the possibility of cross-contamination by radioactivity of the products in the next autoclave cycles.

4.7 All containers of radiopharmaceutical substances, regardless of the stage of manufacture, should be identified by securely attached labels. Cross-contamination should be prevented by the adoption of some or all of the following measures:

- processing and filling in segregated areas;
- avoiding the manufacture of different products at the same time, unless they are effectively segregated;
- containing material transfer by means of airlocks, air extraction, changing clothes and careful washing and decontamination of equipment;
- protecting against the risks of contamination caused by recirculation of untreated air, or by accidental re-entry of extracted air;
- using “closed systems” of manufacture;

- taking care to prevent aerosol formation;
- using sterilized containers.

4.8 Positive pressure areas should be used to process sterile products. In general, any radioactivity should be handled within specifically designed areas maintained under negative pressures. The production of sterile radioactive products should therefore be carried out under negative pressure surrounded by a positive pressure zone ensuring that appropriate air quality requirements are met.

4.9 Separate air-handling units should be used for radioactive and non-radioactive areas. Air from operations involving radioactivity should be exhausted through appropriate filters that are regularly checked for performance.

4.10 Pipework, valves and vent filters should be properly designed to facilitate validated cleaning and decontamination.

5. **Production**

5.1 Standard operating procedures (SOPs) must be available for all operating procedures and should be regularly reviewed and kept up to date for all manufacturing operations. All entries on batch records should be initiated by the operator and independently checked by another operator or supervisor.

5.2 Specifications for starting materials should include details of their source, origin and (where applicable) method of manufacture and of the controls used to ensure their suitability for use. Release of a finished product should be conditional on satisfactory results being obtained in the tests on starting materials.

5.3 Careful consideration should be given to the validation of sterilization methods.

5.4 A wide variety of equipment is used in the preparation of radiopharmaceuticals. Equipment for chromatography should, in general, be dedicated to the preparation and purification of one or several products labelled with the same radionuclide to avoid radioactive cross-contamination. The life span of columns should be defined. Great care should be taken in cleaning, sterilizing and operating freeze-drying equipment used for the preparation of kits.

5.5 A list of critical equipment should be drawn up, including any equipment such as a balance, pyrogen oven, dose calibrator, sterilizing filter, etc., where an error in the reading or function could potentially cause harm to the patient being given the final product. These devices should be calibrated or tested at regular intervals and should

be checked daily or before production is started. The results of these tests should be included in the daily production records.

5.6 Specific equipment for radioactive measurements may be required as well as radioactive reference standards. For the measurement of very short half-lives, national central laboratories should be contacted to calibrate the apparatus. Where this is not possible, alternative approaches, such as documented procedures, may be used.

5.7 In the case of labelling kits, freeze drying should be carried out as an aseptic procedure. If an inert gas such as nitrogen is used to fill vials, it must be filtered to remove possible microbial contamination.

5.8 The dispensing, packaging and transportation of radiopharmaceuticals should comply with the relevant national regulations and international guidelines (5).

6. Labelling

6.1 All products should be clearly identified by labels, which must remain permanently attached to the containers under all storage conditions. An area of the container should be left uncovered to allow inspection of the contents. If the final container is not suitable for labelling, the label should appear on its package. Information on batch coding must be provided to the national and/or regional authorities.

6.2 The labels of radiopharmaceuticals must comply with the relevant national regulations and international agreements. For registered radiopharmaceuticals, the national control authority should approve the labels.

6.3 The label on the container should show:

- (a) the name of the drug product and/or the product identification code;
- (b) the name of the radionuclide;
- (c) the name of the manufacturer or the company and/or the person responsible for placing the drug on the market;
- (d) the radioactivity per unit dose:
 - for liquid preparations, the total radioactivity in the container, or the radioactive concentration per millilitre, at a stated date and, if necessary, hour, and the volume of liquid in the container;
 - for solid preparations, such as freeze-dried preparations, the total radioactivity at a stated date and, if necessary, hour;

- for capsules, the radioactivity of each capsule at a stated date and, if necessary, hour, and the number of capsules in the container;
- where relevant, the international symbol for radioactivity.

6.4 The label on the package should state:

- (a) the qualitative and quantitative composition;
- (b) the radioactive isotopes and the amount of radioactivity at the time of dispatch;
- (c) the route of administration;
- (d) the expiry date;
- (e) any special storage conditions;
- (f) mandatory information related to transport regulations for radioactive materials.

6.5 The leaflet in the package should contain the specific product information and indications for use. This information is especially important for preparation kits (cold kits), and should include:

- (a) the name of the product and a description of its use;
- (b) the contents of the kit;
- (c) the identification and quality requirements concerning the radio-labelling materials that can be used to prepare the radiopharmaceutical, namely:
 - the directions for preparing the radiopharmaceutical, including the range of activity and the volume, together with a statement of the storage requirements for the prepared radiopharmaceutical;
 - a statement of the shelf-life of the prepared radiopharmaceutical;
 - the indications and contraindications (pregnancy, children, drug reactions, etc.) in respect of the prepared radiopharmaceutical;
 - warnings and precautions in respect of the components and the prepared radiopharmaceutical, including radiation safety aspects;
 - where applicable, the pharmacology and toxicology of the prepared radiopharmaceutical, including the route of elimination and the effective half-life;
 - the radiation dose that a patient will receive from the prepared radiopharmaceutical;
 - the precautions to be taken by users and patients during the preparation and administration of the product and the special precautions for the disposal of the container and any unconsumed portions;

- a statement of the recommended use of the prepared radiopharmaceutical and the recommended dosage;
- a statement of the route of administration of the prepared radiopharmaceutical;
- if appropriate for particular kits (i.e. those subject to variability beyond the recommended limits), the methods and specifications needed to check radiochemical purity.

7. **Production and distribution records**

7.1 The processing records of regular production batches must provide a complete account of the manufacturing history of each batch of a radiopharmaceutical, showing that it has been manufactured, tested, dispensed into containers and distributed in accordance with the written procedures.

7.2 Separate records for the receipt, storage, use and disposal of radioactive materials should be maintained in accordance with radiation protection regulations.

7.3 Distribution records should be kept. Since the return of radioactive products is not practical, the purpose of recall procedures for such products is to prevent their use rather than an actual return. If necessary, the return of radioactive products should be carried out in accordance with international and national transport regulations.

8. **Quality assurance and quality control**

8.1 Radiopharmaceuticals are nearly always used before all quality control testing (e.g. tests for sterility, endotoxin, radionuclidic purity, etc.) has been completed. The implementation of and compliance with the quality assurance programme are therefore essential.

8.2 Quality assurance and/or quality control should have the following principal responsibilities:

- (a) the preparation of detailed instructions for each test and analysis;
- (b) ensuring the adequate identification and segregation of test samples to avoid mix-ups and cross-contamination;
- (c) ensuring that environmental monitoring and equipment and process validation are conducted as appropriate for evaluating the adequacy of the manufacturing conditions;
- (d) the release or rejection of starting materials and intermediate products;
- (e) the release or rejection of packaging and labelling materials;
- (f) the release or rejection of each batch of finished preparation;

- (g) the evaluation of the adequacy of the conditions under which the starting materials, intermediate products and finished radiopharmaceutical preparations are stored;
- (h) the evaluation of the quality and stability of the finished products and, when necessary, of the starting materials and intermediate products;
- (i) the establishment of expiry dates on the basis of the validity period related to specified storage conditions;
- (j) the establishment and revision of the control procedures and specifications;
- (k) assuming the responsibility for retaining samples of radiopharmaceutical products;
- (l) assuming the responsibility for keeping adequate records of the distribution of the radiopharmaceutical products.

8.3 Whenever the size of the establishment permits, quality assurance and quality control duties should be organized in separate groups. Quality assurance should also include the monitoring and validation of the production process.

8.4 A manufacturer's quality control laboratory should be separated from the production area. The control laboratory should be designed, equipped and of such a size as to be a self-contained entity, with adequate provision for the storage of documents and samples, the preparation of records and the performance of the necessary tests.

8.5 The performance of all qualitative and quantitative tests mentioned in the specifications for the starting materials may be replaced by a system of certificates issued by the supplier of these materials, provided that:

- (a) there is a history of reliable production;
- (b) the producer or supplier is regularly audited;
- (c) at least one specific identity test is conducted by the manufacturer of the finished radiopharmaceutical.

8.6 Samples of the intermediate and final products should be retained in sufficient amounts and under appropriate storage conditions to allow repeated testing or verification of a batch control. These samples should be kept for an appropriate period in accordance with the shelf-lives of the radioactive components concerned. However, this may sometimes not be applicable, e.g. for radiopharmaceuticals with a short half-life.

8.7 Sampling procedures may be adapted to the purpose of the sampling, the type of controls being applied, and the nature of the mate-

rial being sampled (e.g. a small batch size and/or its radioactive content). The procedure should be described in a written protocol.

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Annex 4

Good Manufacturing Practices for pharmaceutical products: main principles

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Introduction

The first WHO draft text on good manufacturing practices (GMP) was prepared in 1967 by a group of consultants at the request of the Twentieth World Health Assembly (resolution WHA20.34). It was subsequently submitted to the Twenty-first World Health Assembly under the title “Draft requirements for good manufacturing practice in the manufacture and quality control of drugs and pharmaceutical specialities” and was accepted.

The revised text was discussed by the WHO Expert Committee on Specifications for Pharmaceutical Preparations in 1968 and published

as an annex to its twenty-second report. The text was then reproduced (with some revisions) in 1971 in the Supplement to the second edition of *The International Pharmacopoeia*.

In 1969, when the World Health Assembly recommended the first version of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce in resolution WHA22.50, it accepted at the same time the GMP text as an integral part of the Scheme. Revised versions of both the Certification Scheme and the GMP text were adopted in 1975 by resolution WHA28.65. Since then, the Certification Scheme has been extended to include the certification of:

- veterinary products administered to food-producing animals;
- starting materials for use in dosage forms, when they are subject to control by legislation in both the exporting Member State and the importing Member State;
- information on safety and efficacy (resolution WHA41.18, 1988).

In 1992, the revised draft requirements for GMP were presented in three parts, of which only Parts One and Two are reproduced in this document (1).

“Quality management in the drug industry: philosophy and essential elements”, outlines the general concepts of quality assurance as well as the principal components or subsystems of GMP, which are joint responsibilities of top management and of production and quality control management. These include hygiene, validation, self-inspection, personnel, premises, equipment, materials and documentation.

“Good practices in production and quality control”, provides guidance on actions to be taken separately by production and by quality control personnel for the implementation of the general principles of quality assurance.

These two parts were subsequently supplemented by further guidelines which are integral parts of these good manufacturing practices for pharmaceutical products. All these texts are available on the web page of the World Health Organization. (<http://www.who.int/medicines/organization/qsm/activities/qualityassurance/gmp/gmpcover.html>)

Considerable developments in GMP have taken place in the intervening years, and important national and international documents, including new revisions, have appeared (2, 3, 4, 5). Thus the necessity to revise the main principles and incorporate the concept of validation.

General considerations

Licensed pharmaceutical products (marketing authorization) should be manufactured only by licensed manufacturers (holders of a manufacturing authorization) whose activities are regularly inspected by competent national authorities. This guide to GMP shall be used as a standard to justify GMP status, which constitutes one of the elements of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce, through the assessment of applications for manufacturing authorizations and as a basis for the inspection of manufacturing facilities. It may also be used as training material for government drug inspectors, as well as for production, quality control and quality assurance personnel in the industry.

The guide is applicable to operations for the manufacture of drugs in their finished dosage forms, including large-scale processes in hospitals and the preparation of supplies for use in clinical trials.

The good practices outlined below are to be considered general guides¹, and they may be adapted to meet individual needs. The equivalence of alternative approaches to quality assurance, however, should be validated. The guide as a whole does not cover safety aspects for the personnel engaged in manufacture or environmental protection: these are normally governed by national legislation. A new concept of hazard analysis related to the risks in production and personnel safety is also newly recommended (Annex 7). The manufacturer should assure the safety of workers and take the necessary measures to prevent pollution of the external environment. International Nonproprietary Names (INNs) for pharmaceutical substances designated by WHO should be used when available, together with other designated names.

Glossary

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

active pharmaceutical ingredient (API)

Any substance or mixture of substances intended to be used in the manufacture of a pharmaceutical dosage form and that, when so used, becomes an active ingredient of that pharmaceutical dosage form. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body.

¹ The word "should" in the text means a strong recommendation.

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 use either by people or for goods and/or equipment.

authorized person

The person recognized by the national regulatory authority as having the responsibility for ensuring that each batch of finished product has been manufactured, tested and approved for release in compliance with the laws and regulations in force in that country.

batch (or lot)

A defined quantity of starting material, packaging material, or product processed in a single process or series of processes so that it is expected to be homogeneous. It may sometimes be necessary to divide a batch into a number of sub-batches, which are later brought together to form a final homogeneous batch. In the case of terminal sterilization, the batch size is determined by the capacity of the autoclave. In continuous manufacture, the batch must correspond to a defined fraction of the production, characterized by its intended homogeneity. The batch size can be defined either as a fixed quantity or as the amount produced in a fixed time interval.

batch number (or lot number)

A distinctive combination of numbers and/or letters which uniquely identifies a batch on the labels, its batch records and corresponding certificates of analysis, etc.

batch records

All documents associated with the manufacture of a batch of bulk product or finished product. They provide a history of each batch of product and of all circumstances pertinent to the quality of the final product.

bulk product

Any product that has completed all processing stages up to, but not including, final packaging.

calibration

The set of operations that establish, under specified conditions, the relationship between values indicated by an instrument or system for measuring (especially weighing), 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.

clean area

An area 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.

consignment (or delivery)

The quantity of a pharmaceutical(s), made by one manufacturer and 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.

contamination

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

critical operation

An operation in the manufacturing process that may cause variation in the quality of the pharmaceutical product.

cross-contamination

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

finished product

A finished dosage form that has undergone all stages of manufacture, including packaging in its final container and labelling.

in-process control

Checks performed during production in order to monitor and, if necessary, to adjust the process to ensure that the product conforms to its specifications. The control of the environment or equipment may also be regarded as a part of in-process control.

intermediate product

Partly processed product that must undergo further manufacturing steps before it becomes a bulk product.

large-volume parenterals

Sterile solutions intended for parenteral application with a volume of 100ml or more in one container of the finished dosage form.

manufacture

All operations of purchase of materials and products, production, quality control, release, storage and distribution of pharmaceutical products, and the related controls.

manufacturer

A company that carries out operations such as production, packaging, repackaging, labelling and relabelling of pharmaceuticals.

marketing authorization (product licence, registration certificate)

A legal document issued by the competent drug regulatory authority that establishes the detailed composition and formulation of the product and the pharmacopoeial or other recognized specifications of its ingredients and of the final product itself, and includes details of packaging, labelling and shelf-life.

master formula

A document or set of documents specifying the starting materials with their quantities and the packaging materials, together with a description of the procedures and precautions required to produce a specified quantity of a finished product as well as the processing instructions, including the in-process controls.

master record

A document or set of documents that serve as a basis for the batch documentation (blank batch record).

packaging

All operations, including filling and labelling, that a bulk product has to undergo in order to become a finished product. Filling of a sterile product under aseptic conditions or a product intended to be terminally sterilized, would not normally be regarded as part of packaging.

packaging material

Any material, including printed material, employed in the packaging of a pharmaceutical, but excluding any outer packaging used for transportation or shipment. Packaging materials are referred to as primary or secondary according to whether or not they are intended to be in direct contact with the product.

pharmaceutical product

Any material or product intended for human or veterinary use presented in its finished dosage form or as a starting material for use in such a dosage form, that is subject to control by pharmaceutical legislation in the exporting state and/or the importing state.

production

All operations involved in the preparation of a pharmaceutical product, from receipt of materials, through processing, packaging and repackaging, labelling and relabelling, to completion of the finished product.

qualification

Action of proving that any premises, systems and items of equipment work correctly and actually lead to the expected results. The meaning of the word “validation” is sometimes extended to incorporate the concept of qualification.

quality assurance

See Part One (pp. 7–35).

quality control

See Part One (pp. 7–35).

quarantine

The status of starting or packaging materials, intermediates, or bulk or finished products isolated physically or by other effective means while a decision is awaited on their release, rejection or reprocessing.

reconciliation

A comparison between the theoretical quantity and the actual quantity.

recovery

The introduction of all or part of previous batches (or of redistilled solvents and similar products) of the required quality into another batch at a defined stage of manufacture. It includes the removal of impurities from waste to obtain a pure substance or the recovery of used materials for a separate use.

reprocessing

Subjecting all or part of a batch or lot of an in-process drug, bulk process intermediate (final biological bulk intermediate) or bulk

product of a single batch/lot to a previous step in the validated manufacturing process due to failure to meet predetermined specifications. Reprocessing procedures are foreseen as occasionally necessary for biological drugs and, in such cases, are validated and pre-approved as part of the marketing authorization.

reworking

Subjecting an in-process or bulk process intermediate (final biological bulk intermediate) or final product of a single batch to an alternate manufacturing process due to a failure to meet predetermined specifications. Reworking is an unexpected occurrence and is not pre-approved as part of the marketing authorization.

self-contained area

Premises which provide complete and total separation of all aspects of an operation, including personnel and equipment movement, with well established procedures, controls and monitoring. This includes physical barriers as well as separate air-handling systems, but does not necessarily imply two distinct and separate buildings.

specification

A list of detailed requirements with which the products or materials used or obtained during manufacture have to conform. They serve as a basis for quality evaluation.

standard operating procedure (SOP)

An authorized written procedure giving instructions for performing operations not necessarily specific to a given product or material (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.

starting material

Any substance of a defined quality used in the production of a pharmaceutical product, but excluding packaging materials.

validation

Action of proving, in accordance with the principles of GMP, that any procedure, process, equipment, material, activity or system actually leads to the expected results (see also qualification).

Quality management in the drug industry: philosophy and essential elements¹

In the drug industry at large, quality management is usually defined as the aspect of management function that determines and implements the “quality policy”, i.e. the overall intention and direction of an organization regarding quality, as formally expressed and authorized by top management.

The basic elements of quality management are:

- an appropriate infrastructure or “quality system”, encompassing the organizational structure, procedures, processes and resources;
- systematic actions necessary to ensure adequate confidence that a product (or service) will satisfy given requirements for quality. The totality of these actions is termed “quality assurance”.

Within an organization, quality assurance serves as a management tool. In contractual situations, quality assurance also serves to generate confidence in the supplier.

The concepts of quality assurance, GMP and quality control are inter-related aspects of quality management. They are described here in order to emphasize their relationship and their fundamental importance to the production and control of pharmaceutical products.

1. Quality assurance

1.1 *Principle.* “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 assurance therefore incorporates GMP and other factors, including those outside the scope of this guide such as product design and development.

1.2 The system of quality assurance appropriate to the manufacture of pharmaceutical products should ensure that:

- (a) pharmaceutical products are designed and developed in a way that takes account of the requirements of GMP and other

¹ Good manufacturing practices for pharmaceutical products, Part One. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-second report.* Geneva, World Health Organization, 1992, Annex 1 (WHO Technical Report Series, No. 823).

- associated codes such as those of good laboratory practice (GLP)¹ and good clinical practice (GCP);
- (b) production and control operations are clearly specified in a written form and GMP requirements are adopted;
 - (c) managerial responsibilities are clearly specified in job descriptions;
 - (d) arrangements are made for the manufacture, supply and use of the correct starting and packaging materials;
 - (e) all necessary controls on starting materials, intermediate products, and bulk products and other in-process controls, calibrations, and validations are carried out;
 - (f) the finished product is correctly processed and checked, according to the defined procedures;
 - (g) pharmaceutical products are not sold or supplied before the authorized persons (see also sections 9.11 & 9.12) have certified that each production batch has been produced and controlled in accordance with the requirements of the marketing authorization and any other regulations relevant to the production, control and release of pharmaceutical products;
 - (h) satisfactory arrangements exist to ensure, as far as possible, that the pharmaceutical products are stored by the manufacturer, distributed, and subsequently handled so that quality is maintained throughout their shelf-life;
 - (i) there is a procedure for self-inspection and/or quality audit that regularly appraises the effectiveness and applicability of the quality assurance system;
 - (j) deviations are reported, investigated and recorded;
 - (k) there is a system for approving changes that may have an impact on product quality;
 - (l) regular evaluations of the quality of pharmaceutical products should be conducted with the objective of verifying the consistency of the process and ensuring its continuous improvement.

1.3 The manufacturer must assume responsibility for the quality of the pharmaceutical products to ensure that they are fit for their intended use, comply with the requirements of the marketing authorization and do not place patients at risk due to inadequate safety, quality or efficacy. The attainment of this quality objective is the responsibility of senior management and requires the participation and commitment of staff in many different departments and at all levels within the

¹ This is a code governing the testing of chemicals to obtain data on their properties and ensuring safety with respect to human health and the environment. It is different from that described in "Good laboratory practices in governmental drug control laboratories" in the Thirtieth report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations (WHO Technical Report Series, No. 748, 1987, Annex 1).

company, the company's suppliers, and the distributors. To achieve the quality objective reliably there must be a comprehensively designed and correctly implemented system of quality assurance incorporating GMP and quality control. It should be fully documented and its effectiveness monitored. All parts of the quality assurance system should be adequately staffed with competent personnel, and should have suitable and sufficient premises, equipment, and facilities.

2. **Good manufacturing practices for pharmaceutical products (GMP)**

2.1 Good manufacturing practice is 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. GMP are aimed primarily at diminishing the risks inherent in any pharmaceutical production. Such risks are essentially of two types: cross-contamination (in particular of unexpected contaminants) and mix-ups (confusion) caused by, for example, false labels being put on containers. Under GMP:

- (a) all manufacturing processes are clearly defined, systematically reviewed in the light of experience, and shown to be capable of consistently manufacturing pharmaceutical products of the required quality that comply with their specifications;
- (b) qualification and validation are performed;
- (c) all necessary resources are provided, including:
 - (i) appropriately qualified and trained personnel;
 - (ii) adequate premises and space;
 - (iii) suitable equipment and services;
 - (iv) appropriate materials, containers and labels;
 - (v) approved procedures and instructions;
 - (vi) suitable storage and transport;
 - (vii) adequate personnel, laboratories and equipment for in-process controls;
- (d) instructions and procedures are written in clear and unambiguous language, specifically applicable to the facilities provided;
- (e) operators are trained to carry out procedures correctly;
- (f) records are made (manually and/or by recording instruments) during manufacture to show that all the steps required by the defined procedures and instructions have in fact been taken and that the quantity and quality of the product are as expected; any significant deviations are fully recorded and investigated;
- (g) records covering manufacture and distribution, which enable the complete history of a batch to be traced, are retained in a comprehensible and accessible form;

- (h) the proper storage and distribution of the products minimizes any risk to their quality;
- (i) a system is available to recall any batch of product from sale or supply;
- (j) complaints about marketed products are examined, the causes of quality defects investigated, and appropriate measures taken in respect of the defective products to prevent recurrence.

3. **Sanitation and hygiene**

3.1 A high level of sanitation and hygiene should be practised in every aspect of the manufacture of drug products. The scope of sanitation and hygiene covers personnel, premises, equipment and apparatus, production materials and containers, products for cleaning and disinfection, and anything that could become a source of contamination to the product. Potential sources of contamination should be eliminated through an integrated comprehensive programme of sanitation and hygiene. (For *personal hygiene* see section 11, and for *sanitation* see section 12, “Premises”.)

4. **Qualification and validation**

4.1 In accordance with GMP, each pharmaceutical company should identify what qualification and validation work is required to prove that the critical aspects of their particular operation are controlled.

4.2 The key elements of a qualification and validation programme of a company should be clearly defined and documented in a validation master plan.

4.3 Qualification and validation should establish and provide documentary evidence that:

- (a) the premises, supporting utilities, equipment and processes have been designed in accordance with the requirements for GMP (design qualification or DQ);
- (b) the premises, supporting utilities and equipment have been built and installed in compliance with their design specifications (installation qualification or IQ);
- (c) the premises, supporting utilities and equipment operate in accordance with their design specifications (operational qualification or OQ);
- (d) a specific process will consistently produce a product meeting its predetermined specifications and quality attributes (process validation or PV, also called performance qualification or PQ).

4.4 Any aspect of operation, including significant changes to the premises, facilities, equipment or processes, which may affect the quality of the product, directly or indirectly, should be qualified and validated.

4.5 Qualification and validation should not be considered as one-off exercises. An on-going programme should follow their first implementation and should be based on an annual review.

4.6 The commitment to maintain continued validation status should be stated in the relevant company documentation, such as the quality manual or validation master plan.

4.7 The responsibility of performing validation should be clearly defined.

4.8 Validation studies are an essential part of GMP and should be conducted in accordance with predefined and approved protocols.

4.9 A written report summarizing the results recorded and the conclusions reached should be prepared and stored.

4.10 Processes and procedures should be established on the basis of the results of the validation performed.

4.11 It is of critical importance that particular attention is paid to the validation of analytical test methods, automated systems and cleaning procedures.

5. **Complaints**

5.1 *Principle.* All complaints and other information concerning potentially defective products should be carefully reviewed according to written procedures and the corrective action should be taken.

5.2 A person responsible for handling the complaints and deciding the measures to be taken should be designated, together with sufficient supporting staff to assist him or her. If this person is different from the authorized person, the latter should be made aware of any complaint, investigation or recall.

5.3 There should be written procedures describing the action to be taken, including the need to consider a recall, in the case of a complaint concerning a possible product defect.

5.4 Special attention should be given to establishing whether a complaint was caused because of counterfeiting.

5.5 Any complaint concerning a product defect should be recorded with all the original details and thoroughly investigated. The person responsible for quality control should normally be involved in the review of such investigations.

5.6 If a product defect is discovered or suspected in a batch, consideration should be given to whether other batches should be checked in order to determine whether they are also affected. In particular,

other batches that may contain reprocessed product from the defective batch should be investigated.

5.7 Where necessary, appropriate follow-up action, possibly including product recall, should be taken after investigation and evaluation of the complaint.

5.8 All decisions made and measures taken as a result of a complaint should be recorded and referenced to the corresponding batch records.

5.9 Complaints records should be regularly reviewed for any indication of specific or recurring problems that require attention and might justify the recall of marketed products.

5.10 The competent authorities should be informed if a manufacturer is considering action following possibly faulty manufacture, product deterioration, counterfeiting or any other serious quality problems with a product.

6. **Product recalls**

6.1 *Principle.* There should be a system to recall from the market, promptly and effectively, products known or suspected to be defective.

6.2 The authorized person should be responsible for the execution and coordination of recalls. He/she should have sufficient staff to handle all aspects of the recalls with the appropriate degree of urgency.

6.3 There should be established written procedures, which are regularly reviewed and updated, for the organization of any recall activity. Recall operations should be capable of being initiated promptly down to the required level in the distribution chain.

6.4 An instruction should be included in the written procedures to store recalled products in a secure segregated area while their fate is decided.

6.5 All competent authorities of all countries to which a given product has been distributed should be promptly informed of any intention to recall the product because it is, or is suspected of being, defective.

6.6 The distribution records should be readily available to the authorized person, and they should contain sufficient information on wholesalers and directly supplied customers (including, for exported products, those who have received samples for clinical tests and medical samples) to permit an effective recall.

6.7 The progress of the recall process should be monitored and recorded. Records should include the disposition of the product. A final report should be issued, including a reconciliation between the delivered and recovered quantities of the products.

6.8 The effectiveness of the arrangements for recalls should be tested and evaluated from time to time.

7. **Contract production and analysis**

7.1 *Principle.* Contract production and analysis must be correctly defined, agreed and controlled in order to avoid misunderstandings that could result in a product or work or analysis of unsatisfactory quality.

General

7.2 All arrangements for contract manufacture and analysis, including any proposed changes in technical or other arrangements, should be in accordance with the marketing authorization for the product concerned.

7.3 The contract should permit the contract giver to audit the facilities of the contract acceptor.

7.4 In the case of contract analysis, the final approval for release must be given by the authorized person.

The contract giver

7.5 The contract giver is responsible for assessing the competence of the contract acceptor in successfully carrying out the work or tests required, for approval for contract activities, and for ensuring by means of the contract that the principles of GMP described in this guide are followed.

7.6 The contract giver should provide the contract acceptor with all the information necessary to carry out the contracted operations correctly in accordance with the marketing authorization and any other legal requirements. The contract giver should ensure that the contract acceptor is fully aware of any problems associated with the product, work or tests that might pose a hazard to premises, equipment, personnel, other materials or other products.

7.7 The contract giver should ensure that all processed products and materials delivered by the contract acceptor comply with their specifications or that the product has been released by the authorized person.

The contract acceptor

7.8 The contract acceptor must have adequate premises, equipment, knowledge, and experience and competent personnel to carry out satisfactorily the work ordered by the contract giver. Contract manufacture may be undertaken only by a manufacturer who holds a manufacturing authorization.

7.9 The contract acceptor should not pass to a third party any of the work entrusted to him or her under the contract without the contract giver's prior evaluation and approval of the arrangements. Arrangements made between the contract acceptor and any third party should ensure that the manufacturing and analytical information is made available in the same way as between the original contract giver and contract acceptor.

7.10 The contract acceptor should refrain from any activity that may adversely affect the quality of the product manufactured and/or analysed for the contract giver.

The contract

7.11 There must be a written contract between the contract giver and the contract acceptor which clearly establishes the responsibilities of each party.

7.12 The contract must clearly state the way in which the authorized person, in releasing each batch of product for sale or issuing the certificate of analysis, exercises his or her full responsibility and ensures that each batch has been manufactured in, and checked for, compliance with the requirements of the marketing authorization.

7.13 Technical aspects of the contract should be drawn up by competent persons suitably knowledgeable in pharmaceutical technology, analysis and GMP.

7.14 All arrangements for production and analysis must be in accordance with the marketing authorization and agreed by both parties.

7.15 The contract should describe clearly who is responsible for purchasing, testing and releasing materials and for undertaking production and quality controls, including in-process controls, and who has responsibility for sampling and analysis. In the case of contract analysis, the contract should state whether or not the contract acceptor should take samples at the premises of the manufacturer.

7.16 Manufacturing, analytical, distribution records and reference samples should be kept by, or be available to, the contract giver. Any records relevant to assessing the quality of a product in the event of

complaints or a suspected defect must be accessible and specified in the defect/recall procedures of the contract giver.

7.17 The contract should describe the handling of starting materials, intermediate and bulk products and finished products if they are rejected. It should also describe the procedure to be followed if the contract analysis shows that the tested product must be rejected.

8. **Self-inspection and quality audits**

8.1 *Principle.* The purpose of self-inspection is to evaluate the manufacturer's compliance with GMP in all aspects of production and quality control. The self-inspection programme should be designed to detect any shortcomings in the implementation of GMP and to recommend the necessary corrective actions. Self-inspections should be performed routinely, and may be, in addition, performed on special occasions, e.g. in the case of product recalls or repeated rejections, or when an inspection by the health authorities is announced. The team responsible for self-inspection should consist of personnel who can evaluate the implementation of GMP objectively. All recommendations for corrective action should be implemented. The procedure for self-inspection should be documented, and there should be an effective follow-up programme.

Items for self-inspection

8.2 Written instructions for self-inspection should be established to provide a minimum and uniform standard of requirements. These may include questionnaires on GMP requirements covering at least the following items:

- (a) personnel;
- (b) premises including personnel facilities;
- (c) maintenance of buildings and equipment;
- (d) storage of starting materials and finished products;
- (e) equipment;
- (f) production and in-process controls;
- (g) quality control;
- (h) documentation;
- (i) sanitation and hygiene;
- (j) validation and revalidation programmes;
- (k) calibration of instruments or measurement systems;
- (l) recall procedures;
- (m) complaints management;
- (n) labels control;
- (o) results of previous self-inspections and any corrective steps taken.

Self-inspection team

8.3 Management should appoint a self-inspection team consisting of experts in their respective fields and familiar with GMP. The members of the team may be appointed from inside or outside the company.

Frequency of self-inspection

8.4 The frequency at which self-inspections are conducted may depend on company requirements but should preferably be at least once a year. The frequency should be stated in the procedure.

Self-inspection report

8.5 A report should be made at the completion of a self-inspection. The report should include:

- (a) self-inspection results;
- (b) evaluation and conclusions;
- (c) recommended corrective actions.

Follow-up action

8.6 There should be an effective follow-up programme. The company management should evaluate both the self-inspection report and the corrective actions as necessary.

Quality audit

8.7 It may be useful to supplement self-inspections with a quality audit. A quality audit consists of an examination and assessment of all or part of a quality system with the specific purpose of improving it. A quality audit is usually conducted by outside or independent specialists or a team designated by the management for this purpose. Such audits may also be extended to suppliers and contractors (see section 7, “Contract production and analysis”).

Suppliers’ audits and approval

8.8 The person responsible for quality control should have responsibility together with other relevant departments for approving suppliers who can reliably supply starting and packaging materials that meet established specifications.

8.9 Before suppliers are approved and included in the approved supplier’s list or specifications, they should be evaluated. The evaluation should take into account a supplier’s history and the nature of the materials to be supplied. If an audit is required, it should determine the supplier’s ability to conform with GMP standards.

9. Personnel

9.1 *Principle.* The establishment and maintenance of a satisfactory system of quality assurance and the correct manufacture and control of pharmaceutical products and active ingredients rely upon people. For this reason there must be sufficient qualified personnel to carry out all the tasks for which the manufacturer is responsible. Individual responsibilities should be clearly defined and understood by the persons concerned and recorded as written descriptions.

General

9.2 The manufacturer should have an adequate number of personnel with the necessary qualifications and practical experience. The responsibilities placed on any one individual should not be so extensive so as to present any risk to quality.

9.3. All responsible staff should have their specific duties recorded in written descriptions and adequate authority to carry out their responsibilities. Their duties may be delegated to designated deputies of a satisfactory qualification level. There should be no gaps or unexplained overlaps in the responsibilities of personnel concerned with the application of GMP. The manufacturer should have an organization chart.

9.4 All personnel should be aware of the principles of GMP that affect them and receive initial and continuing training, including hygiene instructions, relevant to their needs. All personnel should be motivated to support the establishment and maintenance of high-quality standards.

9.5 Steps should be taken to prevent unauthorized people from entering production, storage and quality control areas. Personnel who do not work in these areas should not use them as a passageway.

Key personnel

9.6 Key personnel include the head of production, the head of quality control and the authorized person. Normally, key posts should be occupied by full-time personnel. The heads of production and quality control should be independent of each other. In large organizations, it may be necessary to delegate some of the functions; however, the responsibility cannot be delegated.

9.7 Key personnel responsible for supervising the manufacture and quality control of pharmaceutical products should possess the qualifications of a scientific education and practical experience required by

national legislation. Their education should include the study of an appropriate combination of:

- (a) chemistry (analytical or organic) or biochemistry;
- (b) chemical engineering;
- (c) microbiology;
- (d) pharmaceutical sciences and technology;
- (e) pharmacology and toxicology;
- (f) physiology;
- (g) other related sciences.

They should also have adequate practical experience in the manufacture and quality assurance of pharmaceutical products. In order to gain such experience, a preparatory period may be required, during which they should exercise their duties under professional guidance. The scientific education and practical experience of experts should be such as to enable them to exercise independent professional judgement, based on the application of scientific principles and understanding to the practical problems encountered in the manufacture and quality control of pharmaceutical products.

9.8 The heads of the production and quality control generally have some shared, or jointly exercised, responsibilities relating to quality. These may include, depending on national regulations:

- (a) authorization of written procedures and other documents, including amendments;
- (b) monitoring and control of the manufacturing environment;
- (c) plant hygiene;
- (d) process validation and calibration of analytical apparatus;
- (e) training, including the application and principles of quality assurance;
- (f) approval and monitoring of suppliers of materials;
- (g) approval and monitoring of contract manufacturers;
- (h) designation and monitoring of storage conditions for materials and products;
- (i) performance and evaluation of in-process controls;
- (j) retention of records;
- (k) monitoring of compliance with GMP requirements;
- (l) inspection, investigation and taking of samples in order to monitor factors that may affect product quality.

9.9 The head of the production generally has the following responsibilities:

- (a) to ensure that products are produced and stored according to the appropriate documentation in order to obtain the required quality;

- (b) to approve the instructions relating to production operations, including the in-process controls, and to ensure their strict implementation;
- (c) to ensure that the production records are evaluated and signed by a designated person;
- (d) to check the maintenance of the department, premises, and equipment;
- (e) to ensure that the appropriate process validations and calibrations of control equipment are performed and recorded and the reports made available;
- (f) to ensure that the required initial and continuing training of production personnel is carried out and adapted according to need.

9.10 The head of the quality control generally has the following responsibilities:

- (a) to approve or reject starting materials, packaging materials, and intermediate, bulk and finished products in relation with their specifications;
- (b) to evaluate batch records;
- (c) to ensure that all necessary testing is carried out;
- (d) to approve sampling instructions, specifications, test methods and other quality control procedures;
- (e) to approve and monitor analyses carried out under contract;
- (f) to check the maintenance of the department, premises and equipment;
- (g) to ensure that the appropriate validations, including those of analytical procedures, and calibrations of control equipment are carried out;
- (h) to ensure that the required initial and continuing training of quality control personnel is carried out and adapted according to need.

Other duties of the quality control are summarized in sections 17.3 and 17.4.

9.11 The authorized person is responsible for compliance with technical or regulatory requirements related to the quality of finished products and the approval of the release of the finished product for sale.

9.12 The authorized person will also be involved in other activities, including the following:

- (a) implementation (and, when needed, establishment) of the quality system;

- (b) participation in the development of the company's quality manual;
- (c) supervision of the regular internal audits or self-inspections;
- (d) oversight of the quality control department;
- (e) participation in external audit (vendor audit);
- (f) participation in validation programmes.

9.13 The function of the approval of the release of a finished batch or a product can be delegated to a designated person with appropriate qualifications and experience who will release the product in accordance with an approved procedure. This is normally done by quality assurance by means of batch review.

9.14 The person responsible for approving a batch for release should always ensure that the following requirements have been met:

- (a) the marketing authorization and the manufacturing authorization requirements for the product have been met for the batch concerned;
- (b) the principles and guidelines of GMP, as laid down in the guidelines published by WHO, have been followed;
- (c) the principal manufacturing and testing processes have been validated, if different;
- (d) all the necessary checks and tests have been performed and account taken of the production conditions and manufacturing records;
- (e) any planned changes or deviations in manufacturing or quality control have been notified in accordance with a well defined reporting system before any product is released. Such changes may need notification to, and approval by, the drug regulatory authority;
- (f) any additional sampling, inspection, tests and checks have been carried out or initiated, as appropriate, to cover planned changes and deviations;
- (g) all necessary production and quality control documentation has been completed and endorsed by supervisors trained in appropriate disciplines;
- (h) appropriate audits, self-inspections and spot-checks are carried out by experienced and trained staff;
- (i) approval has been given by the head of quality control;
- (j) all relevant factors have been considered, including any not specifically associated with the output batch directly under review (e.g. subdivision of output batches from a common input, factors associated with continuous production runs).

10. **Training**

10.1 The manufacturer should provide training in accordance with a written programme for all personnel whose duties take them into manufacturing areas or into control laboratories (including the technical, maintenance and cleaning personnel) and for other personnel as required.

10.2 Besides basic training on the theory and practice of GMP, newly recruited personnel should receive training appropriate to the duties assigned to them. Continuing training should also be given, and its practical effectiveness periodically assessed. Approved training programmes should be available. Training records should be kept.

10.3 Personnel working in areas where contamination is a hazard, e.g. clean areas or areas where highly active, toxic, infectious or sensitizing materials are handled, should be given specific training.

10.4 The concept of quality assurance and all the measures which aid its understanding and implementation should be fully discussed during the training sessions.

10.5 Visitors or untrained personnel should preferably not be taken into the production and quality control areas. If this is unavoidable, they should be given relevant information in advance (particularly about personal hygiene) and the prescribed protective clothing. They should be closely supervised.

10.6 Consultant and contract staff should be qualified for the services they provide. Evidence of this should be included in the training records.

11. **Personal hygiene**

11.1 All personnel, prior to and during employment, as appropriate, should undergo health examinations. Personnel conducting visual inspections should also undergo periodic eye examinations.

11.2 All personnel should be trained in the practices of personal hygiene. A high level of personal hygiene should be observed by all those concerned with manufacturing processes. In particular, personnel should be instructed to wash their hands before entering production areas. Signs to this effect should be posted and instructions observed.

11.3 Any person shown at any time to have an apparent illness or open lesions that may adversely affect the quality of products should not be allowed to handle starting materials, packaging materials,

in-process materials or drug products until the condition is no longer judged to be a risk.

11.4 All employees should be instructed and encouraged to report to their immediate supervisor any conditions (relating to plant, equipment or personnel) that they consider may adversely affect the products.

11.5 Direct contact should be avoided between the operator's hands and starting materials, primary packaging materials and intermediate or bulk product.

11.6 To ensure protection of the product from contamination, personnel should wear clean body coverings appropriate to the duties they perform, including appropriate hair covering. Used clothes, if reusable, should be stored in separate closed containers until properly laundered and, if necessary, disinfected or sterilized.

11.7 Smoking, eating, drinking, chewing, and keeping plants, food, drink, smoking material and personal medicines should not be permitted in production, laboratory and storage areas, or in any other areas where they might adversely influence product quality.

11.8 Personal hygiene procedures including the use of protective clothing should apply to all persons entering production areas, whether they are temporary or full-time employees or non-employees, e.g. contractors' employees, visitors, senior managers, and inspectors.

12. **Premises**

12.1 *Principle.* Premises must be located, designed, constructed, adapted, and maintained to suit the operations to be carried out.

General

12.2 The layout and design of premises must aim to minimize the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination, build-up of dust or dirt, and, in general, any adverse effect on the quality of products.

12.3 Where dust is generated (e.g. during sampling, weighing, mixing and processing operations, packaging of powder), measures should be taken to avoid cross-contamination and facilitate cleaning.

12.4 Premises should be situated in an environment that, when considered together with measures to protect the manufacturing process, presents minimum risk of causing any contamination of materials or products.

12.5 Premises used for the manufacture of finished products should be suitably designed and constructed to facilitate good sanitation.

12.6 Premises should be carefully maintained, and it should be ensured that repair and maintenance operations do not present any hazard to the quality of products.

12.7 Premises should be cleaned and, where applicable, disinfected according to detailed written procedures. Records should be maintained.

12.8 Electrical supply, lighting, temperature, humidity and ventilation should be appropriate and such that they do not adversely affect, directly or indirectly, either the pharmaceutical products during their manufacture and storage, or the accurate functioning of equipment.

12.9 Premises should be designed and equipped so as to afford maximum protection against the entry of insects, birds or other animals. There should be a procedure for rodent and pest control.

12.10 Premises should be designed to ensure the logical flow of materials and personnel.

Ancillary areas

12.11 Rest and refreshment rooms should be separate from manufacturing and control areas.

12.12 Facilities for changing and storing clothes and for washing and toilet purposes should be easily accessible and appropriate for the number of users. Toilets should not communicate directly with production or storage areas.

12.13 Maintenance workshops should if possible be separated from production areas. Whenever parts and tools are stored in the production area, they should be kept in rooms or lockers reserved for that use.

12.14 Animal houses should be well isolated from other areas, with separate entrance (animal access) and air-handling facilities.

Storage areas

12.15 Storage areas should be of sufficient capacity to allow orderly storage of the various categories of materials and products with proper separation and segregation: starting and packaging materials, intermediates, bulk and finished products, products in quarantine, and released, rejected, returned or recalled products.

12.16 Storage areas should be designed or adapted to ensure good storage conditions. In particular, they should be clean, dry, sufficiently

lit and maintained within acceptable temperature limits. Where special storage conditions are required (e.g. temperature, humidity) these should be provided, controlled, monitored and recorded where appropriate.

12.17 Receiving and dispatch bays should be separated and 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.

12.18 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 the physical quarantine should give equivalent security.

12.19 Segregation should be provided for the storage of rejected, recalled, or returned materials or products.

12.20 Highly active and radioactive materials, narcotics, other dangerous drugs, and substances presenting special risks of abuse, fire or explosion should be stored in safe and secure areas.

12.21 Printed packaging materials are considered critical to the conformity of the pharmaceutical product to its labelling and special attention should be paid to sampling and the safe and secure storage of these materials.

12.22 There should normally be a separate sampling area for starting materials. (If sampling is performed in the storage area, it should be conducted in such a way as to prevent contamination or cross-contamination.)

Weighing areas

12.23 The weighing of starting materials and the estimation of yield by weighing should be carried out in separate weighing areas designed for that use, for example with provisions for dust control. Such areas may be part of either storage or production areas.

Production areas

12.24 In order to minimize the risk of a serious medical hazard due to cross-contamination, dedicated and self-contained facilities must be available for the production of particular pharmaceutical products, such as highly sensitizing materials (e.g. penicillins) or biological preparations (e.g. live microorganisms). The production of certain other highly active products, such as some antibiotics, hormones, cytotoxic substances and certain non-pharmaceutical products, should not be conducted in the same facilities. In exceptional cases,

the principle of campaign working in the same facilities can be accepted provided that specific precautions are taken and the necessary validations (including cleaning validation) are made. The manufacture of technical poisons, such as pesticides and herbicides, should not be allowed in premises used for the manufacture of pharmaceutical products.

12.25 Premises should preferably be laid out in such a way as to allow the production to take place in areas connected in a logical order corresponding to the sequence of the operations and to the requisite cleanliness levels.

12.26 The adequacy of the working and in-process storage space should permit the orderly and logical positioning of equipment and materials so as to minimize the risk of confusion between different pharmaceutical products or their components, to avoid cross-contamination, and to minimize the risk of omission or wrong application of any of the manufacturing or control steps.

12.27 Where starting and primary packaging materials and intermediate or bulk products are exposed to the environment, interior surfaces (walls, floors and ceilings) should be smooth and free from cracks and open joints, should not shed particulate matter, and should permit easy and effective cleaning and, if necessary, disinfection.

12.28 Pipework, light fittings, ventilation points and other services should be designed and sited to avoid the creation of recesses that are difficult to clean. As far as possible, for maintenance purposes, they should be accessible from outside the manufacturing areas.

12.29 Drains should be of adequate size and designed and equipped to prevent back-flow. Open channels should be avoided where possible, but if they are necessary they should be shallow to facilitate cleaning and disinfection.

12.30 Production areas should be effectively ventilated, with air-control facilities (including filtration of air to a sufficient level to prevent contamination and cross-contamination, as well as control of temperature and, where necessary, humidity) appropriate to the products handled, to the operations undertaken and to the external environment. These areas should be regularly monitored during both production and non-production periods to ensure compliance with their design specifications.

12.31 Premises for the packaging of pharmaceutical products should be specifically designed and laid out so as to avoid mix-ups or cross-contamination.

12.32 Production areas should be well lit, particularly where visual on-line controls are carried out.

Quality control areas

12.33 Quality control laboratories should be separated from production areas. Areas where biological, microbiological or radioisotope test methods are employed should be separated from each other.

12.34 Quality control laboratories should be designed to suit the operations to be carried out in them. Sufficient space should be given to avoid mix-ups and cross-contamination. There should be adequate suitable storage space for samples, reference standards (if necessary, with cooling), solvents, reagents and records.

12.35 The design of the laboratories should take into account the suitability of construction materials, prevention of fumes and ventilation. There should be separate air supply to laboratories and production areas. Separate air-handling units and other provisions are needed for biological, microbiological and radioisotope laboratories.

12.36 A separate room may be needed for instruments to protect them against electrical interference, vibration, contact with excessive moisture and other external factors, or where it is necessary to isolate the instruments.

13. Equipment

13.1 Equipment must be located, designed, constructed, adapted, and maintained to suit the operations to be carried out. The layout and design of equipment must aim to minimize the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination, build-up of dust or dirt, and, in general, any adverse effect on the quality of products.

13.2 Equipment should be installed in such a way as to minimize any risk of error or of contamination.

13.3 Fixed pipework should be clearly labelled to indicate the contents and, where applicable, the direction of flow.

13.4 All service pipings and devices should be adequately marked and special attention paid to the provision of non-interchangeable connections or adaptors for dangerous gases and liquids.

13.5 Balances and other measuring equipment of an appropriate range and precision should be available for production and control operations and should be calibrated on a scheduled basis.

13.6 Production equipment should be thoroughly cleaned on a scheduled basis.

13.7 Laboratory equipment and instruments should be suited to the testing procedures undertaken.

13.8 Washing, cleaning and drying equipment should be chosen and used so as not to be a source of contamination.

13.9 Production equipment should not present any hazard to the products. The parts of the production equipment that come into contact with the product must not be reactive, additive, or absorptive to an extent that would affect the quality of the product.

13.10 Defective equipment should be removed from production and quality control areas. If this is not possible, it should be clearly labelled as defective to prevent use.

13.11 Closed equipment should be used whenever appropriate. Where open equipment is used or equipment is opened, precautions should be taken to minimize contamination.

13.12 Non-dedicated equipment should be cleaned according to validated cleaning procedures between production of different pharmaceutical products to prevent cross-contamination.

13.13 Current drawings of critical equipment and support systems should be maintained.

14. **Materials**

14.1 *Principle.* The main objective of a pharmaceutical plant is to produce finished products for patients' use from a combination of materials (starting and packaging).

14.2 Materials include starting materials, packaging materials, gases, solvents, process aids, reagents and labelling materials.

General

14.3 No materials used for operations such as cleaning, lubrication of equipment and pest control, should come into direct contact with the product. Where possible, such materials should be of a suitable grade (e.g. food grade) to minimize health risks.

14.4 All incoming materials and finished products should be quarantined immediately after receipt or processing, until they are released for use or distribution.

14.5 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 by a first-expire, first-out rule.

14.6. Water used in the manufacture of pharmaceutical products should be suitable for its intended use.

Starting materials

14.7 The purchase of starting materials is an important operation that should involve staff who have a particular and thorough knowledge of the products and suppliers.

14.8 Starting materials should be purchased only from approved suppliers and, where possible, directly from the producer. It is also recommended that the specifications established by the manufacturer for the starting materials be discussed with the suppliers. It is of benefit that all critical aspects of the production and control of the starting material in question, including handling, labelling and packaging requirements as well as complaints and rejection procedures, are contractually agreed between the manufacturer and the supplier.

14.9 For each consignment, the containers should be checked for at least integrity of package and seal and for correspondence between the order, the delivery note, and the supplier's labels.

14.10 All incoming materials should be checked to ensure that the consignment corresponds to the order. Containers should be cleaned where necessary and labelled, if required, with the prescribed information. Where additional labels are attached to containers, the original information should not be lost.

14.11 Damage to containers and any other problem that might adversely affect the quality of a material should be recorded and reported to the quality control department and investigated.

14.12 If one delivery of material is made up of different batches, each batch must be considered as separate for sampling, testing and release.

14.13 Starting materials in the storage area should be appropriately labelled. Labels should bear at least the following information:

- (a) the designated name of the product and the internal code reference where applicable;
- (b) the batch number given by the supplier and, on receipt, the control or batch number given by the manufacturer, if any, documented so as to ensure traceability;
- (c) the status of the contents (e.g. on quarantine, on test, released, rejected, returned, recalled);

- (d) where appropriate, an expiry date or a date beyond which retesting is necessary.

When fully validated computerized storage systems are used, not all of the above information need be in a legible form on the label.

14.14 There should be appropriate procedures or measures to ensure the identity of the contents of each container of starting material. Bulk containers from which samples have been drawn should be identified.

14.15 Only starting materials released by the quality control department and within their shelf-life should be used.

14.16 Starting materials should be dispensed only by designated persons, following a written procedure, to ensure that the correct materials are accurately weighed or measured into clean and properly labelled containers.

14.17 Each dispensed material and its weight or volume should be independently checked and the check recorded.

14.18 Materials dispensed for each batch of the final product should be kept together and conspicuously labelled as such.

Packaging materials

14.19 The purchase, handling and control of primary and printed packaging materials should be as for starting materials.

14.20 Particular attention should be paid to printed packaging materials. They should be stored in secure conditions so as to exclude the possibility of unauthorized access. Roll feed labels should be used wherever possible. Cut labels and other loose printed materials should be stored and transported in separate closed containers so as to avoid mix-ups. Packaging materials should be issued for use only by designated personnel following an approved and documented procedure.

14.21 Each delivery or batch of printed or primary packaging material should be given a specific reference number or identification mark.

14.22 Outdated or obsolete primary packaging material or printed packaging material should be destroyed and its disposal recorded.

14.23 All products and packaging materials to be used should be checked on delivery to the packaging department for quantity, identity and conformity with the packaging instructions.

Intermediate and bulk products

14.24 Intermediate and bulk products should be kept under appropriate conditions.

14.25 Intermediate and bulk products purchased as such should be handled on receipt as though they were starting materials.

Finished products

14.26 Finished products should be held in quarantine until their final release, after which they should be stored as usable stock under conditions established by the manufacturer.

14.27 The evaluation of finished products and the documentation necessary for release of a product for sale are described in section 17, "Good practices in quality control".

Rejected, recovered, reprocessed and reworked materials

14.28 Rejected materials and products should be clearly marked as such and stored separately in restricted areas. They should either be returned to the suppliers or, where appropriate, reprocessed or destroyed in a timely manner. Whatever action is taken should be approved by authorized personnel and recorded.

14.29 The reworking or recovery of rejected products should be exceptional. It is permitted only if the quality of the final product is not affected, if the specifications are met, and if it is done in accordance with a defined and authorized procedure after evaluation of the risks involved. A record should be kept of the reworking or recovery. A reworked batch should be given a new batch number.

14.30 The introduction of all or part of earlier batches, conforming to the required quality, into a batch of the same product at a defined stage of manufacture should be authorized beforehand. This recovery should be carried out in accordance with a defined procedure after evaluation of the risks involved, including any possible effect on shelf-life. The recovery should be recorded.

14.31 The need for additional testing of any finished product that has been reprocessed, reworked or into which a recovered product has been incorporated, should be considered by the quality control department.

Recalled products

14.32 Recalled products should be identified and stored separately in a secure area until a decision is taken on their fate. The decision should be made as soon as possible.

Returned goods

14.33 Products returned from the market should be destroyed unless it is certain that their quality is satisfactory; in such cases they may be considered for resale or relabelling, or alternative action taken only after they have been critically assessed by the quality control function in accordance with a written procedure. The nature of the product, any special storage conditions it requires, 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. Any action taken should be appropriately recorded.

Reagents and culture media

14.34 There should be records for the receipt and preparation of reagents and culture media.

14.35 Reagents made up in the laboratory should be prepared according to written procedures and appropriately labelled. The label should indicate the concentration, standardization factor, shelf-life, the date when restandardization is due, and the storage conditions. The label should be signed and dated by the person preparing the reagent.

14.36 Both positive and negative controls should be applied to verify the suitability of culture media each time they are prepared and used. The size of the inoculum used in positive controls should be appropriate to the sensitivity required.

Reference standards

14.37 Whenever official reference standards exist, these should preferably be used.

14.38 Official reference standards should be used only for the purpose described in the appropriate monograph.

14.39 Reference standards prepared by the producer should be tested, released and stored in the same way as official standards. They should be kept under the responsibility of a designated person in a secure area.

14.40 Secondary or working standards may be established by the application of appropriate tests and checks at regular intervals to ensure standardization.

14.41 Reference standards should be properly labelled with at least the following information:

- (a) name of the material;
- (b) batch or lot number and control number;
- (c) date of preparation;
- (d) shelf-life;
- (e) potency;
- (f) storage conditions.

14.42 All in-house reference standards should be standardized against an official reference standard, when available, initially and at regular intervals thereafter.

14.43 All reference standards should be stored and used in a manner that will not adversely affect their quality.

Waste materials

14.44 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.

14.45 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.

Miscellaneous

14.46 Rodenticides, insecticides, fumigating agents and sanitizing materials should not be permitted to contaminate equipment, starting materials, packaging materials, in-process materials or finished products.

15. Documentation

15.1 *Principle.* Good documentation is an essential part of the quality assurance system and, as such, should exist for all aspects of GMP. Its aims are to define the specifications and procedures for all materials and methods of manufacture and control; to ensure that all personnel concerned with manufacture know what to do and when to do it; to ensure that authorized persons have all the information necessary to decide whether or not to release a batch of a drug for sale, to ensure the existence of documented evidence, traceability, and to provide records and an audit trail that will permit investigation. It ensures the availability of the data needed for validation, review and statistical analysis. The design and use of documents depend upon the manufac-

turer. In some cases some or all of the documents described below may be brought together, but they will usually be separate.

General

15.2 Documents should be designed, prepared, reviewed and distributed with care. They should comply with the relevant parts of the manufacturing and marketing authorizations.

15.3 Documents should be approved, signed and dated by the appropriate responsible persons. No document should be changed without authorization and approval.

15.4 Documents should have unambiguous contents: the title, nature and purpose should be clearly stated. They should be laid out in an orderly fashion and be easy to check. Reproduced documents should be clear and legible. The reproduction of working documents from master documents must not allow any error to be introduced through the reproduction process.

15.5 Documents should be regularly reviewed and kept up to date. When a document has been revised, a system should exist to prevent inadvertent use of the superseded version. Superseded documents should be retained for a specific period of time.

15.6 Where documents require the entry of data, these entries should be clear, legible and indelible. Sufficient space should be provided for such entries.

15.7 Any alteration made to a document should be signed and dated; the alteration should permit the reading of the original information. Where appropriate, the reason for the alteration should be recorded.

15.8 Records should be made or completed when any action is taken and in such a way that all significant activities concerning the manufacture of pharmaceutical products are traceable. Records should be retained for at least one year after the expiry date of the finished product.

15.9 Data (and records for storage) may be recorded by electronic data-processing systems or by photographic or other reliable means. Master formulae and detailed standard operating procedures relating to the system in use should be available and the accuracy of the records should be checked. If documentation is handled by electronic data-processing methods, only authorized persons should be able to enter or modify data in the computer, and there should be a record of changes and deletions; access should be restricted by passwords or other means and the entry of critical data should be independently

checked. Batch records stored electronically should be protected by back-up transfer on magnetic tape, microfilm, paper print-outs or other means. It is particularly important that, during the period of retention, the data are readily available.

Documents required

Labels

15.10 Labels applied to containers, equipment or premises should be clear, unambiguous and in the company's agreed format. It is often helpful in addition to the wording on the labels to use colours to indicate status (e.g. quarantined, accepted, rejected, clean).

15.11 All finished drug products should be identified by labelling, as required by the national legislation, bearing at least the following information:

- (a) the name of the drug product;
- (b) a list of the active ingredients (if applicable, with the INNs), showing the amount of each present and a statement of the net contents (e.g. number of dosage units, weight, volume);
- (c) the batch number assigned by the manufacturer;
- (d) the expiry date in an uncoded form;
- (e) any special storage conditions or handling precautions that may be necessary;
- (f) directions for use, and warnings and precautions that may be necessary;
- (g) the name and address of the manufacturer or the company or the person responsible for placing the product on the market.

15.12 For reference standards, the label and/or accompanying document should indicate potency or concentration, date of manufacture, expiry date, date the closure is first opened, storage conditions and control number, as appropriate.

Specifications and testing procedures

15.13 Testing procedures described in documents should be validated in the context of available facilities and equipment before they are adopted for routine testing.

15.14 There should be appropriately authorized and dated specifications, including tests on identity, content, purity and quality, for starting and packaging materials and for finished products; where appropriate, they should also be available for intermediate or bulk products. Specifications for water, solvents and reagents (e.g. acids and bases) used in production should be included.

15.15 Each specification should be approved, signed and dated, and maintained by quality control, quality assurance unit or documentation centre. Specifications for starting materials, intermediates, and bulk, finished products and packaging materials are referred to in sections 15.18–15.21.

15.16 Periodic revisions of the specifications may be necessary to comply with new editions of the national pharmacopoeia or other official compendia.

15.17 Pharmacopoeias, reference standards, reference spectra and other reference materials should be available in the quality control laboratory.

Specifications for starting and packaging materials

15.18 Specifications for starting, primary and printed packaging materials should provide, if applicable, a description of the materials, including:

- (a) the designated name (if applicable, the INN) and internal code reference;
- (b) the reference, if any, to a pharmacopoeial monograph;
- (c) qualitative and quantitative requirements with acceptance limits.

Depending on the company's practice other data may be added to the specification, such as:

- (a) the supplier and the original producer of the materials;
- (b) a specimen of printed materials;
- (c) directions for sampling and testing, or a reference to procedures;
- (d) storage conditions and precautions;
- (e) the maximum period of storage before re-examination.

Packaging material should conform to specifications, and should be compatible with the material and/or with the drug product it contains. The material should be examined for compliance with the specification, and for defects as well as for the correctness of identity markings.

15.19 Documents describing testing procedures should state the required frequency for re-assaying each starting material, as determined by its stability.

Specifications for intermediate and bulk products

15.20 Specifications for intermediate and bulk products should be available. The specifications should be similar to specifications for starting materials or for finished products, as appropriate.

Specifications for finished products

15.21 Specifications for finished products should include:

- (a) the designated name of the product and the code reference, where applicable;
- (b) the designated name(s) of the active ingredient(s) (if applicable, with the INN(s));
- (c) the formula or a reference to the formula;
- (d) a description of the dosage form and package details;
- (e) directions for sampling and testing or a reference to procedures;
- (f) the qualitative and quantitative requirements, with acceptance limits;
- (g) the storage conditions and precautions, where applicable;
- (h) the shelf-life.

Master formulae

15.22 A formally authorized master formula should exist for each product and batch size to be manufactured.

15.23 The master formula should include:

- (a) the name of the product, with a product reference code relating to its specification;
- (b) a description of the dosage form, strength of the product and batch size;
- (c) a list of all starting materials to be used (if applicable, with the INNs), with the amount of each, described using the designated name and a reference that is unique to that material (mention should be made of any substance that may disappear in the course of processing);
- (d) a statement of the expected final yield with the acceptable limits, and of relevant intermediate yields, where applicable;
- (e) a statement of the processing location and the principal equipment to be used;
- (f) the methods, or reference to the methods, to be used for preparing and operating the critical equipment, e.g. cleaning (especially after a change in product), assembling, calibrating, sterilizing, use;
- (g) detailed step-wise processing instructions (e.g. checks on materials, pretreatments, sequence for adding materials, mixing times, temperatures);
- (h) the instructions for any in-process controls with their limits;
- (i) where necessary, the requirements for storage of the products, including the container, the labelling, and any special storage conditions;
- (j) any special precautions to be observed.

Packaging instructions

15.24 Formally authorized packaging instructions should exist for each product, pack size and type. These should normally include, or make reference to:

- (a) the name of the product;
- (b) a description of its pharmaceutical form, strength and, where applicable, method of application;
- (c) the pack size expressed in terms of the number, weight or volume of the product in the final container;
- (d) a complete list of all the packaging materials required for a standard batch size, including quantities, sizes and types, with the code or reference number relating to the specifications for each packaging material;
- (e) where appropriate, an example or reproduction of the relevant printed packaging materials and specimens, indicating where the batch number and expiry date of the product have been marked;
- (f) special precautions to be observed, including a careful examination of the packaging area and equipment in order to ascertain the line clearance before and after packaging operations;
- (g) a description of the packaging operation, including any significant subsidiary operations, and equipment to be used;
- (h) details of in-process controls with instructions for sampling and acceptance limits.

Batch processing records

15.25 A batch processing record should be kept for each batch processed. It should be based on the relevant parts of the currently approved specifications on the record. The method of preparation of such records should be designed to avoid errors. (Copying or validated computer programmes are recommended. Transcribing from approved documents should be avoided.)

15.26 Before any processing begins, a check should be made that the equipment and work station are clear of previous products, documents, or materials not required for the planned process, and that the equipment is clean and suitable for use. This check should be recorded.

15.27 During processing, the following information should be recorded at the time each action is taken, and after completion the record should be dated and signed by the person responsible for the processing operations:

- (a) the name of the product;
- (b) the number of the batch being manufactured;

- (c) dates and times of commencement, of significant intermediate stages, and of completion of production;
- (d) the name of the person responsible for each stage of production;
- (e) the initials of the operator(s) of different significant steps of production and, where appropriate, of the person(s) who checked each of these operations (e.g. weighing);
- (f) the batch number and/or analytical control number and the quantity of each starting material actually weighed (including the batch number and amount of any recovered or reprocessed material added);
- (g) any relevant processing operation or event and the major equipment used;
- (h) the in-process controls performed, the initials of the person(s) carrying them out, and the results obtained;
- (i) the amount of product obtained at different and pertinent stages of manufacture (yield), together with comments or explanations for significant deviations from the expected yield;
- (j) notes on special problems including details, with signed authorization for any deviation from the master formula.

Batch packaging records

15.28 A batch packaging record should be kept for each batch or part batch processed. It should be based on the relevant parts of the approved packaging instructions, and the method of preparing such records should be designed to avoid errors. (Copying or validated computer programmes are recommended. Transcribing from approved documents should be avoided.)

15.29 Before any packaging operation begins, checks should be made that the equipment and work station are clear of previous products, documents or materials not required for the planned packaging operations, and that equipment is clean and suitable for use. These checks should be recorded.

15.30 The following information should be recorded at the time each action is taken, and the date and the person responsible should be clearly identified by signature or electronic password:

- (a) the name of the product, the batch number and the quantity of bulk product to be packed, as well as the batch number and the planned quantity of finished product that will be obtained, the quantity actually obtained and the reconciliation;
- (b) the date(s) and time(s) of the packaging operations;
- (c) the name of the responsible person carrying out the packaging operation;

- (d) the initials of the operators of the different significant steps;
- (e) the checks made for identity and conformity with the packaging instructions, including the results of in-process controls;
- (f) details of the packaging operations carried out, including references to equipment and the packaging lines used, and, when necessary, the instructions for keeping the product unpacked or a record of returning product that has not been packaged to the storage area;
- (g) whenever possible, samples of the printed packaging materials used, including specimens bearing the approval for the printing of and regular check (where appropriate) of the batch number, expiry date, and any additional overprinting;
- (h) notes on any special problems, including details of any deviation from the packaging instructions, with written authorization by an appropriate person;
- (i) the quantities and reference number or identification of all printed packaging materials and bulk product issued, used, destroyed or returned to stock and the quantities of product obtained to permit an adequate reconciliation.

Standard operating procedures (SOPs) and records

15.31 Standard operating procedures and associated records of actions taken or, where appropriate, conclusions reached should be available for:

- (a) equipment assembly and validation;
- (b) analytical apparatus and calibration;
- (c) maintenance, cleaning and sanitization;
- (d) personnel matters including qualification, training, clothing and hygiene;
- (e) environmental monitoring;
- (f) pest control;
- (g) complaints;
- (h) recalls;
- (i) returns.

15.32 There should be standard operating procedures and records for the receipt of each delivery of starting material and primary and printed packaging material.

15.33 The records of the receipts should include:

- (a) the name of the material on the delivery note and the containers;
- (b) the “in-house” name and/or code of material if different from (a);
- (c) the date of receipt;
- (d) the supplier’s name and, if possible, manufacturer’s name;

- (e) the manufacturer's batch or reference number;
- (f) the total quantity, and number of containers received;
- (g) the batch number assigned after receipt;
- (h) any relevant comment (e.g. state of the containers).

15.34 There should be standard operating procedures for the internal labelling, quarantine and storage of starting materials, packaging materials and other materials, as appropriate.

15.35 Standard operating procedures should be available for each instrument and piece of equipment (e.g. use, calibration, cleaning, maintenance) and placed in close proximity to the equipment.

15.36 There should be standard operating procedures for sampling, which specify the person(s) authorized to take samples.

15.37 The sampling instructions should include:

- (a) the method of sampling and the sampling plan;
- (b) the equipment to be used;
- (c) any precautions to be observed to avoid contamination of the material or any deterioration in its quality;
- (d) the amount(s) of sample(s) to be taken;
- (e) instructions for any required subdivision of the sample;
- (f) the type of sample container(s) to be used, and whether they are for aseptic sampling or for normal sampling, and labelling;
- (g) any specific precautions to be observed, especially in regard to the sampling of sterile or noxious material.

15.38 There should be a standard operating procedure describing the details of the batch (lot) numbering system, with the objective of ensuring that each batch of intermediate, bulk or finished product is identified with a specific batch number.

15.39 The standard operating procedures for batch numbering that are applied to the processing stage and to the respective packaging stage should be related to each other.

15.40 The standard operating procedure for batch numbering should ensure that the same batch numbers will not be used repeatedly; this applies also to reprocessing.

15.41 Batch-number allocation should be immediately recorded, e.g. in a logbook. The record should include at least the date of allocation, product identity and size of batch.

15.42 There should be written procedures for testing materials and products at different stages of manufacture, describing the methods and equipment to be used. The tests performed should be recorded.

15.43 Analysis records should include at least the following data:

- (a) the name of the material or product and, where applicable, dosage form;
- (b) the batch number and, where appropriate, the manufacturer and/or supplier;
- (c) references to the relevant specifications and testing procedures;
- (d) test results, including observations and calculations, and reference to any specifications (limits);
- (e) date(s) and reference number(s) of testing;
- (f) the initials of the persons who performed the testing;
- (g) the date and initials of the persons who verified the testing and the calculations, where appropriate;
- (h) a clear statement of release or rejection (or other status decision) and the dated signature of the designated responsible person.

15.44 Written release and rejection procedures should be available for materials and products, and in particular for the release for sale of the finished product by an authorized person.

15.45 Records should be maintained of the distribution of each batch of a product in order, e.g. to facilitate the recall of the batch if necessary.

15.46 Records should be kept for major and critical equipment, as appropriate, of any validations, calibrations, maintenance, cleaning, or repair operations, including dates and the identity of the people who carried these operations out.

15.47 The use of major and critical equipment and the areas where products have been processed should be appropriately recorded in chronological order.

15.48 There should be written procedures assigning responsibility for cleaning and sanitation and describing in sufficient detail the cleaning schedules, methods, equipment and materials to be used and facilities and equipment to be cleaned. Such written procedures should be followed.

16. **Good practices in production**

16.1 *Principle.* Production operations must follow clearly defined procedures in accordance with manufacturing and marketing authorizations, with the objective of obtaining products of the requisite quality.

General

16.2 All handling of materials and products, such as receipt and cleaning, quarantine, sampling, storage, labelling, dispensing, processing, packaging and distribution should be done in accordance with written procedures or instructions and, where necessary, recorded.

16.3 Any deviation from instructions or procedures should be avoided as far as possible. If deviations occur, they should be done in accordance with an approved procedure. The authorization of the deviation should be approved in writing by a designated person, with the involvement of the quality control department, when appropriate.

16.4 Checks on yields and reconciliation of quantities should be carried out as necessary to ensure that there are no discrepancies outside acceptable limits.

16.5 Operations on different products should not be carried out simultaneously or consecutively in the same room or area unless there is no risk of mix-up or cross-contamination.

16.6 At all times during processing, all materials, bulk containers, major items of equipment, and where appropriate, the rooms and packaging lines being used should be labelled or otherwise identified with an indication of the product or material being processed, its strength (where applicable) and the batch number. Where applicable, this indication should also mention the stage of production. In some cases it may be useful to record also the name of the previous product that has been processed.

16.7 Access to production premises should be restricted to authorized personnel.

16.8 Normally, non-medicinal products should not be produced in areas or with equipment destined for the production of pharmaceutical products.

16.9 In-process controls are usually performed within the production area. The performance of such in-process controls should not have any negative effect on the quality of the product or another product (e.g. cross-contamination or mix-up).

Prevention of cross-contamination and bacterial contamination during production

16.10 When dry materials and products are used in production, special precautions should be taken to prevent the generation and dissemination of dust. Provision should be made for proper air control (e.g. supply and extraction of air of suitable quality).

16.11 Contamination of a starting material or of a product by another material or product must be avoided. This risk of accidental cross-contamination arises from the uncontrolled release of dust, gases, particles, vapours, sprays or organisms from materials and products in process, from residues on equipment, from intruding insects, and from operators' clothing, skin, etc. The significance of this risk varies with the type of contaminant and of the product being contaminated. Among the most hazardous contaminants are highly sensitizing materials, biological preparations such as living organisms, certain hormones, cytotoxic substances, and other highly active materials. Products in which contamination is likely to be most significant are those administered by injection or applied to open wounds and those given in large doses and/or over a long time.

16.12 Cross-contamination should be avoided by taking appropriate technical or organizational measures, for example:

- (a) carrying out production in dedicated and self-contained areas (which may be required for products such as penicillins, live vaccines, live bacterial preparations and certain other biologicals);
- (b) conducting campaign production (separation in time) followed by appropriate cleaning in accordance with a validated cleaning procedure;
- (c) providing appropriately designed airlocks, pressure differentials, and air supply and extraction systems;
- (d) minimizing the risk of contamination caused by recirculation or re-entry of untreated or insufficiently treated air;
- (e) wearing protective clothing where products or materials are handled;
- (f) using cleaning and decontamination procedures of known effectiveness;
- (g) using a "closed system" in production;
- (h) testing for residues;
- (i) using cleanliness status labels on equipment.

16.13 Measures to prevent cross-contamination and their effectiveness should be checked periodically according to standard operating procedures.

16.14 Production areas where susceptible products are processed should undergo periodic environmental monitoring (e.g. for microbiological monitoring and particulate matter where appropriate).

Processing operations

16.15 Before any processing operation is started, steps should be taken to ensure that the work area and equipment are clean and free

from any starting materials, products, product residues, labels or documents not required for the current operation.

16.16 Any necessary in-process controls and environmental controls should be carried out and recorded.

16.17 Means should be instituted of indicating failures of equipment or of services (e.g. water, gas) to equipment. Defective equipment should be withdrawn from use until the defect has been rectified. After use, production equipment should be cleaned without delay according to detailed written procedures and stored under clean and dry conditions in a separate area or in a manner that will prevent contamination.

16.18 Time limits for storage of equipment after cleaning and before use should be stated and based on data.

16.19 Containers for filling should be cleaned before filling. Attention should be given to avoiding and removing any contaminants such as glass fragments and metal particles.

16.20 Any significant deviation from the expected yield should be recorded and investigated.

16.21 Checks should be carried out to ensure that pipelines and other pieces of equipment used for the transportation of products from one area to another are connected in a correct manner.

16.22 Pipes used for conveying distilled or deionized water and, where appropriate, other water pipes should be sanitized and stored according to written procedures that detail the action limits for microbiological contamination and the measures to be taken.

16.23 Measuring, weighing, recording, and control equipment and instruments should be serviced and calibrated at prespecified intervals and records maintained. To ensure satisfactory functioning, instruments should be checked daily or prior to use for performing analytical tests. The date of calibration and servicing and the date when recalibration is due should be clearly indicated, preferably on a label attached to the instrument.

16.24 Repair and maintenance operations should not present any hazard to the quality of the products.

Packaging operations

16.25 When the programme for packaging operations is being set up, particular attention should be given to minimizing the risk of cross-contamination, mix-ups or substitutions. Different products should

not be packaged in close proximity unless there is physical segregation or an alternative system that will provide equal assurance.

16.26 Before packaging operations are begun, steps should be taken to ensure that the work area, packaging lines, printing machines and other equipment are clean and free from any products, materials or documents used previously and which are not required for the current operation. The line clearance should be performed according to an appropriate procedure and checklist, and recorded.

16.27 The name and batch number of the product being handled should be displayed at each packaging station or line.

16.28 Normally, filling and sealing should be followed as quickly as possible by labelling. If labelling is delayed, appropriate procedures should be applied to ensure that no mix-ups or mislabelling can occur.

16.29 The correct performance of any printing (e.g. of code numbers or expiry dates) done separately or in the course of the packaging should be checked and recorded. Attention should be paid to printing by hand, which should be rechecked at regular intervals.

16.30 Special care should be taken when cut labels are used and when overprinting is carried out off-line, and in hand-packaging operations. Roll-feed labels are normally preferable to cut labels in helping to avoid mix-ups. On-line verification of all labels by automated electronic means can be helpful in preventing mix-ups, but checks should be made to ensure that any electronic code readers, label counters, or similar devices are operating correctly. When labels are attached manually, in-process control checks should be performed more frequently.

16.31 Printed and embossed information on packaging materials should be distinct and resistant to fading or erasing.

16.32 Regular on-line control of the product during packaging should include at least checks on:

- (a) the general appearance of the packages;
- (b) whether the packages are complete;
- (c) whether the correct products and packaging materials are used;
- (d) whether any overprinting is correct;
- (e) the correct functioning of line monitors.

Samples taken away from the packaging line should not be returned.

16.33 Products that have been involved in an unusual event during packaging should be reintroduced into the process only after special inspection, investigation and approval by authorized personnel. A detailed record should be kept of this operation.

16.34 Any significant or unusual discrepancy observed during reconciliation of the amount of bulk product and printed packaging materials and the number of units produced should be investigated, satisfactorily accounted for, and recorded before release.

16.35 Upon completion of a packaging operation, any unused batch-coded packaging materials should be destroyed and the destruction recorded. A documented procedure requiring checks to be performed before returning unused materials should be followed if uncoded printed materials are returned to stock.

17. **Good practices in quality control**

17.1 Quality control is the part of GMP concerned with sampling, specifications and testing, and with the organization, documentation and release procedures which ensure that the necessary and relevant tests are actually carried out and that materials are not released for use, nor products released for sale or supply, until their quality has been judged to be satisfactory. Quality control is not confined to laboratory operations but must be involved in all decisions concerning the quality of the product.

17.2 The independence of quality control from production is considered fundamental.

17.3 Each manufacturer (the holder of a manufacturing authorization) should have a quality control function. The quality control function should be independent of other departments and under the authority of a person with appropriate qualifications and experience, who has one or several control laboratories at his or her disposal. Adequate resources must be available to ensure that all the quality control arrangements are effectively and reliably carried out. The basic requirements for quality control are as follows:

- (a) adequate facilities, trained personnel and approved procedures must be available for sampling, inspecting, and testing starting materials, packaging materials, and intermediate, bulk, and finished products, and where appropriate for monitoring environmental conditions for GMP purposes;
- (b) samples of starting materials, packaging materials, intermediate products, bulk products and finished products must be taken by methods and personnel approved of by the quality control department;
- (c) qualification and validation must be performed;
- (d) records must be made (manually and/or by recording instruments) demonstrating that all the required sampling, inspecting

- and testing procedures have actually been carried out and that any deviations have been fully recorded and investigated;
- (e) the finished products must contain ingredients complying with the qualitative and quantitative composition of the product described in the marketing authorization; the ingredients must be of the required purity, in their proper container and correctly labelled;
 - (f) records must be made of the results of inspecting and testing the materials and intermediate, bulk and finished products against specifications; product assessment must include a review and evaluation of the relevant production documentation and an assessment of deviations from specified procedures;
 - (g) no batch of product is to be released for sale or supply prior to certification by the authorized person(s) that it is in accordance with the requirements of the marketing authorization. In certain countries, by law, the batch release is a task of the authorized person from production together with the authorized person from quality control;
 - (h) sufficient samples of starting materials and products must be retained to permit future examination of the product if necessary; the retained product must be kept in its final pack unless the pack is exceptionally large.

17.4 Quality control as a whole will also have other duties, such as to establish, validate and implement all quality control procedures, to evaluate, maintain, and store the reference standards for substances, to ensure the correct labelling of containers of materials and products, to ensure that the stability of the active pharmaceutical ingredients and products is monitored, to participate in the investigation of complaints related to the quality of the product, and to participate in environmental monitoring. All these operations should be carried out in accordance with written procedures and, where necessary, recorded.

17.5 Assessment of finished products should embrace all relevant factors, including the production conditions, the results of in-process testing, the manufacturing (including packaging) documentation, compliance with the specification for the finished product, and an examination of the finished pack.

17.6 Quality control personnel must have access to production areas for sampling and investigation as appropriate.

Control of starting materials and intermediate, bulk and finished products

17.7 All tests should follow the instructions given in the relevant written test procedure for each material or product. The result should

be checked by the supervisor before the material or product is released or rejected.

17.8 Samples should be representative of the batches of material from which they are taken in accordance with the approved written procedure.

17.9 Sampling should be carried out so as to avoid contamination or other adverse effects on quality. The containers that have been sampled should be marked accordingly and carefully resealed after sampling.

17.10 Care should be taken during sampling to guard against contamination or mix-up of, or by, the material being sampled. All sampling equipment that comes into contact with the material should be clean. Some particularly hazardous or potent materials may require special precautions.

17.11 Sampling equipment should be cleaned and, if necessary, sterilized before and after each use and stored separately from other laboratory equipment.

17.12 Each sample container should bear a label indicating:

- (a) the name of the sampled material;
- (b) the batch or lot number;
- (c) the number of the container from which the sample has been taken;
- (d) the number of the sample;
- (e) the signature of the person who has taken the sample;
- (f) the date of sampling.

17.13 Out-of-specification results obtained during testing of materials or products should be investigated in accordance with an approved procedure. Records should be maintained.

Test requirements

Starting and packaging materials

17.14 Before releasing a starting or packaging material for use, the quality control manager should ensure that the materials have been tested for conformity with specifications for identity, strength, purity and other quality parameters.

17.15 An identity test should be conducted on a sample from each container of starting material (see also section 14.14).

17.16 Each batch (lot) of printed packaging materials must be examined following receipt.

17.17 In lieu of testing by the manufacturer, a certificate of analysis may be accepted from the supplier, provided that the manufacturer establishes the reliability of the supplier's analysis through appropriate periodic validation of the supplier's test results (see sections 8.8 and 8.9) and through on-site audits of the supplier's capabilities. (This does not affect section 17.15). Certificates must be originals (not photocopies) or otherwise have their authenticity assured. Certificates must contain at least the following information (6):

- (a) identification (name and address) of the issuing supplier;
- (b) signature of the competent official, and statement of his or her qualifications;
- (c) the name of the material tested;
- (d) the batch number of the material tested;
- (e) the specifications and methods used;
- (f) the test results obtained;
- (g) the date of testing.

In-process control

17.18 In-process control records should be maintained and form a part of the batch records (see section 15.25).

Finished products

17.19 For each batch of drug product, there should be an appropriate laboratory determination of satisfactory conformity to its finished product specification prior to release.

17.20 Products failing to meet the established specifications or any other relevant quality criteria should be rejected.

Batch record review

17.21 Production and quality control records should be reviewed as part of the approval process of batch release. Any divergence or failure of a batch to meet its specifications should be thoroughly investigated. The investigation should, if necessary, extend to other batches of the same product and other products that may have been associated with the specific failure or discrepancy. A written record of the investigation should be made and should include the conclusion and follow-up action.

17.22 Retention samples from each batch of finished product should be kept for at least one year after the expiry date. Finished products should usually be kept in their final packaging and stored under the recommended conditions. If exceptionally large packages are produced, smaller samples might be stored in appropriate containers. Samples of active starting materials should be retained for at least one

year beyond the expiry date of the corresponding finished product. Other starting materials (other than solvents, gases, and water) should be retained for a minimum of two years if their stability allows. Retention samples of materials and products should be of a size sufficient to permit at least two full re-examinations.

Stability studies

17.23 Quality control should evaluate the quality and stability of finished pharmaceutical products and, when necessary, of starting materials and intermediate products.

17.24 Quality control should establish expiry dates and shelf-life specifications on the basis of stability tests related to storage conditions.

17.25 A written programme for ongoing stability determination should be developed and implemented to include elements such as:

- (a) a complete description of the drug involved in the study;
- (b) the complete set of testing parameters and methods, describing all tests for potency, purity, and physical characteristics and documented evidence that these tests indicate stability;
- (c) provision for the inclusion of a sufficient number of batches;
- (d) the testing schedule for each drug;
- (e) provision for special storage conditions;
- (f) provision for adequate sample retention;
- (g) a summary of all the data generated, including the evaluation and the conclusions of the study.

17.26 Stability should be determined prior to marketing and following any significant changes in processes, equipment, packaging materials, etc.

References

1. Good Manufacturing Practices for pharmaceutical products. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Twenty-second report*. Geneva, World Health Organization, 1992 Annex 1 (WHO Technical Report Series, No. 823).
2. Validation of analytical procedures used in the examination of pharmaceutical materials. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-second report*. Geneva, World Health Organization, 1992: Annex 5 (WHO Technical Report Series, No. 823).
3. *Good manufacturing practice for medicinal products in the European Community*. Brussels, Commission of the European Communities, 1992.

4. Pharmaceutical Inspection Convention, Pharmaceutical Inspection Co-operation Scheme (PIC/S). In: *Guide to good manufacturing practice for medicinal plants*, Geneva, PIC/S Secretariat, 2000.
5. *Quality assurance of pharmaceuticals. A compendium of guidelines and related materials. Volume 2. Good manufacturing practices and inspection*. Geneva, World Health Organization, 1999.
6. Model certificate of analysis. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-sixth report*. Geneva, World Health Organization, 2002, Annex 10 (WHO Technical Report Series, No. 902).

Annex 5

Model certificate of Good Manufacturing Practices

A model certificate of Good Manufacturing Practices (GMP) for a manufacturing site is suggested (see below). This is not part of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce but is intended to serve in situations where a specific GMP certificate is requested by importers, exporters, procurement agencies and regulatory authorities. It is suggested that the certificate should remain valid for a period of 2 years from the date of issue, but not exceeding 3 years after the inspection was carried out.

It is recommended that, where possible, GMP certificates should have, e.g. security seals, watermarks or holograms, to help prevent counterfeiting, tampering and other fraudulent activities.

Letterhead of regulatory authority

Model Certificate of Good Manufacturing Practices

This one-page certificate conforms to the format recommended by the World Health Organization (general instructions and explanatory notes attached).¹

Certificate No: _____

On the basis of the inspection carried out on ____ [date] ____ we certify that the site indicated on this certificate complies with Good Manufacturing Practices for the dosage forms, categories and activities listed in Table 1.

1. Name and address of site:

2. Manufacturer's licence number:

3. Table 1:

Dosage form(s)	Category(ies)	Activity(ies)

The responsibility for the quality of the individual batches of the pharmaceutical products manufactured through this process lies with the manufacturer.

This certificate remains valid until ____ [date] ____ It becomes invalid if the activities and/or categories certified herewith are changed or if the site is no longer considered to be in compliance with GMP.

Address of certifying authority:

Name and function of responsible person:

Email: _____ Telephone no.: _____ Fax no.: _____

Signature:

Stamp and date:

¹ This model certificate for GMP is not part of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce.

Explanatory notes

- (1) This certificate, which is in the format recommended by WHO, certifies the status of the Site listed in point 1 of the certificate.
- (2) The certification number should be traceable within the regulatory authority issuing the certificate.
- (3) Where the regulatory authority issues a licence for the site this number should be specified. Record “not applicable” in case where there is no legal framework for the issuing of a licence.
- (4) Table 1

List the dosage forms, starting materials, categories and activities. Examples give below.

Example 1

<i>Pharmaceutical Product(s)</i> ²	<i>Category(ies)</i>	<i>Activity(ies)</i>
<i>Dosage form(s):</i>		
Tablets	Cytotoxic	Packaging
	Hormone	Production, packaging, quality control
	Penicillin	Repackaging and labelling
Injectables	Cefalosporin	Aseptic preparation, packaging, labelling

Example 2

<i>Pharmaceutical Product(s)</i> ²	<i>Category(ies)</i>	<i>Activity(ies)</i>
<i>Starting material(s):</i> ³		
Paracetamol	Analgesic	Synthesis, purification, packing, labelling

² Pharmaceutical Products: Any medicine intended for human use or veterinary product administered to food-producing animals, presented in its finished dosage form or as a starting material for use in such a dosage form, that is subject to control by pharmaceutical legislation in both the exporting state and the importing state.

³ Starting Materials: Any substance of a defined quality used in the production of a pharmaceutical product, but excluding packaging materials.

Use, whenever available, International Nonproprietary Names (INNs) or otherwise national nonproprietary names.

(5) The certificate remains valid until the specified date. The certificate becomes invalid if the activities and/or categories certified are changed or if the site is no longer considered to be in compliance with GMP.

(6) The requirements for good practices in the manufacture and quality control of drugs referred to in the certificate are those included in *Quality Assurance of Pharmaceuticals: a compendium of guidelines and related materials. Good manufacturing practices and inspection, Volume 2*, 1999. World Health Organization, Geneva and subsequent updates.

Annex 6

Guidance on Good Manufacturing Practices (GMP): inspection report

When a site at which pharmaceutical products are manufactured is inspected, the inspector(s) responsible must draw up a report containing the items listed below. Where relevant, the appropriate section of the WHO GMP (Annex 4) is indicated.

A. **Manufacturer**

- (a) Name of inspected manufacturer.
- (b) Address of inspected manufacturer (including telephone, fax, email and 24-hour telephone numbers).
- (c) Address of manufacturing site if different from that given above.
- (d) Site number (e.g. site master file or number allocated by the responsible authority).
- (e) Manufacturing licence number, if applicable.
- (f) Activities.
- (g) Pharmaceutical products manufactured.
- (h) Key personnel.
- (i) Key persons met.

B. **Inspection details**

- (a) Date(s) of inspection(s).
- (b) Previous inspection date.
- (c) Type of inspection.
- (d) Scope of inspection.
- (e) The regulatory authority.
- (f) GMP guidelines used for assessing compliance.
- (g) For foreign inspections state whether, the national regulatory authority (NRA) of the country where the inspection took place was informed and whether it took part in the inspection.
- (h) Brief report of inspection activities undertaken.
- (i) Samples taken and results obtained.
- (j) Assessment of the site master file.
- (k) GMP-related recalls from the market of any product in the last 2 years.

C. **Inspector(s)**

- (a) Name(s) of inspector(s) and accompanying experts.

D. Introduction

- (a) Brief summary of the manufacturing activities.
- (b) Other manufacturing activities carried out on the site (e.g. manufacture of cosmetics, research and development).
- (c) Use of outside scientific, analytical, or other technical assistance in manufacture and quality control.
- (d) Brief description of the quality management system of the firm responsible for manufacture. Reference can be made to a site master file if one is available.

E. Observations

The observations made during the inspection that are considered to be non-compliant with GMP should be listed. Where positive observations are included in the report, clear distinction should be made between “positive” and “non-compliant”. Non-compliant observations can be classified, e.g. as “critical”, “major” and “minor” if the Member State concerned has defined these terms. The date by which corrective action and completion are requested in accordance with the policy of the national regulatory authority should be given.

E.1 Quality assurance (see WHO GMP, section 1)

- (a) Quality system and documented quality policy of the manufacturer, e.g. as described in the quality manual.

E.2 Organization and personnel (see WHO GMP, section 9)

- (a) Organizational chart showing the arrangements for quality assurance, including production and quality control.
- (b) Qualifications, experience and responsibilities of key personnel.
- (c) Outline of arrangements for basic and in-service training and method of keeping records.
- (d) Health requirements for personnel engaged in production.
- (e) Personnel hygiene requirements, including clothing.

E.3 Premises (see WHO GMP, section 12)

- (a) Manufacturing areas (design, location etc.) used e.g. for storage and manufacturing (e.g. weighing, production, packaging) and flow of personnel and material.
- (b) Special areas for the handling of highly toxic, hazardous and sensitizing materials.
- (c) Nature of construction and finishes.
- (d) Systems such as drainage, ventilation, air conditioning, and supply of steam and gas. Detailed description of critical areas with potential risks of contamination and cross-contamination.

- (e) Classification of the rooms used for the manufacture of products, including clean rooms.
- (f) Water systems.
- (g) Planned preventative maintenance programme.
- (h) Qualification of premises and systems as appropriate.

E.4 *Equipment (see WHO GMP, section 13)*

- (a) Design, location and adaptation of equipment used in production and control laboratories.
- (b) Planned preventative maintenance programmes for equipment and records.
- (c) Qualification and calibration, including records.

E.5 *Materials (see WHO GMP, section 14)*

- (a) Sourcing of materials.
- (b) Control, storage and handling of materials, including:
 - starting materials;
 - packaging materials;
 - intermediate and bulk products;
 - finished products;
 - returned and rejected materials;
 - reagents and culture media;
 - reference standards;
 - waste material.

E.6 *Good practices in production (see WHO GMP, section 16)*

- (a) Transport, handling and use of starting materials, packaging materials, and bulk and finished products.
- (b) Production operations and important parameters (e.g. sampling, quarantine, weighing, process operations and conditions, acceptance limits).
- (c) Validation (e.g. process).
- (d) Change control and deviation reporting.

E.7 *Quality control (see WHO GMP, section 17)*

- (a) Activities of quality control (including quarantine control, sampling, chemical and microbial analysis).
- (b) Organization and personnel.
- (c) Premises.
- (d) Equipment and instrumentation.
- (e) Materials.
- (f) Documentation (e.g. specifications, procedures, reports, records).

- E.8 **Sanitation and hygiene (see WHO GMP, section 3)**
- (a) Procedures for sanitation and/or cleaning (e.g. of premises and equipment) and records.
 - (b) Personal hygiene.
- E.9 **Validation (see WHO GMP, section 4)**
- (a) Validation master plan.
 - (b) Validation and qualification protocols and reports for qualification and validation (e.g. of premises, systems, equipment, process, computer, cleaning, analytical methods).
 - (c) Stages of validation.
 - (d) Types of validation.
- E.10 **Documentation (see WHO GMP, section 15)**
- (a) Documentation (e.g. specifications, procedures, records, protocols, reports).
 - (b) Preparation, revision and distribution of documentation.
 - (c) Reports on production, quality control (including environmental control), engineering and other relevant areas.
- E.11 **Complaints (see WHO GMP, section 5)**
- (a) Procedure, records and investigation.
- E.12 **Product recalls (see WHO GMP, section 6)**
- (a) Procedure, records and investigation.
- E.13 **Contract production and analysis (see WHO GMP, section 7)**
- (a) Responsibilities of contract giver.
 - (b) Responsibilities of contract acceptor.
 - (c) Contract (containing clearly defined responsibilities).
 - (d) GMP compliance of the contract acceptor (initial assessment and continued compliance audited at regular intervals).
- E.14 **Self-inspection and quality audits (see WHO GMP, section 8)**
- (a) Procedure, programme and compliance.
 - (b) Items for self-inspection.
 - (c) Self-inspection team.
 - (d) Frequency of self-inspection.
 - (e) Self-inspection report.
 - (f) Follow-up action.
 - (g) Quality audit.
 - (h) Suppliers' audits.

F. **Summary**

Brief summary of the findings, and recommendations (where applicable).

G. **Conclusions**

A statement regarding the GMP status.

Name: _____ Signature: _____ Date: _____

Annex 7

Application of Hazard Analysis and Critical Control Point (HACCP) methodology to pharmaceuticals

1. Introduction

Traditionally, the Hazard Analysis and Critical Control Point (HACCP) methodology has been considered to be a food safety management system. It aims to prevent known hazards and to reduce the risks that they will occur at specific points in the food chain. The same principles are also increasingly being applied, in other industries, such as the car industry, aviation and the chemical industry.

This text provides general guidance on the use of the HACCP system to ensure the quality of pharmaceuticals, while recognizing that the details of its application may vary depending on the circumstances (see Appendix 1). It does not provide detailed information on major hazards.

Hazards affecting quality are controlled to a certain extent through the validation of critical operations and processes in the manufacture of finished pharmaceutical products in accordance with Good Manufacturing Practices (GMP). However, GMP do not cover the safety of the personnel engaged in manufacture, while both aspects are covered by HACCP.

Procedures, including GMP, address operational conditions and provide the basis for HACCP. HACCP is a systematic method for the identification, assessment and control of safety hazards. Such hazards are defined as biological, chemical, or physical agents or operations that are reasonably likely to cause illness or injury if not controlled. In the manufacture of pharmaceuticals,¹ these may include the manufacture of certain antibiotics, hormones, cytotoxic substances or other highly active pharmaceuticals, together with operations such as fluid-bed drying, granulation is an example of hazard unit operations. The use of inflammable solvents (solutions) and certain laboratory operations may also constitute hazards.

¹ Safety hazards are common in the manufacture of active pharmaceutical ingredients; e.g., dangerous chemical conversions such as catalytic hydrogenation or nitration, or handling reactions with extremely hazardous chemicals such as phosgene or methyl-isocyanate require special precaution and control measures.

The following elements of the HACCP methodology are integral parts of the validation master file:

- development of a flow diagram of the process;
- verification of the flow diagram on site.

In addition, HACCP will extend this concept to include an analysis of the critical quality variables as well as the assessment of hazards affecting the safety of workers and environmental pollution hazards directly related to the process (in particular in open systems) concerned.

GMP for pharmaceutical products require the validation of critical processes as well as of changes in the manufacturing process which may affect the quality of the final product. Experience shows that most manufacturing processes contain steps that are “critical” from the point of view of variations in final product quality.

HACCP should not be confused with validation since its approach is broader; it thereby helps to identify matters on which validation should concentrate. It is science-based and systematic, and identifies specific hazards and measures for their control, as well as providing information on environmental protection and labour safety. HACCP is a tool to assess hazards and establish, control systems that focus on prevention rather than relying on corrective action based on end-product testing. All HACCP systems are capable of accommodating changes, such as advances in equipment design and processing procedures or technological developments.

HACCP should not replace GMP; however, its application may be used as a first step towards GMP.

In countries where appropriate regulations exist and are enforced, compliance with GMP (including validation), drug regulatory activities and inspections provide good assurance that risks are largely controlled. In countries where control is less effective, however, patients may be put at risk through the production of drugs of inadequate quality. The assessment of individual risks related to specific products and starting materials, and the recognition of hazards at specific stages of production or distribution should permit regulatory authorities to improve drug control by increasing the effectiveness of their activities within the limits of the available resources.

The present guidelines are aimed at assisting industry to develop and implement effective HACCP plans covering activities such as research and development, sourcing of materials, manufacturing, packaging, testing and distribution.

2. **Links with other programmes**

In each stage of the manufacture and supply of pharmaceuticals, the necessary conditions should be provided and met to protect the pharmaceuticals concerned. This has traditionally been accomplished through the application of Good Clinical Practice (GCP), Good Laboratory Practice (GLP), GMP and other guidelines, which are considered to be essential to the development and implementation of effective HACCP plans. HACCP plans are focused on hazards, the overall objective being to ensure that pharmaceuticals are safe for use. The existence and effectiveness of GCP, GLP and GMP should be assessed when drawing up HACCP plans.

3. **Definitions**

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

control (verb)

The taking of all necessary actions to ensure and maintain compliance with the criteria established in the HACCP plan.

control (noun)

The state wherein correct procedures are being followed and criteria are being met.

control measure

Any action and activity that can be used to prevent or eliminate a pharmaceutical quality hazard or reduce it to an acceptable level.

corrective action

Any action to be taken when the results of monitoring at the CCP (see below) indicate a loss of control.

critical control point (CCP)

A step at which control can be applied and is essential to prevent or eliminate a pharmaceutical quality hazard or reduce it to an acceptable level.

critical limit

A criterion which separates acceptability from unacceptability.

deviation

Failure to meet a critical limit.

flow diagram

A systematic representation of the sequence of steps or operations used in the production, control and distribution of a particular pharmaceutical.

HACCP plan

A document prepared in accordance with the principles of HACCP to ensure the control of hazards which are significant for pharmaceutical quality in the production and supply chain.

hazard

Any circumstance in the production, control and distribution of a pharmaceutical which can cause an adverse health effect.

hazard analysis

The process of collecting and evaluating information on hazards which should be addressed in the HACCP plan.

monitor

The act of conducting a planned sequence of observations or measurements of control parameters to assess whether a CCP is under control.

pharmaceuticals

All products related to pharmacy, including starting materials (active pharmaceutical ingredients and excipients), finished dosage forms, and biological and other specific products.

validation

The collection and evaluation of data, beginning at the process development stage and continuing through the production phase, which ensure that the manufacturing processes — including equipment, buildings, personnel and materials — are capable of achieving the intended results on a consistent and continuous basis. Validation is the establishment of documented evidence that a system does what it is supposed to do.

verification

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

4. Principles

The HACCP system is based on seven principles. In applying these principles, 12 stages are recommended and are discussed in section 7.

Some stages are linked to specific principles while others serve as an introduction to the concept.

The seven principles are:

1. Conduct a hazard analysis.
2. Determine the critical control points (CCPs).
3. Establish target levels and critical limit(s).
4. Establish a system to monitor the CCPs.
5. Establish the corrective action to be taken when monitoring indicates that a particular CCP is not under control.
6. Establish procedures to verify that the HACCP system is working effectively.
7. Establish documentation concerning all procedures and keep records appropriate to these principles and their application.

5. **Guidelines for the application of the HACCP system**

The following guidelines will be found useful in applying the HACCP system:

- Before HACCP is applied to any sector, that sector should be operating in accordance with the principles of good practices and the relevant legislation.
- Management commitment is necessary if an effective HACCP system is to be implemented.
- HACCP should be applied to each specific operation separately.
- CCPs identified in any given example in any reference document (including GMP guidelines) may not be the only ones identified for a specific application or may be of a different nature.
- The HACCP application should be reviewed and necessary changes made when any modification is made in the product or process, or in any step.
- It is important, when applying HACCP, to take into account the nature and size of the operation.
- There should be a HACCP plan. The format of such plans may vary, but they should preferably be specific to a particular product, process or operation. Generic HACCP plans can serve as useful guides in the development of product and process HACCP plans; however, it is essential that the unique conditions within each facility are considered during the development of all components of the HACCP plan.

6. **Training and education**

As HACCP is a relatively new concept in the pharmaceutical industry, training of personnel in industry, government and universities in

HACCP principles and applications is essential for its effective implementation.

In developing specific training to support a HACCP plan, working instructions and procedures should be drawn up which define the tasks of the operating personnel to be stationed at each critical control point. Specific training should be provided in the tasks of employees monitoring each CCP.

Cooperation between producers, traders and responsible authorities is of vital importance. Opportunities should be provided for the joint training of industrial staff and the control authorities to encourage and maintain a continuous dialogue and create a climate of understanding in the practical application of HACCP.

The success of a HACCP system depends on educating and training management and employees in the importance of their role in producing safe pharmaceuticals. Information should also be provided on the control of hazards at all stages of production and supply.

Employees must understand what HACCP is, learn the skills necessary to make it function properly, and must also be given the materials and equipment necessary to control the CCPs.

7. **Application**

The application of HACCP principles consists of the following 12 stages, as identified in the logic sequence for application of HACCP.

7.1 ***Assemble a HACCP team***

The pharmaceutical manufacturer should assure that product-specific knowledge and expertise are available for the development of an effective HACCP plan. This may be best accomplished by assembling a multidisciplinary team. Team members should therefore represent all the relevant disciplines, such as research and development, production, quality control, quality assurance, microbiology, engineering and distribution or others as applicable.

Team members should have specific knowledge and expertise regarding the product and process. Where such expertise is not available on site, expert advice should be obtained from other sources.

Team members should be able to:

- (a) conduct a hazard analysis;
- (b) identify potential hazards;
- (c) identify hazards which should be controlled;
- (d) recommend controls and critical limits;

- (e) devise procedures for monitoring and verification;
- (f) recommend appropriate corrective action where deviations occur;
- (g) verify the HACCP plan.

The scope of the HACCP plan should be defined. The scope should describe the segment of the process involved and the classes of hazards to be addressed should be identified.

7.2 ***Describe the product and process***

A full description of the product and the process should be drawn up, including relevant quality information such as the composition, physical/chemical properties, structure, pH, temperatures, method of cleaning, bactericidal/bacteriostatic treatments (e.g. heat-treatment), drying, screening, mixing, blending, packaging, and the storage conditions. The method of distribution and transport should also be described, especially where products are thermolabile.

7.3 ***Identify the intended use***

The intended use should be based on the expected uses of the product by the end user or consumer. In specific cases, vulnerable population groups, e.g. geriatric patients, infants and immunocompromised patients, may have to be considered.

7.4 ***Construct a flow diagram***

The flow diagram should be constructed by the HACCP team, and should cover all operations and decisions in a process.

When applying HACCP to a given operation, the steps preceding and following that operation should also be considered.

A block-type diagram may be sufficiently descriptive.

7.5 ***On-site confirmation of flow diagram***

The HACCP team should confirm the processing operation against the flow diagram during all stages and hours of operation. Amendments to the flow diagram may be made where appropriate, and should be documented.

7.6 ***List all potential hazards associated with each step, conduct a hazard analysis, and consider any measures to control identified hazards (Principle 1)***

When hazard analysis is conducted, safety concerns must be distinguished from quality concerns.

The HACCP team should list all the hazards that may be reasonably expected to occur at each step from production, testing and distribution up to the point of use. It should then conduct a hazard analysis to identify for the HACCP plan which hazards are of such a nature that their elimination or reduction to acceptable levels is essential.

A thorough hazard analysis is required to ensure an effective control point. A two-stage hazard analysis is recommended. During the first stage, the team should review the materials, activities, equipment, storage, distribution and intended use of the product. A list of the potential hazards (biological, chemical and physical) which may be introduced, increased or controlled in each step should be drawn up.

In the hazard analysis, the following should be included wherever possible:

- the probable occurrence of hazards and the severity of their adverse health effects;
- the qualitative and/or quantitative evaluation of the presence of hazards;
- the survival or multiplication of microorganisms of concern;
- the production or persistence in drugs of toxins, chemicals or physical agents;
- the conditions leading to the above.

During the second stage, a hazard evaluation should be conducted, i.e. the severity of the potential hazards and the probability of their occurrence should be estimated.

The team should then decide which potential hazards should be addressed in the HACCP plan, and what control measures, if any, exist that can be applied for each hazard. More than one control measure may be required to control a specific hazard(s) and more than one hazard may be controlled by a specified control measure.

Potential hazards in relation to at least the following should be considered:

- materials and ingredients;
- physical characteristics and composition of the product;
- processing procedures;
- microbial limits, where applicable;
- premises;
- equipment;
- packaging;
- sanitation and hygiene;
- personnel;

- risk of explosions;
- mix-ups.

Common examples of failures are given in Appendix 2.

7.7 Determine critical control points (Principle 2)

A CCP in the HACCP system can be more easily determined by the use of a decision-tree, which facilitates a logical approach. The way that a decision-tree is used will depend on the operation concerned, e.g. production, packing, reprocessing, storage, distribution. Training in the use of decision-trees should be given.

If a hazard has been identified at a step where control is necessary for safety, and no control measure exists at that step, or any other, the product or process should be modified at that step, or at an earlier or later stage, to include such a control measure.

7.8 Establish critical limits for each CCP (Principle 3)

Critical limits must be specified and verified, if possible, for each critical control point. More than one critical limit may sometimes be elaborated at a particular step. The criteria used often include measurements of temperature, time, moisture level, pH, and sensory parameters, such as visual appearance and texture. Critical limits should be scientifically based.

7.9 Establish a monitoring system for each CCP (Principle 4)

Monitoring is the scheduled measurement or observation of a CCP relative to its critical limits. Monitoring should be recorded.

The monitoring procedures used must be able to detect loss of control at the CCP, and this information should ideally be available in time to make adjustments to ensure control of the process and prevent violations of the critical limits. Where possible, process adjustments should be made when monitoring results indicate a trend towards loss of control at a CCP. These adjustments should be made before a deviation occurs.

Data derived from monitoring must be evaluated by a designated person with the knowledge and authority to carry out corrective actions when indicated.

If monitoring is not continuous, the amount or frequency of monitoring must be sufficient to guarantee that the CCP is under control.

Most monitoring procedures for CCPs will need to be done rapidly because they relate to on-line processes and there will not be time for

lengthy analytical testing. For this reason, physical and chemical measurements are often preferred to microbiological tests because they can be done rapidly and can often indicate the microbiological control of the product.

The personnel conducting the monitoring of CCPs and control measures should be engaged in production (e.g. line supervisors, maintenance staff) and, where appropriate, staff from quality control. They should be trained in monitoring procedures.

Where continuous monitoring is possible, a reliable monitoring procedure and frequency should be identified. Statistically designed data collection or sampling systems should then be used.

All records and documents associated with monitoring CCPs must be signed and dated by the person(s) carrying out the monitoring and by a responsible reviewing official(s) of the company.

7.10 ***Establish corrective actions (Principle 5)***

Specific corrective actions should be developed for each CCP in the HACCP system in order to deal with deviations when they occur. These actions should ensure that the CCP is brought under control. Corrective actions should include at least the following:

- (a) determination and correction of the cause of non-compliance;
- (b) determination of the disposition of the non-compliant product;
- (c) recording of the corrective actions that have been taken.

Specific corrective actions should be developed in advance for each CCP and included in the HACCP plan. As a minimum, this plan should specify what is to be done when a deviation occurs, who is responsible for implementing the corrective actions, and that a record will be kept and maintained of the actions taken. Individuals who have a thorough understanding of the process, product and HACCP plan should be assigned the responsibility for the oversight of corrective actions.

As appropriate, experts may be consulted to review the information available and to assist in determining the disposition of non-compliant product. Actions taken must also include the proper disposition of the affected product.

Deviation and product disposition procedures must be documented in the HACCP records.

7.11 ***Establish verification procedures (Principle 6)***

Procedures should be established for verification.

Verification and auditing methods, procedures and tests, including random sampling and analysis, can be used to determine whether the HACCP system is working correctly. The frequency of verification should be sufficient to confirm the proper functioning of the HACCP system.

Examples of verification activities include:

- review of the HACCP system and its records;
- review of deviations and product dispositions;
- confirmation that CCPs are kept under control.

Initial verification of the HACCP plan is necessary to determine whether it is scientifically and technically sound, that all hazards have been identified, and that, if the HACCP plan is properly implemented, these hazards will be effectively controlled.

Information reviewed to verify the HACCP plan should include:

- (a) expert advice and scientific studies;
- (b) in-plant observations, measurements and evaluations. For example, verification of the moist heat sterilization process for sterile injectables should include the scientific justification of the heating times, pressure and temperatures needed to obtain an appropriate destruction of pathogenic microorganisms (i.e. enteric pathogens) and studies to confirm that the sterilization conditions ensure that the whole load is kept at the required temperature for the time required.

Subsequent verifications should be performed and documented by a HACCP team or an independent expert, as needed. For example, verifications may be conducted when there is an unexplained system failure, a significant change in product, process or packaging occurs, or new hazards are recognized.

In addition, a periodic comprehensive evaluation of the HACCP system by an unbiased, independent third party is useful. This should include a technical evaluation of the hazard analysis and each element of the HACCP plan as well as an on-site review of all flow diagrams and appropriate records of the operation of the plan. Such a comprehensive verification is independent of other verification procedures and must be performed in order to ensure that the HACCP plan is resulting in the control of the hazards. If the results of the comprehensive verification identify deficiencies, the HACCP team should modify the HACCP plan as necessary.

Individuals doing verification should have appropriate technical expertise to perform this function.

Where possible, verification should include actions to confirm the efficacy of all elements of the HACCP plan.

7.12 ***Establish documentation and record keeping (Principle 7)***

Efficient and accurate documentation and record keeping are essential to the application of a HACCP system and should be appropriate to the nature and size of the operation.

Examples of activities for which documentation is required include:

- hazard analysis;
- CCP determination;
- HACCP plan;
- critical limit determination.

Examples of activities for which records are required include:

- CCP monitoring activities;
- process steps;
- associated hazards;
- critical limits;
- verification procedures and schedule;
- deviations;
- associated corrective actions;
- modifications to the HACCP system.

Appendix 1

Illustrative examples of major industrial hazards that may form part of a HACCP plan

The increasing use of hazardous chemicals in industry and trade further influences the quality and safety of processes and the personnel responsible for production. It is important that both on-site and off-site safety should be considered in all projects involving the storage and use of such chemicals.

This Appendix is intended only as a reminder of the major hazards that may be associated with the production, control and distribution of pharmaceuticals. Other relevant literature should be consulted, depending on the type of pharmaceuticals concerned (e.g. active pharmaceutical ingredients, vaccines).

1. Explosions and fires

Explosions can cause damage to buildings, injuries to personnel and hazards to products. Types of explosions that should be considered include detonations, gas and dust explosions, and confined and unconfined vapour-cloud explosions. Because of the possibility of explosions and fires, industry is required to control operations to prevent such hazards. An appropriate hazard-control system should therefore be in place at each site where such hazards are identified.

2. Workers' safety

3. External environment

3.1 Hazardous waste

3.2 Spillage

Appendix 2

Examples of common failures

Common failures should be identified and suitable control measures implemented.

1. **Component failures**

Causes of such failures include bad design, pressure, corrosive media, high temperatures, mechanical failure of pumps, blowers and stirrers, failure of control systems, such as sensors, failure of welds and flanges, and failure of safety systems (e.g. valves).

2. **Deviations from normal operating conditions**

Deviations from normal operating conditions include failures in the monitoring of crucial process parameters (e.g. pressure, temperature), failures in utilities such as steam, cooling, electricity and compressed air, failures in shut-down and start-up procedures, and formation of by-products, residues and impurities.

3. **Human and organizational errors**

A wide variety of errors can be made by operating personnel. Common errors include operator error, pressing wrong buttons, disconnecting alarms, mix-ups of materials, communication errors, and incorrect maintenance and repairs.

4. **Natural forces**

External impacts may be caused by natural forces such as wind, water, sunlight and lightning.

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Annex 8

Procedure for assessing the acceptability, in principle, of pharmaceutical products for purchase by United Nations agencies

WHO, UNICEF, UNAIDS and several other UN organizations are involved in the procurement of drugs. Without a documented quality system in place, organizations could risk sourcing sub-standard, counterfeit and/or contaminated medicines, leading to product complaints and product recalls, waste of money, and most seriously, health risks to patients.

WHO is currently undertaking a pilot project which will be used as a model for sourcing pharmaceuticals for other priority diseases. WHO will draft a model quality assessment system for procurement organizations through continued liaison with the relevant organizations.

This general procedure for the assessing the acceptability, in principle, of pharmaceutical products for purchase by United Nations agencies is considered to form the basis of the quality assessment system for procurement of pharmaceuticals.

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1. Introduction

The World Health Organization (WHO) could provide United Nations agencies advice on the acceptability, in principle, of pharmaceutical products which are found to meet WHO recommended quality standards, for purchase by such UN agencies. This will be done through a standardized quality assessment procedure.

The purpose of the quality assessment procedure is to evaluate whether the pharmaceutical products meet the requirements recommended by WHO for multisource (generic) pharmaceutical products as appropriateⁱ and are manufactured in compliance with Good Manufacturing Practices (GMP)ⁱⁱ.

The quality assessment procedure established by WHO is based on the following principles:

- Reliance on the information supplied by the National Drug Regulatory Authority (DRA);
- General understanding of the production and quality control activities of the manufacturers;
- Evaluation of product information submitted by manufacturers including product formulation, manufacture and test data and results;
- Assessment of consistency in production and quality control through compliance with GMP;
- Random sampling and testing of drugs supplied;
- Distribution of products;
- Handling of complaints and recalls;
- Monitoring of complaints from agencies and countries¹.

WHO could also collaborate with DRAs in the quality assessment. WHO recommends that manufacturers expressing interest to supply drugs through the UN agencies inform the DRAs of their intention and request the DRA to collaborate with WHO in the quality assessment process. It is recommended that the manufacturers provide the DRA with the necessary authorization to discuss the relevant product files with WHO representatives during inspections where relevant or required (subject to appropriate confidentiality provisions, if necessary).

WHO will advise UN agencies of the manufacturers whose products have been found acceptable in principle for procurement through a

¹ The guiding principles are based on the report (Annex 8) adopted by the 37th WHO Expert Committee on Specifications for Pharmaceutical Preparations meeting held in Geneva 22–26 October 2001 (forthcoming).

procedure of quality assessment based on WHO recommended guidelines and standards.

2. **Steps of the procedure**

WHO requires information related to the manufacturing and control of the products, and the manufacturing and testing companies. Interested manufacturers provide this information by submitting a product file with the required information, and information as requested about the manufacturing company. In addition to the evaluation of the product information submitted, a manufacturing site inspection(s) may be performed. The WHO reserves the right to terminate the quality assessment procedure of a manufacturer when the manufacturer is not able or fails to provide the required information in a specified time period, or when inadequate information is supplied to complete the quality assessment effectively.

2.1 ***Publication of Invitation for Expression of Interest (EOI)***

WHO will publish an invitation widely in the international press and on the web pages at regular intervals when necessary for specific groups of products, to request manufacturers to submit an Expression of Interest (EOI) to supply pharmaceutical products to UN agencies. The invitation should be open and transparent, inviting all manufacturers to submit the EOI for the drugs listed in the invitation.

Manufacturers should submit their EOI with the relevant information requested, before the date specified by WHO.

WHO will receive the EOI and record the receiving of EOI from each manufacturer. Guidelines developed for the submission of the Dossiers shall then be sent to the interested manufacturers.

2.2 ***Submission of Dossiers***

Each interested manufacturer should provide the focal point indicated in the EOI with a dossier containing the required information, before a specified date as determined by WHO.

The information should be submitted in the format reflecting the information summarized below. Alternatively, a standard dossier as prepared for or submitted to the DRA can be submitted, provided that it contains the information as required. In such cases, a covering letter cross-referencing the information should be provided by the manufacturer.

The following aspects must be covered:

For innovator products (from manufacturers whose products are manufactured and registered in a country with a stringent drug regulatory authority, including *inter alia* USA, EU/EEA and Japan):

- (a) A WHO-type Certificate of a Pharmaceutical Product² issued by one of the regulatory authorities of ICH regions together with the summary of product characteristics (SmPC).
- (b) Assessment report(s) issued by the respective DRA.
- (c) WHO-type batch certificate from the manufacturer.
- (d) In case the packaging of the product is different from the one approved by the drug regulatory authorities of the ICH regions, then stability testing data should be submitted.
- (e) In case the formulation, strength, specifications, etc. are different from the product for which the WHO-type Product Certificate(s) was issued, arguments and/or data to support the applicability of the certificate(s) despite the differences should be submitted.

For multisource (generic products); the data and information to be submitted shall be as described in “Marketing Authorization of Pharmaceutical Products with Special Reference to Multisource (Generic) Products. A Manual for a Drug Regulatory Authority. Regulatory Support Series, No.5 (WHO/DMP/RGS/98.5). Geneva, World Health Organization, 1999”; including (as summarized below)

- (a) Details of the product.
- (b) Regulatory situation in other countries.
- (c) Active pharmaceutical ingredient(s) (API):
 - (i) Properties of the active pharmaceutical ingredient(s),
 - (ii) Sites of manufacture,
 - (iii) Route(s) of synthesis,
 - (iv) Specifications:
API described in a pharmacopoeia,
API not described in a pharmacopoeia,
 - (v) Stability testing.
- (d) Finished product:
 - (i) Formulation,
 - (ii) Sites of manufacture,
 - (iii) Manufacturing procedure,
 - (iv) Specifications for excipients,

² The WHO type certificate of a Pharmaceutical Product refers to the certificate issued by the international drug regulatory authority in accordance with the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce. Further information, and the full text of the WHO document “Guidelines on the implementation of the WHO certification scheme on the quality of pharmaceutical products moving in international commerce” can be found in the web site <http://www.who.int/medicines/>

- (v) Specifications for the finished product,
- (vi) Container/closure system(s) and other packaging,
- (vii) Stability testing,
- (viii) Container labelling,
- (ix) Product information,
- (x) Patient information and package inserts,
- (xi) Justification for any differences to the product in the country or countries issuing the submitted WHO-type certificate(s),
- (xii) Interchange-ability,
- (xiii) Summary of pharmacology, toxicology and efficacy of the product.

2.3 **Screening of dossiers submitted**

Each dossier submitted by the manufacturer will be screened for completeness prior to the evaluation of the dossier.

Dossiers that are incomplete will not be considered for evaluation. The manufacturer will be informed that an incomplete dossier has been received, and be requested to complete the dossier within a specified time period. In the event this is not complied with, the dossier will in principle be rejected on grounds of incompleteness and returned to the manufacturer.

Dossiers that are in compliance with the requirements of the WHO will be (a) retained for evaluation purposes and (b) the manufacturing site will be considered for a possible manufacturing site inspection (i.e. if warranted based on the outcome of the evaluation of the dossier).

2.4 **Dossier assessment**

The dossiers will be evaluated by a team of experts appointed by the WHO in the field of pharmaceutical development, pharmaceuticals, bio-equivalence and other appropriate related fields. Evaluators will be appointed in accordance with a Standard Operating Procedure (SOP) established by WHO for appointment of evaluators of product information, and will be from Regulatory Authorities. The evaluation will be done in accordance with an SOP established by WHO for assessing product files based on the WHO guidelines to ensure uniformity in evaluation.

WHO will give technical support for the evaluation of product information supplied, if required.

2.5 ***Site Inspection***

Dependent on the outcome of the evaluation of the product dossier, WHO will plan and co-ordinate performance of inspections at the manufacturing sites to assess compliance with Good Manufacturing Practices as recommended by WHO (2). The inspection will be performed by a team of inspectors consisting of experts appointed by WHO, preferably from Regulatory Authority Inspectorates. The experts will be of three main areas including production, quality control and GMP. A WHO staff member will co-ordinate the team and the team members will act on a temporary basis as expert advisers to WHO. The team(s) will perform the inspections and report on the findings in accordance with SOP's established by WHO for planning and performing site inspections to ensure a standard harmonized approach. The WHO GMP checklist will be used during the inspection.

A representative(s) of the DRA of the country of manufacture would normally be expected to accompany the team to the manufacturing and testing facility to assess the compliance with GMP.

Evaluators and inspectors must have the relevant qualifications and experience.

2.6 ***Report and outcome of evaluation***

The evaluators and inspection team(s) will finalize a report according to the established WHO format describing the findings and including recommendations to the manufacturers. This will be communicated to the manufacturers.

If any additional information is required, or corrective action has to be taken by the manufacturer, WHO will postpone its final recommendations until such information has been evaluated, or the corrective action has been taken and found satisfactory in light of the specified standards.

In the event of any disagreement between a manufacturer and WHO, an SOP established by WHO for the handling of appeals and complaints will be followed to discuss and resolve the issue.

As WHO is responsible for the quality assessment, the ownership of the reports lies with WHO (without prejudice, however, to any confidential and proprietary information of the manufacturer contained in this report).

2.7 **Assessment results**

Once WHO is satisfied that the quality assessment process is complete for the manufacturer of the relevant product and that the product is acceptable in principle for procurement by UN Agencies (i.e. it has been found to meet the WHO recommended standards), the product, as produced at the specified manufacturing site, will be included in the list.

Manufacturers on the list will be considered to be manufacturing the relevant listed pharmaceutical products, of acceptable quality, and in compliance with WHO recommended GMP guidelines and other recommended standards, such as described in “Marketing Authorization of Pharmaceutical Products with Special Reference to Multisource (Generic) Products. A Manual for a Drug Regulatory Authority. Regulatory Support Series, No.5 (WHO/DMP/RGS/98.5). Geneva, World Health Organization, 1999. The quality assessment is valid only for those product(s) submitted by the manufacturer in the EOI, evaluated by WHO, and appearing on the list.

Each manufacturer receives a letter from WHO informing the manufacturer of the outcome of the quality assessment process in regard of the particular product(s) of that particular manufacturer. A copy of this letter will be sent to the DRA of the country of manufacture.

The list will be compiled in accordance with an SOP established by WHO for final decision making for inclusion in the list and will be subjected to review at least once a year. The list will be published and be included on the WHO web page.

2.8 **Procurement, sourcing and supply**

The WHO quality assessment procedure shall be independent from procurement. The UN agencies may use the list to guide them in sourcing of pharmaceutical products.

2.9 **Re-evaluation**

- i. Re-qualification should be done at regular intervals.
- ii. Suppliers will be required to communicate changes that may have impact on the safety, efficacy or quality of the product, to WHO.
- iii. Re-inspections of manufacturers will be done at regular intervals at least once every 3 years.
- iv. Change to key personnel or the manufacturing site could also result in a re-inspection.
- v. Re-evaluation of dossiers will be done every 3 years, or sooner should any change regarding the formula, manufacturing method, or manufacturing site be implemented by the manufacturer.

Re-evaluation may also be done in the following situations:

- If any fraud or omissions by the manufacturer in the initial assessment procedure or during the follow-up activities is evident in relation to the requirements, including compliance with the Good Manufacturing Practices (GMP), recommended by the WHO.
- If any batch or batches of supplied product(s) are considered by WHO or one or more of the UN agencies or organizations not to be in compliance with the agreed specification of the product;
- If a complaint considered to be serious in nature has been received by the WHO or one or more of the UN agencies or organizations;
- If suspension of supply is equal to or greater than one year;
- If, in the opinion of the WHO, changes made in the sourcing of the Active Pharmaceutical Ingredients (API), formulation, manufacturing method, facility or other production aspects require that a re-assessment be made.

2.10 **Testing of samples**

Random samples of pharmaceutical product(s) supplied by listed suppliers, will be taken for independent testing of final product characteristics. Certificates of Analysis of final products released by the manufacturer and specifications for test methods should be provided by the manufacturer to the WHO, for review, on request.

In the event of failure to meet the established criteria for re-evaluation and testing, WHO will investigate the problem and communicate this to the manufacturer.

2.11 **Monitoring of Complaint(s)**

Complaint(s) concerning a pharmaceutical product(s) or batch of product(s) supplied by the manufacturer, communicated to WHO, will be investigated in accordance with an SOP established by WHO.

After investigation, WHO will provide a written report of the problem and include recommendations for action where relevant.

A copy of the report will be sent to the DRA of the country where the manufacturing site is located. The DRA could be invited to participate in the investigation of the complaint.

WHO will make a copy of the report available to the manufacturer.

2.12 **Cost Recovery**

WHO reserves the right to charge for the quality assessment procedure on a cost recovery basis.

2.13 **Confidentiality Undertaking**

The evaluators and inspectors will treat all information to which they will gain access during the evaluations and inspections, or otherwise in connection with the discharge of their responsibilities in regard to the above-mentioned project, as 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 evaluators of product dossiers and inspectors (team members participating in site visits) within the scope of the quality assessment procedure of pharmaceutical products.

Evaluators and inspectors will take all reasonable measures to ensure

- (a) that confidential information is not used for any other purpose than the evaluation/inspection activities described in this document, and
- (b) that it 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.

2.14 **Conflict of Interest**

Before undertaking the work, each evaluator and inspector will also (in addition to the above mentioned confidentiality undertaking) be required to sign a Declaration of Interest. If based on this Declaration of Interest, it is felt that there is no risk of a real or perceived conflict of interest and it is thus deemed appropriate for the evaluator or inspector in question to undertake this work, he/she will discharge his/her functions exclusively as adviser to WHO. In this connection, each evaluator and inspector is required to confirm that the information disclosed by him/her in the Declaration of Interest is correct and that no situation of real, potential or apparent conflict of interest is known to him/her, including that he/she has no financial or other interest in, and/or relationship with a party, which:

- (a) may have vested commercial interest in obtaining access to any Confidential Information disclosed to him/her in the course of the evaluation/inspection activities described in this document; and/or
- (b) may have a vested interest in the outcome of the evaluation activities/inspection including, but not limited to, parties such as the manufacturers whose products are subject to evaluation or manufacturers of competing products.

Each evaluator and inspector will undertake to promptly advise WHO of any change in the above circumstances, including if an issue arises during the course of his/her work for WHO.

All inspectors furthermore agree, that at the manufacturer's request, WHO will advise the manufacturer in advance of the identity of each inspector and composition of the team performing the site inspection, and provide curricula vitae of the inspectors. The manufacturer then has the opportunity to express possible concerns regarding any of the inspectors to WHO prior to the visit. If such concerns cannot be resolved in consultation with WHO, the manufacturer may object to a team member's participation in the site visit. Such an objection must be made known to WHO by the manufacturer within ten days of receipt of the proposed team composition. In the event of such an objection, WHO reserves the right to cancel its agreement with the inspector, and the activities to be undertaken by that inspector, in whole or in part.

Appendix

Provisions for evaluators of product dossiers 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 the 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 behalf 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) _____

Institute _____

Place _____ Date _____

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- ⁱ Marketing Authorization of Pharmaceutical Products with Special Reference to Multisource (Generic) Products. A Manual for a Drug Regulatory Authority. Regulatory Support Series, No.5 (WHO/DMP/RGS/98.5). Geneva, World Health Organization, 1999.
- ⁱⁱ Quality assurance of pharmaceuticals. A compendium of guidelines and related materials. Volume 2. Good manufacturing practices and inspection. Geneva, World Health Organization, 1999.

Annex 9

Guide to good storage practices for pharmaceuticals¹

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1. Introduction

This guide is intended for those involved in the storage, transportation and distribution of pharmaceuticals. It is closely linked to other existing guides recommended by the WHO Expert Committee on Specifications for Pharmaceutical Preparations, such as:

- Good trade and distribution practice (GTDP) of pharmaceutical starting materials (1);
- The stability testing of pharmaceutical products containing well-established drug substances in conventional dosage forms (information given in connection with regulation for marketing authorization) (2);
- Good manufacturing practices (GMP) (3);

¹ This guidance has been prepared in close collaboration with the International Pharmaceutical Federation (FIP).

- The cold chain, especially for vaccines and biologicals;
- *The International Pharmacopoeia (4)*.

The objective of this guide is to supplement the above-mentioned documents by describing the special measures considered appropriate for the storage and transportation of pharmaceuticals. However, they may be adapted to meet individual needs where necessary, provided that the desired standards of quality are still achieved.

The guidelines are applicable not only to manufacturers of medicinal products but also to pharmaceutical importers, contractors and wholesalers, and community and hospital pharmacies. They should be adjusted in line with the type of activity where the storage of pharmaceuticals is taking place. National or regional regulations should be followed for all related activities.

2. **Glossary**

The definitions given below of some of the terms used in this document take into account the terminology of current regulations and recommendations.

active pharmaceutical ingredient (API)

Any substance or mixture of substances intended to be used in the manufacture of a pharmaceutical dosage form and that, when used in the production of a drug, becomes an active ingredient of that drug. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease, or to affect the structure and function of the body.

contamination

The undesired introduction of impurities of a chemical or microbiological nature, or of foreign matter, into or onto a starting material, or intermediate or finished product during production, sampling, packaging or repackaging, storage or transport.

cross-contamination

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

excipient

A substance, other than the active ingredient, which has been appropriately evaluated for safety and is included in a drug delivery system to:

- aid in the processing of the drug delivery system during its manufacture;
- protect, support or enhance stability, bioavailability, or patient acceptability;
- assist in product identification; or
- enhance any other attribute of the overall safety and effectiveness of the drug during storage or use.

expiry date

The date given on the individual container (usually on the label) of a drug 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.

labelling

The action involving the selection of the correct label, with the required information, followed by line clearance and application of the label.

manufacture

All operations of purchase of materials and products, production, quality control, release, storage and distribution of finished 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.

packaging material

Any material, including printed material, employed in the packaging of a pharmaceutical product, but excluding any outer packaging used for transportation or shipment. Packaging materials are referred to as primary or secondary according to whether or not they are intended to be in direct contact with the product.

pharmaceutical product

Any medicine intended for human use or veterinary product administered to food-producing animals, presented in its finished dosage form or as a starting material for use in such a dosage form, that is subject to control by pharmaceutical legislation in both the exporting state and the importing state.

production

All operations involved in the preparation of a pharmaceutical product, from receipt of materials, through processing, packaging and repackaging, labelling and relabelling, to completion of the finished product.

retest date

The date when a material should be re-examined to ensure that it is still suitable for use.

storage

The storing of pharmaceutical products and materials up to their point of use.

supplier

A person providing pharmaceutical products and materials on request. Suppliers may be agents, brokers, distributors, manufacturers or traders. Where possible, suppliers should be authorized by a competent authority.

3. Personnel

3.1 At each storage site (e.g. that of a manufacturer, distributor, wholesaler, community or hospital pharmacy) there should be an adequate number of qualified personnel to achieve pharmaceutical quality assurance objectives. National regulations on qualifications should be followed.

3.2 All personnel should receive proper training in relation to good storage practice, regulations, procedures and safety.

3.3 All members of staff should be trained in, and observe high levels of, personal hygiene and sanitation.

3.4 Personnel employed in storage areas should wear suitable protective or working garments appropriate for the activities they perform.

4. Premises and facilities

Storage areas

4.1 Precautions must be taken to prevent unauthorized persons from entering storage areas.

4.2 Storage areas should be of sufficient capacity to allow the orderly storage of the various categories of materials and products, namely starting and packaging materials, intermediates, bulk and finished products, products in quarantine, and released, rejected, returned or recalled products.

4.3 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. Where special storage conditions are required on the label (e.g. temperature, relative humidity), these should be provided, checked, monitored and recorded. Materials and 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.

4.4 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 the materials and pharmaceutical products. There should be appropriate procedures for the clean up of any spillage to ensure complete removal of any risk of contamination.

4.5 Receiving and dispatch bays should protect materials and products from the weather. Reception areas should be designed and equipped to allow containers of incoming materials and pharmaceutical products to be cleaned, if necessary, before storage.

4.6 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.

4.7 There should normally be a separate sampling area for starting materials in a controlled environment. 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.

4.8 Physical or other equivalent validated (e.g. electronic) segregation should be provided for the storage of rejected, expired, recalled or returned materials or products. The materials or products, and areas concerned should be appropriately identified.

4.9 Highly active and radioactive materials, narcotics and other hazardous, sensitive and/or dangerous materials and pharmaceutical products, as well as substances presenting special risks of abuse, fire or explosion, (e.g. combustible liquids and solids and pressurized

gases) should be stored in a dedicated area that is subject to appropriate additional safety and security measures.

4.10 Materials and pharmaceutical products should be handled and distributed according to GMP as defined in this document.

4.11 Materials and pharmaceutical products should be handled and stored in such a manner as to prevent contamination, mix-ups and cross-contamination.

4.12 Materials and pharmaceutical products should be stored in conditions which assure that their quality is maintained, and stock should be appropriately rotated. The “first expired/first out” (FEFO) principle should be followed.

4.13 Rejected materials and 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.

4.14 Narcotic drugs should be stored in compliance with international conventions, and national laws and regulations on narcotics.

4.15 Broken or damaged items should be withdrawn from usable stock and separated.

4.16 Storage areas should provide adequate lighting to enable all operations to be carried out accurately and safely.

Storage conditions

4.17 Storage conditions for pharmaceutical products and materials should be in compliance with the labelling, which is based on the results of stability testing (see Appendix).

Monitoring of storage conditions

4.18 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 material or product plus 1 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.

4.19 Equipment used for monitoring should also be calibrated at defined intervals.

5. **Storage requirements**

Documentation: written instructions and records

5.1 Written instructions and records should be available which document all activities in the storage areas including the handling of expired stock. These should adequately describe the storage procedures and define the route of materials and pharmaceutical products and information through the organization in the event of a product recall being required.

5.2 Permanent information, written or electronic, should exist for each stored material or 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.

5.3 Records should be kept 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. Where national regulations prescribe that records must be retained for a certain period, this must be observed. (Otherwise such records should be retained for a period equal to the shelf-life of the incoming materials and products, where applicable, plus 1 year).

5.4 Comprehensive records should be maintained showing all receipts and issues of materials and pharmaceutical products according to a specified system, e.g. by batch number.

Labelling and containers

5.5 All materials and pharmaceutical products should be stored in containers which do not adversely affect the quality of the materials or products concerned, and which offer adequate protection from external influences. In some circumstances, this could include bacterial contamination.

5.6 All containers should be clearly labelled with at least the name of the material, the batch number, the expiry date or retest date, the specified storage conditions and reference to the pharmacopoeia, where applicable. Unauthorized abbreviations, names or codes should not be used.

Receipt of incoming materials and pharmaceutical products

5.7 On receipt, each incoming delivery should be checked against the relevant purchase order and each container physically verified, e.g. by the label description, batch number, type of material or pharmaceutical product and quantity.

5.8 The consignment should be examined for uniformity of the containers and, if necessary, should be subdivided according to the supplier's batch number should the delivery comprise more than one batch.

5.9 Each container should be carefully inspected for possible contamination, tampering and damage, and any suspect containers or, if necessary, the entire delivery should be quarantined for further investigation.

5.10 When required, samples should be taken only by appropriately trained and qualified personnel and in strict accordance with written sampling instructions. Containers from which samples have been taken should be labelled accordingly.

5.11 Following sampling, the goods should be subject to quarantine. Batch segregation should be maintained during quarantine and all subsequent storage.

5.12 Materials and pharmaceutical products should remain in quarantine until an authorized release or rejection is obtained.

5.13 Measures should be taken to ensure that rejected materials and pharmaceutical products cannot be used. They should be stored separately from other materials and pharmaceutical products while awaiting destruction or return to the supplier.

Stock rotation and control

5.14 Periodic stock reconciliation should be performed by comparing the actual and recorded stocks.

5.15 All significant stock discrepancies should be investigated as a check against inadvertent mix-ups and/or incorrect issue.

5.16 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 have been opened or partly used should be used up before those in unopened containers.

5.17 Damaged containers should not be issued unless the quality of the material has been shown to be unaffected. Where possible, this 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 pharmaceutical products

5.18 All stocks should be checked regularly for obsolete and outdated materials and pharmaceutical products. All due precautions should be observed to prevent the issue of outdated materials and pharmaceutical products.

6. Returned goods

6.1 Returned goods, including recalled goods, should be handled in accordance with approved procedures and records should be maintained.

6.2 All returned goods should be placed in quarantine and returned to saleable stock only after this has been approved by a nominated, responsible person following a satisfactory quality re-evaluation.

6.3 Any stock reissued should be so identified and recorded in stock records. Pharmaceuticals returned from patients to the pharmacy should not be taken back as stock, but should be destroyed.

7. Dispatch and transport

7.1 Materials and pharmaceutical products should be transported in such a way that their integrity is not impaired and that storage conditions are maintained.

7.2 Special care should be exercised when using dry ice in cold chains. In addition observing to safety precautions, it must be ensured that the materials or product does not come in into contact with dry ice, as this may adversely affect the product quality, e.g. by freezing.

7.3 Where appropriate, the use of devices to monitor conditions such as temperature during transportation is recommended. Monitoring records should be available for review.

7.4 The dispatch and transport of materials and pharmaceutical products should be carried out only after receipt of a delivery order. The receipt of the delivery order and the dispatch of the goods must be documented.

7.5 Dispatch procedures should be established and documented, taking into account the nature of the materials and pharmaceutical products concerned and any special precautions that might be required.

7.6 The outside container should offer adequate protection from all external influences and should be indelibly and clearly labelled.

7.7 Records for dispatch should be retained, stating at least:

- the date of dispatch;
- the customer's name and address;
- the product description, e.g. name, dosage form and strength (if appropriate), batch number and quantify;
- the transport and storage conditions.

7.8 All records should be readily accessible and available on request.

8. Product recall

8.1 There should be a procedure to recall from the market, promptly and effectively, pharmaceutical products and materials known or suspected to be defective.

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Appendix

Storage and labelling conditions²

Normal storage conditions

Storage in dry, well-ventilated premises at temperatures of 15–25°C or, depending on climatic conditions, up to 30°C. Extraneous odours, other indications of contamination, and intense light must be excluded.

Defined storage instructions

Drug products that must be stored under defined conditions require appropriate storage instructions. Unless otherwise specifically stated (e.g. continuous maintenance of cold storage) deviation may be tolerated only during short-term interruptions, for example, during local transportation.

The use of the following labelling instructions are recommended:

<i>On the label</i>	<i>Means</i>
“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 in normal storage conditions; to be provided to the patient in a moisture-resistant container.
“Protect from light”	to be provided to the patient in a light-resistant container.

² The text was adopted by the WHO Expert Committee on Specifications for Pharmaceutical Preparations at its 34th meeting (*WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-Fourth report*. Geneva, World Health Organization, 1996, Annex 5 (WHO Technical Report Series No. 863).

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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. (in press)

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. 1999 (201 pages)

Quality control methods for medicinal plant materials.

1998 (123 pages)

WHO Expert Committee on Specifications for Pharmaceutical Preparations.

Thirty-sixth report.

WHO Technical Report Series, No. 902, 2002 (215 pages)

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The use of essential drugs.

Ninth report of the WHO Expert Committee (including the revised Model List of Essential Drugs).

WHO Technical Report Series, No. 895, 2000 (66 pages)

WHO Expert Committee on Biological Standardization.

Fiftieth report.

WHO Technical Report Series, No. 904, 2002 (113 pages)

Further information on these and other WHO publications can be obtained from
Marketing and Dissemination, World Health Organization, 1211 Geneva 27, Switzerland

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. Of particular relevance to drug regulatory authorities and pharmaceutical manufacturers, the report discusses activities related to the development of *The International Pharmacopoeia* and basic tests for pharmaceutical substances and dosage forms, as well as quality control of reference materials, good manufacturing practices (GMP), stability studies, inspection, hazard analysis, procurement, storage and other aspects of quality assurance of pharmaceuticals, and regulatory issues.

The report is complemented by a number of annexes, including recommendations on the risk of transmitting animal spongiform encephalopathy agents via medicinal products, guidelines on GMP for pharmaceutical products, a model certificate for GMP and guidance on a GMP inspection report. The final annexes provide guidance on the application of Hazard Analysis and Critical Control Point (HACCP) method to pharmaceuticals, good storage practices and a procedure for assessing acceptability of pharmaceutical products for purchase by United Nations agencies.



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