The Expert Committee on Specifications for Pharmaceutical Preparations works towards clear, independent and practical standards and guidelines for the quality assurance of medicines. Standards are developed by the Committee through worldwide consultation and an international consensus-building process. The following new guidelines were adopted and recommended for use, in addition to 20 monographs and general texts for inclusion in *The International Pharmacopoeia* and 11 new International Chemical Reference Substances. *The International Pharmacopoeia* – updating mechanism for the section on radiopharmaceuticals; WHO good manufacturing practices for pharmaceutical products: main principles; Model quality assurance system for procurement agencies; Assessment tool based on the model quality assurance system for procurement agencies: aide-memoire for inspection; Guidelines on submission of documentation for prequalification of finished pharmaceutical products approved by stringent regulatory authorities; and Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product: quality part.

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WHO Expert Committee on Specifications for Pharmaceutical Preparations

Forty-eighth report

World Health Organization

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SELECTED WHO PUBLICATIONS OF RELATED INTEREST

The International Pharmacopoeia, fourth edition.
Volume 1: general notices; monographs for pharmaceutical substances (A–O)
Volume 2: monographs for pharmaceutical substances (P–Z); monographs for dosage forms and radiopharmaceutical preparations; methods of analysis; reagents.
2006 (1500 pages), also available on CD-ROM and online
First, second and third supplements: general notices; monographs for pharmaceutical substances; monographs for dosage forms; general and specific monographs; methods of analysis; International Chemical Reference Substances; International Infrared Reference Spectra; reagents, test solutions and volumetric solutions.
First supplement: 2008 (309 pages), also available on CD-ROM and online
Second supplement: 2011 (CD-ROM and online)
Third supplement: 2013 (CD-ROM and online)

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: WHO guidelines, related guidance and GXP training modules
Updated edition, 2013 (CD-ROM and online).

WHO Expert Committee on Specifications for Pharmaceutical Preparations
Forty-sixth report.
WHO Technical Report Series, No. 970, 2012 (235 pages)

Forty-seventh report.
WHO Technical Report Series, No. 981, 2013 (188 pages)

International Nonproprietary Names (INN) for pharmaceutical substances
Cumulative List No. 15
2013 (available on CD-ROM only)

The selection and use of essential medicines
Report of the WHO Expert Committee (including the 17th WHO Model List of Essential Medicines and the 3rd WHO Model List of Essential Medicines for Children)
WHO Technical Report Series, No. 965, 2011 (263 pages)

WHO Expert Committee on Biological Standardization
Sixty-second report
WHO Technical Report Series, No. 979, 2012 (366 pages)

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WHO Expert Committee on Specifications for Pharmaceutical Preparations

Forty-eighth report

This report contains the collective views of an international group of experts and does not necessarily represent the decisions or the stated policy of the World Health Organization

World Health Organization

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WHO Expert Committee on Specifications for Pharmaceutical Preparations

Geneva, 14–18 October 2013

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[1] Professor S. Bawazir had to leave urgently on 15 October. Ms M. Hirschhorn, who was designated Co-Chairperson, took over the proceedings as Chairperson.

[2] Unable to attend.

[3] Ms M. Hirschhorn, who was designated Co-Chairperson, took over the proceedings as Chairperson from 15 October 2013 as Professor S. Bawazir had to leave urgently on that date.

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United Nations Children's Fund (UNICEF)

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Representation from specialized agencies and related organizations[6]

The Global Fund to Fight AIDS, Tuberculosis and Malaria

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International Atomic Energy Agency (IAEA)

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[4] Unable to attend.

[5] Unable to attend: United Nations Development Programme, New York, NY, USA.

[6] Unable to attend: United Nations Industrial Development Organization, Vienna, Austria; World Intellectual Property Organization, Geneva, Switzerland; World Bank, Washington, DC, USA; World Customs Organization, Brussels, Belgium.

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and

Ms N. Sandepeen, Research Associate, Intellectual Property Division, Geneva, Switzerland

Representation from intergovernmental organizations[7]

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and

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Council of Europe
Dr A. Lodi, European Directorate for the Quality of Medicines & HealthCare, Strasbourg, France

Representation from nongovernmental organizations[9]

European Chemical Industry Council (CEFIC)/APIC
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International Federation of Pharmaceutical Manufacturers and Associations (IFPMA)
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and

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and

Dr R. Torano, GlaxoSmithKline, England

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[7] Unable to attend: European Commission, Brussels, Belgium.

[8] Participated via audio connection for certain agenda items.

[9] Unable to attend: Commonwealth Pharmacists Association, London, England; International Generic Pharmaceutical Alliance, Brussels, Belgium; International Society for Pharmaceutical Engineering, Tampa, FL, USA.

Observers[10]

Pharmacopoeias[11]

British Pharmacopoeia Commission

Mrs M. Vallender, Editor-in-Chief, BP and Laboratory Services, London, England

and

Ms H. Corns, Higher Pharmacopoeial Scientist

State Pharmacopoeia of the Russian Federation

Dr E.I. Sakanjan, Director, Centre of Pharmacopoeia and International Cooperation, Federal State Budgetary Institution, "Scientific Centre for Expert Evaluation of Medicinal Products" (FSBI "SCEMP"), Ministry of Health of the Russian Federation

and

Dr K. Bichenova, Research Associate, FSBI "SCEMP", Ministry of Health of the Russian Federation

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and

Dr E. Gonikberg, Director, Chemical Medicines, Rockville, MD, USA

WHO Secretariat

Health Systems and Innovation (HIS)

Dr M.-P. Kieny, Assistant Director-General

Essential Medicines and Health Products (HIS/EMP)

Mr C. de Joncheere, Director, Essential Medicines and Health Products (EMP)

Dr D.J. Wood, Coordinator, Technologies, Standards and Norms (EMP/TSN)

Quality Assurance and Safety: Medicines (EMP/QSM)

Dr S. Kopp, Manager, Medicines Quality Assurance Programme, QSM (Secretary)

Dr H. Schmidt, QSM

Mr. F.J. Hagelstein

Ms T. Burkard (Intern)

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[10] Unable to attend: Pharmaceutical Inspection Co-operation Scheme, Geneva, Switzerland.

[11] Unable to attend: Farmacopea Argentina; Farmacopéia Brasileira; Pharmacopoeia of the People's Republic of China; Indian Pharmacopoeia Commission; Indonesian Pharmacopoeia Commission; Committee of the Japanese Pharmacopoeia; Pharmacopoeia of the Republic of Korea.

Dr L. Rägo, Head of Regulation of Medicines and Other Health Technologies (EMP/RHT)

Dr S. Azatyan, Regulatory Systems Strengthening (RSS/RHT)

Dr R.G. Balocco Mattavelli, Manager, International Nonproprietary Names (INN) Programme, QSM

Dr A. Fake, Prequalification of Medicines Programme, QSM

Dr D. Mubangizi, Prequalification of Medicines Programme, QSM

Dr J. Sabartova, Prequalification of Medicines Programme, QSM

Dr K. Weerasuriya, Policy Access and Rational Use (EMP/PAU)

Traditional Medicine (Health Policy, Development and Services (HDS)/TRM)[12]

Blood Products and Related Biologicals, QSM[12]

Medicines Regulatory Support Programme (MRS), QSM[12]

Mr D. Bramley (report writer)

[12] Unable to attend.

Declarations of interest

Members and temporary advisers of the WHO Expert Committee on Specifications for Pharmaceutical Preparations reported the following:

Professor S. Bawazir, Dr L. Cargill, Dr A. Nasiri Kapour Chali, Professor T.G. Dekker, Dr X. Ge, Ms M. Hirschhorn, Professor J. Hoogmartens, Professor S. Jin, Dr B. Li, Dr L. Paleshnuik, Dr S. Parra, Dr J. Prakash, Ms L. Slamet and Dr J. Welink reported no conflict of interest.

Professor J.B. Dressman reported that she was involved in a European Union (EU) research project partially related to biowaiver, under a grant issued to the University of Frankfurt, with no personal value. She also reported that she was a member of the European Medicines Agency (EMA) Guidance Drafting Committee 2012–2013 and has been a member of the International Pharmaceutical Federation (FIP) Focus Group on "BCS/Biowaiver" since 2005, an unpaid position.

Professor H.G. Kristensen reported that he has provided testimonies as an independent expert on questions on validity and for infringement of patients at courts in Denmark, Norway and Sweden. In all cases testimony is related to drug formulations. No items conflicted with the subjects of the meeting.

Ms G.N. Mahlangu reported that she would receive an out-of-pocket allowance from her current employer, the Medicines Control Authority of Zimbabwe, in accordance with the travel allowances schedule for sponsored travel.

Dr A.J. van Zyl reported that he has acted as a consultant for: the United States Pharmacopeia; the Global Fund to Fight AIDS, Tuberculosis and Malaria, and the pharmaceutical industry; he further declared that he has prepared documentation and presented it for consideration by the Global Fund.

The declarations of interest were presented to the Expert Committee for information. There were no comments from Committee members or advisers.

1. Introduction

The WHO Expert Committee on Specifications for Pharmaceutical Preparations met in Geneva from 14 to 18 October 2013. Dr M.-P. Kieny, Assistant Director-General of Health Systems and Innovation at the World Health Organization (WHO), welcomed participants on behalf of the Director-General. Dr Kieny thanked the experts for their valuable contributions to the work of WHO, noting that standard-setting continues to be a pillar of WHO's activities and priorities and that the Expert Committee structure is the backbone of WHO's standard-setting process. She stressed that the numerous and practical outputs emanating from the Expert Committee, developed as international guidelines and ready for implementation, enable countries to move forward towards their goals of universal health coverage, including access to safe quality medical products for their people.

Referring to the ongoing WHO reform process, Dr Kieny pointed out that health systems – including essential medicines and universal health coverage – are one of the six priority categories of the Organization. In addition one of WHO's "leadership priorities" is to increase access to essential high-quality and affordable medical products. She noted that the work of the Expert Committee had contributed in many ways to assisting national and regional authorities, including through development and guidance in the area of quality control laboratories, development of techniques for routine quality assurance and also in cases of "suspect" medicines.

In the area of substandard/spurious/falsely-labelled/falsified/counterfeit (SSFFC) medical products, Dr Kieny noted that WHO Member States met in November 2012 to establish the areas of work and set the workplan, structure and governance of the new Member State mechanism for addressing this issue. The mechanism established an open-ended working group, which met in mid-2013, to identify the actions, activities and behaviour that result in SSFFC medical products. She pointed out that that a number of activities outlined in the workplan of the Member State mechanism related to the Expert Committee's agenda, including detection technologies, good practices in distribution for active pharmaceutical ingredients (APIs), products and terminology used by this Expert Committee.

Participants were reminded that they participated in the meeting in their personal capacity as experts and not as representatives of their employing organizations.

The meeting elected Professor S.A. Bawazir as Chairperson, Ms M. Hirschhorn as Co-Chairperson, and Dr S. Parra and Dr A.J. van Zyl as Rapporteurs.

The Secretary of the Expert Committee outlined the history of the Committee and its role in advising the Director-General of WHO in the furtherance of the Organization's work. The Expert Committee system is enshrined in the constitution of WHO. The process of guidelines development was explained.

Open session

The open session of the meeting, held during the morning of Monday, 14 October 2013, was opened by Mr C. de Joncheere, Director, Essential Medicines and Health Products (EMP), who welcomed the representatives of the permanent missions to the United Nations Office and other International Organizations at Geneva, from Brazil, Bulgaria and Italy.

He stated that the open session had been organized to respond to the interest expressed by Member States during the meetings of the World Health Assembly and Executive Board, especially in connection with the quality of medicines, with a focus on prevention and control of SSFFC medical products. He noted that the aim of the session was to provide more information on this Expert Committee in an open and transparent manner. All the Expert Committee-related materials, concerning both the past and ongoing work, were posted on the respective websites.

Mr de Joncheere noted that the Organization had been involved in medicines quality assurance and quality control since 1948. The Expert Committee was created in the very first World Health Assembly and was thus one of WHO's oldest advisory bodies. More recently, the work of the Expert Committee had provided considerable support to, among others, the Prequalification of Medicines Programme (PQP) of the United Nations and feedback from that Programme and others had resulted in several updates and the development of new standards. He emphasized that essential medicines and other health technologies were identified as a "leadership priority" by WHO and were critical to achieving the objectives of other areas of WHO's work.

He pointed out that the Expert Committee had developed 75 guidelines, good practices and guidance documents in the area of medicines quality assurance, all of which were available in electronic form on the Internet and on CD-ROM. Supplement Three of the Fourth Edition of *The International Pharmacopoeia* (Ph.Int) published in 2013 included 439 monographs on pharmaceutical substances, 161 specific monographs on dosage forms, nine general monographs on dosage forms, 60 texts on methods of analysis and 27 monographs on radiopharmaceuticals. In addition, 236 physical standards (i.e. International Chemical Reference Substances (ICRS)) had been established.

Mr de Joncheere described the three main pillars of EMP as: Public Health, Innovation and Intellectual Property; Policy, Access and Use; and

Regulation of Medicines and other Health Technologies. Under the Regulation of Medicines and other Health Technologies area come the four teams: Technologies, Standards and Norms; Regulatory Systems Strengthening; Safety and Vigilance; and Prequalification. He noted that EMP houses four of the Expert Committees of WHO, as well as the Programme on International Nonproprietary Names (INN), and four Advisory Committees.

2. General policy

2.1 Cross-cutting pharmaceutical quality assurance issues

2.1.1 Update from the Expert Committee on the Selection and Use of Essential Medicines

The Expert Committee on Specifications for Pharmaceutical Preparations received an update from the Expert Committee on the Selection and Use of Essential Medicines. It was reported that the nineteenth meeting of the Expert Committee on the Selection and Use of Essential Medicines had taken place in April 2013. During the meeting, both the seventeenth WHO Model List of essential medicines (EML) and the third WHO Model List of essential medicines for children were reviewed and updated.

The Committee considered more than 50 applications as well as 15 reviews and discussed a number of medicines proposed for inclusion in or deletion from the list. In addition, the Committee approved the addition of 17 new medicines to the EML and the deletion of one medicine from it; approved new indications for three medicines already listed on the EML, as well as a new dosage form or strength for four medicines already on the list; and approved two medicines for neonatal care. New inclusions comprised some new medicines, some older medicines, and some new formulations. It was noted that the WHO list is a "model list" and that countries should consider the list and decide which medicines are appropriate to their needs.

The Expert Committee welcomed the report.

2.1.2 Update from the Expert Committee on Biological Standardization

The Expert Committee on Specifications for Pharmaceutical Preparations also received an update from the Expert Committee on Biological Standardization which was due to meet the following week. Among other topics coming before the Expert Committee on Biological Standardization in 2013 were the nonclinical evaluation of adjuvanted vaccines, biologicals derived by recombinant DNA (rDNA) technology, typhoid conjugate vaccines, and a strategic plan for blood and blood products. In the longer term, agenda items in 2014 were likely to include inactivated polio vaccine, changes in manufacturing, and regulatory risk assessment. It was further reported that implementation workshops are organized under the auspices of the Expert Committee on Biological Standardization, with recent workshop themes including the stability evaluation of vaccines, standardization of biotherapeutic products, vaccine lot release, combined vaccines based on diphtheria-tetanus-pertussis (DTP), and regulatory risk assessment.

The Expert Committee on Specifications for Pharmaceutical Preparations was informed that a process was under way to revise the good manufacturing practices (GMP) for biological products, which had originally been published in 1992 as an annex to the GMP for pharmaceutical products. A working group met

in 2008 to initiate the revision, a gap analysis compared WHO GMP with other GMP in practice, and a drafting group for the revision was formed. The drafting group was due to meet in October 2013 and a consultation was planned for 2014. It was expected that the Expert Committee on Biological Standardization would review and adopt the new GMP for biological products in 2015.

The Expert Committee on Specifications for Pharmaceutical Preparations noted the report.

2.1.3 Temperature mapping of a storage area

The document on Model guidance for storage and transport of time- and temperature-sensitive pharmaceutical products was developed in consultation with the WHO Task Force on Regulatory Oversight on Pharmaceutical Cold Chain Management and was published in 2011 as Annex 9 to the forty-fifth report of the Expert Committee on Specifications for Pharmaceutical Preparations. The intention was that the guidance should be directly applicable in less-developed countries as well as in developed countries since experience with vaccine supply chain assessments in many less-developed countries demonstrates that the mandatory standards set out in the document can be achieved, and that some countries are also capable of meeting many of the optional requirements.

It was reported that the Secretariat had worked with a number of experts in order to develop a set of 18 technical supplements. Each supplement follows the same format (acronyms, glossary, requirements and objectives, procedure, related documents and references). The technical supplements had been reviewed by a group of external experts and were being finalized prior to electronic publication. They would be distributed to all regulatory agencies, ministries of health, international organizations, the public and private pharmaceutical industry and supply chain professionals.

The Expert Committee recommended that the documents should be subject to the usual consultation process and should be submitted to the Expert Committee on Biological Standardization and the Expert Committee on Specifications for Pharmaceutical Preparations in 2014.

2.2 International collaboration

2.2.1 Collaboration with international organizations and agencies

United Nations Children's Fund (UNICEF) [1]

The United Nations Children's Fund (UNICEF) was established in 1946 to protect and promote the rights of children. Its core commitments are health

[1] UNICEF presented after the Open session due to unexpected delay.

and nutrition, education, water and sanitation, child protection, and human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS). UNICEF has its headquarters in New York and employs some 10 000 staff worldwide. UNICEF's Supply Division, located in Denmark, carries out procurement and quality assurance of supplies for UNICEF and its partners, with vaccines and pharmaceuticals being the largest commodity groups. Antiretrovirals currently account for the largest share of pharmaceuticals. Inspections of suppliers are carried out to check compliance with WHO GMP guidelines.

The Expert Committee noted the report for 2012 and thanked UNICEF for its continuing support in ensuring that the procurement and supply process adheres to the highest quality standards.

The Global Fund to Fight AIDS, Tuberculosis and Malaria

The work of the Global Fund to Fight AIDS, Tuberculosis and Malaria was summarized for members of the Expert Committee. The Global Fund is an international financing institution but it is the countries that implement the programmes. It was stressed that the Global Fund funding is performance-based. The selection process includes consideration of value for money and high-impact programmes.

The Global Fund has so far funded antiretroviral treatment for 5.2 million people, treatment for 11 million new cases of infectious tuberculosis, and has distributed 340 million insecticide-treated nets. On average, 39% of the funds are used for the procurement of medicines and other health products. It was pointed out that the Global Fund's quality assurance policy includes not only clinical criteria but also quality criteria (i.e. all products should be prequalified) and monitoring of quality throughout the supply chain. The Global Fund's Expert Review Panel (ERP), which is hosted by WHO/EMP/Quality Assurance and Safety: Medicines (QSM), reviews the dossiers of products. The recommendations of the panel have a maximum validity of nine months.

Procurement is done according to model quality assurance system (MQAS) principles and according to national and international laws. The process of quality control conducted by the Global Fund at the various levels of manufacture, procurement, distribution and monitoring was outlined for the Expert Committee on Specifications for Pharmaceutical Preparations.

The Expert Committee noted that WHO/QSM supports the Global Fund through the prequalification programmes for medicines and quality control laboratories, QSM technical expertise, the monographs (on antiretrovirals, artemisinin combination therapies, antituberculosis and anti-infective medicines) of the Ph.Int. and in the development and updating of guidelines.

The Expert Committee thanked the Global Fund for its report and expressed appreciation for its commitment to ensuring the highest quality standards during the procurement and supply process.

International Atomic Energy Agency

The International Atomic Energy Agency (IAEA) provided the Expert Committee with an update on the development of radiopharmaceutical monographs. Since the last meeting of the Expert Committee on Specifications for Pharmaceutical Preparations, consultants' meetings had been organized by IAEA at its headquarters in Vienna in December 2012 and May 2013 to discuss the update of the radiopharmaceutical monographs of the Ph.Int. It was agreed that the radiopharmaceutical monographs should be updated as soon as possible as it was a long time since some had been published and in that time there had been new developments in radiopharmaceuticals and new documentation on them had been published by IAEA. It was also agreed that there should be an attempt to ensure convergence of the radiopharmaceutical texts in different pharmacopoeias and to include such texts in pharmacopoeias that do not yet have them. An annual radiopharmaceutical pharmacopoeia update meeting would be held, with the next one being scheduled for February 2014.

It was noted that an initial review had been completed of all existing technetium 99m monographs. In addition, three monographs had been submitted to the Expert Committee for consideration, nine further monographs were in the final review stage, and completion of the reviews of the remaining monographs was planned by December 2013 (see also section 3.3.4).

The Expert Committee expressed its appreciation for the collaboration with IAEA and thanked the agency for its report.

2.2.2 Pharmacopoeial Discussion Group

The Expert Committee on Specifications for Pharmaceutical Preparations received a report of the most recent meeting of the Pharmacopoeial Discussion Group (PDG), which was hosted by the European Directorate for the Quality of Medicines & HealthCare (EDQM) in Strasbourg, France, in June 2013. The Committee was informed that 28 of the 35 general chapters and 45 of the 62 excipient monographs in the current work programme had been harmonized. The PDG meeting had also approved two new excipient monographs on isomalt and hydroxypropylcellulose and two revisions on saccharin and sodium starch glycolate. Discussion on 18 additional items in the work programme had taken place with a view to resolving outstanding issues. The PDG also discussed expansion of its scope, as regards both its composition and its work programme, including further reflections on interactions with trade associations. The next PDG meeting would be hosted by the Japanese Pharmacopoeia in Tokyo, Japan, in November 2013.

The Expert Committee took note of the report.

2.2.3 International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)

Since the previous Expert Committee meeting the ICH Steering Committee and its expert working groups had met twice (in November 2012 and June 2013). The Steering Committee finalized procedural changes implementing new principles of governance that better define the roles of regulator and industry parties within ICH. From now on, the agendas and the reports of the Steering Committee meetings, as well as the workplans of active expert working groups, will be published on the ICH website. A new ICH organizational structure will be adopted and will set the framework for new rules on governance, decision-making and membership. Two new groups have been established to address evolving science, including one for nonclinical development of medicinal products.

The Q3D expert working group on "Elemental impurities" reached step 2a/2b in June 2013 and the draft guideline had been released for public consultation. The guideline's three elements are the evaluation of the toxicity data for potential elemental impurities, the establishment of a permitted daily exposure (PDE) for each element of toxicological concern, and the development of controls designed to limit the inclusion of elemental impurities in finished pharmaceutical products to levels at or below the PDE. Additionally, the Q7 Informal working group on "Good manufacturing practice guide for active pharmaceutical ingredients" met for the second time with the aim of developing a question and answer document to address current issues raised by the use of the Q7 guideline. This work is carried out in collaboration with the Pharmaceutical Inspection Convention and the Pharmaceutical Inspection Co-operation Scheme (jointly referred to as the Pharmaceutical Inspection Co-operation Scheme (PIC/S)). The next meeting of the ICH would be held in November 2013 in Osaka, Japan.

The Committee noted that the guideline would impact on its own work, especially in the area of the Ph.Int. once the new guideline on elemental impurities, which will apply both to new products and to revisions of existing products, had passed the final step 4. WHO was also part of the discussions in both the ICH and PIC/S contexts. This was considered to be of importance because the WHO GMP for active pharmaceutical ingredients (APIs) is based on the ICH text.

The Expert Committee noted the report and supported the involvement of WHO in the work of ICH. In the area of GMP for APIs it was recommended that the "General notes: additional clarifications and explanations" published together with the WHO GMP texts may need to be revised in light of the outcome of current discussions.

2.2.4 International Conference of Drug Regulatory Authorities

The Expert Committee received a report on the International Conference of Drug Regulatory Authorities (ICDRA) which is a forum for medicines regulatory authorities of WHO Member States to meet and discuss topics of interest and ways to strengthen convergence and collaboration. It is usually attended by regulators from 90–120 Member States. The 15th ICDRA meeting was hosted by the Estonian State Agency of Medicines (with the support of the EDQM for the pre-meeting) in Tallinn, Estonia, in October 2012. The main four-day ICDRA meeting is for regulators only. However, since 2004, the pharmaceutical industry and other interested parties have had the opportunity to attend a two-day pre-meeting, which has a different topic each time (the quality of APIs was the topic in Tallinn). The Expert Committee was informed about the programme, recommendations and major events associated with the 15th ICDRA (for more information please see: http://www.icdra.ee/ and recommendations at: http://www.who.int/medicines/areas/quality_safety/regulation_legislation/icdra/en/).

The 15th ICDRA marked the first time that the session on medical devices had been included in the programme and it was also the first time that a one-day after-meeting, introducing the work of the host agency (held in State Agency of Medicines premises in Tartu), had taken place. ICDRA meetings are held every two years and it was announced that the next will be hosted by the Brazilian regulatory authority, ANVISA, in Rio de Janeiro, Brazil, in August 2014. It is open to all interested parties; the two-day pre-conference meeting will focus on actual regulatory and access issues related to similar biotherapeutic products (biosimilars).

The Expert Committee thanked the WHO Secretariat for the report, which was duly noted.

Asia Pacific Economic Cooperation (APEC) Regulatory Harmonization Steering Committee (RHSC)

The Expert Committee was informed of a recent partnership between the Asia Pacific Economic Cooperation (APEC) Regulatory Harmonization Steering Committee (RHSC) and WHO to develop a mature draft document that is intended to lead to WHO guidelines on good review practices (GRevP). Such a set of guidelines would be the first of its kind globally and would address an important gap identified at the 2012 ICDRA meeting. Although the RHSC does not directly produce guidelines, contributing to WHO guidelines is in line with the RHSC's principle of working with appropriate partners to achieve common objectives. In June 2013 the RHSC convened an expert working group with WHO representation to develop a draft GRevP document, which will cover both medicines and medical devices, for submission to WHO in early 2014. The draft

document would subsequently undergo the required WHO consultation process with a view to further development into WHO guidelines for adoption by the Expert Committee on Specifications for Pharmaceutical Preparations and the Expert Committee on Biological Standardization.

The Expert Committee expressed its support for the initiative.

3. Quality control – specifications and tests

3.1 *The International Pharmacopoeia*

3.1.1 Monographs under elaboration

The Expert Committee noted a list of all monographs on dosage forms, general monographs and other texts that are currently being elaborated or are under revision for eventual adoption by the Expert Committee and subsequent publication in the Ph.Int.

3.1.2 Monographs proposed for elaboration or withdrawal from *The International Pharmacopoeia*

In addition, the Expert Committee received a document proposing monographs for future elaboration for, or withdrawal from, the Ph.Int. The document presented a comparison of medicines for which a monograph has been incorporated in the Ph.Int. with medicines listed according to:

- inclusion on the EML;
- mention on the invitations to manufacturers to submit an Expression of Interest (EOI) to the WHO PQP;
- inclusion in other United Nations/WHO documents recommending use of medicines for treatment of specific diseases and/or for use by treatment programmes.

These three categories were applied to eight groups of monographs. Following this comparison, a number of monographs were proposed for elaboration or withdrawal relating to:

1) maternal and newborn health medicines
2) child and adolescent health medicines
3) antimalarial medicines
4) antiviral medicines
5) antituberculosis medicines
6) neglected tropical diseases medicines
7) noncommunicable diseases and mental health medicines
8) other anti-infective medicines.

A number of monographs were proposed for elaboration if they were listed in one of the above-mentioned publications but a Ph.Int. monograph had not yet been developed, while some were proposed as priorities if they also have not yet been the subject of a monograph in another major pharmacopoeia.

Monographs that had been withdrawn from the EML and that were not mentioned in invitations to manufacturers to submit an EOI to PQP were proposed for withdrawal from the Ph.Int.

The Expert Committee expressed some reservations about withdrawing monographs from the Ph.Int. The Expert Committee asked the Secretariat to prepare, for consideration at its next meeting, a policy describing a set of criteria for withdrawal of monographs from the Ph.Int.

3.2 Specifications for medicines, including children's medicines

3.2.1 Maternal, newborn, child and adolescent health medicines

Medroxyprogesterone acetate

Following the adoption of the monograph on medroxyprogesterone injection at the forty-sixth meeting of the Expert Committee in 2011, it was decided to revise the monograph on medroxyprogesterone acetate. The draft revision was discussed at the consultation on specifications for medicines and quality control laboratory standards in June 2013, after which further comments were solicited and received. The monograph was still subject to consultation. The revised draft was presented to the Expert Committee.

The Expert Committee adopted the monograph subject to further comments on the modification being reviewed by a small group of experts.

Medroxyprogesterone injection

The monograph on medroxyprogesterone injection was adopted by the Expert Committee in 2011 but new changes to the monograph were proposed in order to align the nomenclature of the prescribed reference substances with the draft proposal for revision of the monograph on medroxyprogesterone acetate. The draft revision of the monograph on medroxyprogesterone injection was discussed at the consultation on specifications for medicines and quality control laboratory standards in June 2013 and was presented to the Expert Committee for further consideration.

The Expert Committee adopted the monograph subject to the amendments agreed.

3.2.2 Antimalarial medicines

Chloroquine monographs

Following investigations by a user of the Ph.Int., it was proposed to revise the assay tests in the monographs on chloroquine phosphate tablets, chloroquine sulfate tablets and chloroquine sulfate oral solution. A first draft of the proposed revision was discussed at the consultation on specifications for medicines and

quality control laboratory standards in June 2013 and was submitted to the Expert Committee.

The Expert Committee adopted the monographs subject to the amendments agreed.

3.2.3 Antiviral medicines

Aciclovir API

Following its submission by a WHO Collaborating Centre, the proposed monograph on aciclovir API was discussed at the informal consultation on new medicines, quality control and laboratory standards in June 2013. A subsequent revised draft was circulated for comments, which had been collated, and both the draft and the comments were presented to the Expert Committee for discussion.

The Expert Committee adopted the monograph subject to the amendments agreed.

Aciclovir tablets

Following its submission by a WHO Collaborating Centre, the proposed monograph on aciclovir tablets was discussed at the informal consultation on new medicines, quality control and laboratory standards in June 2013. A subsequent revised draft was circulated for comments, which had been collated, and both the draft and the comments were presented to the Expert Committee for discussion.

The Expert Committee adopted the monograph subject to the amendments agreed.

Aciclovir for injection

Following its submission by a WHO Collaborating Centre, the proposed monograph on aciclovir for injection was discussed at the informal consultation on new medicines, quality control and laboratory standards in June 2013. A subsequent revised draft was circulated for comments, which had been collated, and both the draft and the comments were presented to the Expert Committee for discussion.

The Expert Committee adopted the monograph subject to the amendments agreed.

3.2.4 Antituberculosis medicines

Streptomycin for injection

It was proposed to harmonize the colorimetric identification test in the monograph on Streptomycin for injection in the Ph.Int. with that in the *British Pharmacopoeia* and to delete the requirement for the colour of the solution. The first draft of the revised monograph was discussed at the informal consultation on

new medicines, quality control and laboratory standards in June 2013. The text was subsequently circulated for comments, which had been collated. The revised text, including some suggested editorial changes, was presented to the Expert Committee. The Expert Committee's discussion was facilitated by a laboratory report on streptomycin for injection.

The Expert Committee adopted the monograph subject to the amendments agreed. Future revision of this monograph to replace the microbiological assay should be considered.

3.2.5 Medicines for neglected tropical diseases

Albendazole chewable tablets

Originally prepared by a WHO Collaborating Centre in 2011, the draft proposal for a monograph on albendazole chewable tablets was reviewed and presented to the Expert Committee meeting that year. The draft was then further reviewed before being submitted to the 2012 meeting of the Committee. In April 2012 a second revision of the monograph was undertaken and was discussed by an informal consultation on new medicines, quality control and laboratory standards before being circulated for further review. The reviewed draft was presented to the Expert Committee.

The Expert Committee adopted the monograph subject to the amendments agreed, including the additional dissolution test as discussed during the meeting.

Niclosamide and niclosamide tablets

Following investigations by a WHO Collaborating Centre into pseudopolymorphic and polymorphic forms and transformations of niclosamide, it was proposed to revise the monographs on niclosamide and niclosamide tablets. The first draft of the revisions was prepared in September 2013 and circulated for comments, which had been collated. A laboratory report was provided to support the revisions. The Expert Committee considered the revised monographs.

The Expert Committee adopted the monographs subject to the amendments agreed.

Pentamidine isetionate and pentamidine for injection

Following investigations into the polymorphism of pentamidine isetionate, it was proposed to revise the monographs on pentamidine isetionate and pentamidine isetionate for injection. The first draft of the revision was discussed at the informal consultation on new medicines, quality control and laboratory standards in June 2013, and was subsequently circulated for comments, which

had been collated. Some editorial changes were also proposed. A laboratory report on pentamidine isetionate was submitted to the Committee for information.

The Expert Committee adopted the monographs subject to the amendments agreed.

Sulfamethoxazole and trimethoprim intravenous infusion and oral suspension

The draft monographs on sulfamethoxazole and trimethoprim intravenous infusion and oral suspension were discussed by the Expert Committee in October 2012 when a number of changes were proposed. Both documents subsequently underwent further revision and review, including at the informal consultation to discuss new medicines, quality control and laboratory standards in June 2013. Revised drafts of the two documents were then circulated for further comment, and the comments received were consolidated by the Secretariat.

The Expert Committee adopted the monographs subject to the amendments agreed.

3.2.6 Other anti-infective medicines

Fluconazole, fluconazole capsules and fluconazole for injection

In 2012 the Expert Committee reviewed the drafts of monographs on fluconazole, fluconazole capsules and fluconazole for injection, noted progress in the development of the monographs, and proposed further amendments. Following consideration during the informal consultation to discuss new medicines, quality control and laboratory standards in June 2013, the revised drafts were circulated for comments. The comments received were subsequently consolidated by the Secretariat.

Fluconazole API

Comments received on the monograph on fluconazole API were discussed. The Expert Committee adopted the monograph subject to the amendments agreed.

Fluconazole capsules

Comments received on the monograph on fluconazole capsules were discussed. The Expert Committee noted progress in development of the monograph and requested further revision for review at its next meeting.

Fluconazole for injection

Comments received on the monograph on fluconazole for injection were discussed. The Expert Committee noted the progress in development of the monograph and requested further revision for review at its next meeting.

3.2.7 Other medicines

Testosterone enantate

Subsequent to a proposal to revise the monograph on testosterone enantate to enable the user to perform the assay without the use of a reference substance, a draft revision was presented to the consultation on specifications for medicines and quality control laboratory standards in June 2013. The draft was revised in accordance with the comments received and was discussed by the Expert Committee.

The Expert Committee adopted the monograph subject to the amendments agreed.

3.3 General monographs for dosage forms and associated method texts

Melting temperature and melting range

It has been proposed to list the International Chemical Reference Substances, which are issued to calibrate melting-point instruments, in the general chapter 1.2.1 Melting temperature and melting range of the Ph.Int. Following drafting by the Secretariat, the text was reviewed by the informal consultation to discuss new medicines, quality control and laboratory standards in June 2013. It was subsequently circulated for further review and the comments had been collated before being presented to the Expert Committee. It was noted that comments were particularly sought on alternatives to the previous description of mercury-containing thermometers.

The Expert Committee adopted the general chapter subject to the amendments agreed.

Limits for the test for bacterial endotoxins

At the forty-seventh meeting of the Expert Committee in October 2012 a revision of the general monograph on parenteral preparations was adopted. One of the major changes to the monograph was the required compliance of all parenteral preparations with the test for bacterial endotoxins (or, where justified, pyrogens). Consequently, individual monographs on injectable dosage forms in the Ph.Int. were investigated with a view to adding a limit for bacterial endotoxins to each monograph that currently does not include such a requirement. A document on the introduction of the new limit into the general monograph was drafted in early 2013 and was reviewed at the informal consultation to discuss new medicines, quality control and laboratory standards in June 2013. The revised document was circulated for further review and the comments received had been collated by the Secretariat.

The Expert Committee reviewed the comments received. The Expert Committee requested that the monograph should be revised according to the

amendments agreed during its discussion and should subsequently be circulated for further review.

Revision of information on the strength of medicines

Following the publication of the eighteenth edition of the EML it had been proposed to revise the information given on the strength of medicines under the section on Additional information in the Ph.Int. in order to bring it into line with the respective information in the current EML. To this end a document was prepared for discussion by the Expert Committee.

The Expert Committee noted the proposed changes to the information on the strength of medicines, as well as some changes to the names of some products on the EML, and expressed concern regarding the impact on the accuracy of the strengths in some cases. The Secretariat was asked to look into the matter.

The Expert Committee adopted the revised information subject to the amendments agreed, and to further clarification by the Secretariat.

3.3.1 Supplementary information

Dissolution testing of tablets and capsules

At its forty-seventh meeting in 2012, the Expert Committee adopted a revision of the general monograph 5.5 on dissolution testing for oral solid dosage forms. The revision was based on the internationally-harmonized texts developed by the PDG. As it was not intended that the revision should apply retrospectively, further clarification had been requested by the Expert Committee at its last meeting. To this effect, a document was prepared in December 2012 for inclusion in the Supplementary information section of the Ph.Int. The text was reviewed at the informal consultation on new medicines, quality control and laboratory standards in June 2013. Subsequently it was circulated for wider review and the comments received had been collated. The text was presented to the Expert Committee for consideration and discussion.

The Expert Committee adopted the text for inclusion in the Supplementary information section of the Ph.Int. subject to the amendments agreed.

3.3.2 Reagents, test solutions and volumetric solutions

The Secretariat informed the Expert Committee that the chapter on reagents, test solutions and volumetric solutions was under revision. The aim was to ensure that for all reagents, test solutions and volumetric solutions referred to in monographs, further information would be given in the above-mentioned chapter. A survey had been conducted by a collaborating centre and editorial changes would be incorporated in the next supplement. Other changes would be submitted to the next meeting of the Expert Committee for further review.

3.3.3 General policy

The Secretariat requested the advice of the Expert Committee concerning the General policy of the Ph.Int. The Expert Committee requested the Secretariat to prepare a general document on the criteria under which the Ph.Int. should begin the withdrawal of a monograph. The Expert Committee also requested the Secretariat to develop a policy on the naming of monographs.

3.3.4 Radiopharmaceuticals

Updating radiopharmaceutical monographs of *The International Pharmacopoeia*

A consultants' meeting organized by the IAEA was held on 6–10 May 2013 to discuss the update of the radiopharmaceutical monographs of the Ph.Int. This followed up on previous collaboration between the IAEA and WHO, and on a consultants' meeting held on 3–7 December 2012 at the IAEA headquarters in Vienna, Austria.

The outcome of the May meeting was an agreement to develop a detailed workplan for updating the radiopharmaceutical monographs of the Ph.Int.

It was agreed that these radiopharmaceutical monographs would be updated as soon as possible because some of them had been established for a long time and there had been new developments in radiopharmaceuticals and new documentation had been published by IAEA on radiopharmaceuticals.

A priority list of radiopharmaceuticals which needed urgent attention was drawn up and an updating mechanism was formulated and proposed as part of the overall workplan.

It was felt that the Ph.Int. could be updated without major changes and without placing a major administrative burden on WHO. A regular updating mechanism was proposed for implementation to ensure that the Ph.Int. would be up to date in addressing current issues.

In addition, new radiopharmaceutical monographs were identified that needed to be prepared for submission to the Ph.Int.:

- 5 technetium 99m radiopharmaceuticals,
- 12 PET radiopharmaceuticals,
- 5 radiopharmaceuticals with other radionuclides,
- 7 chemical precursors and accessory medicines.

Template for preparation of radiopharmaceuticals monographs

A consultation held at the IAEA headquarters in May 2013 discussed a process and workplan for updating and developing new monographs for inclusion in the Ph.Int. In this context a template was developed by IAEA staff and was discussed in detail. The template is intended to be used for the current monographs as well

as for new versions that will be developed, for purposes of consistency. Feedback on the proposed process was being sought through the usual consultation process and, within this context, members of the Expert Committee were invited to submit comments which would be forwarded to IAEA.

The Expert Committee noted the template which will be used for the further review of the monographs.

The International Pharmacopoeia updating mechanism for the section on radiopharmaceuticals

The official process for developing monographs for inclusion in the Ph.Int., as outlined in WHO Technical Report Series, No. 970 (Annex 1), was discussed during the consultation held at the IAEA headquarters in Vienna, Austria, on 6–10 May 2012. A proposal was elaborated for the revision process for monographs related to radiopharmaceuticals.

The Secretariat presented to the Expert Committee the 12-stage process for updating the section on radiopharmaceuticals in the Ph.Int. and the procedures to be followed to ensure that the monographs would undergo a thorough review and consultation process, such as occurs for other content of the Ph.Int.

The Expert Committee gave its approval to the process and procedures and expressed its gratitude to IAEA for its readiness to take on the major share of administration and to provide its valuable expertise with regard to the process of revision of the radiopharmaceutical monographs (Annex 1).

General monograph on radiopharmaceuticals

Two joint meetings of WHO and IAEA were held, leading to the revision of the General monograph on radiopharmaceuticals. This monograph is intended to be read in conjunction with the individual monographs on radiopharmaceutical preparations. The first revision of the text was prepared by IAEA and was then discussed at the informal consultation on new medicines, quality control and laboratory standards in June 2013. The draft was then revised and circulated for comments, which were collated by the Secretariat.

The Expert Committee agreed that, in accordance with the approved procedure for the revision of monographs on radiopharmaceuticals, comments on the General monograph on radiopharmaceuticals would be sent to IAEA for further review. The same procedure would be followed for comments received on the following monographs and supplementary information:

- radiopharmaceutical monograph on sodium iodide solution
- radiopharmaceutical monograph on technetium exametazime complex

- radiopharmaceutical monograph on thallous chloride injection
- radiopharmaceuticals, Supplementary information, Methods of analysis: R3, Biological methods
- monographs and radiopharmaceuticals, Supplementary information, Testing – additional guidance
- radiopharmaceuticals, Supplementary information, Safety considerations
- radiopharmaceuticals, Supplementary information, Shelf-life.

4. Quality control – International Reference Materials (International Chemical Reference Substances and Infrared Reference Spectra)

4.1 Update on International Chemical Reference Substances

4.1.1 Overview

International Chemical Reference Substances (ICRS) are used as primary standards in physical and chemical tests that are described in the Ph.Int., as well as for setting official secondary standards. ICRS are used to identify and determine the purity of or conduct an assay of pharmaceutical substances and preparations or to verify the performance of test methods. The standards are officially adopted by the Expert Committee.

4.1.2 Release procedure for International Chemical Reference Substances

The Expert Committee was informed of the implementation of the new release procedure for ICRS agreed in 2012.

4.1.3 Report from the ICRS Board

At its forty-seventh meeting the Expert Committee established the ICRS Board which became operational immediately after the meeting. It was reported that, as of the time of the forty-eighth meeting of the Expert Committee, the ICRS Board had reviewed 19 ICRS establishment or monitoring reports. The decisions taken by the Board led to the adoption of the following reference substances:

- biperiden HCl ICRS 1
- clofazimine ICRS 1
- cytarabine ICRS 1
- dextromethorphan hydrobromide ICRS 1
- gallamine triethiodide ICRS 1
- glibenclamide ICRS 1
- quinidine sulfate ICRS 1
- salbutamol sulfate ICRS 1
- timolol maleate ICRS 1
- valproic acid ICRS 1
- verapamil HCl ICRS 1

The custodian centre for ICRS, EDQM, began distribution of these ICRS immediately after their adoption by the ICRS Board. It was noted that establishment reports were available upon request from the Secretariat.

The Expert Committee endorsed the adoption of the ICRS listed.

It was further reported that the establishment reports on iopanoic acid ICRS 1, metoclopramide HCl ICRS 1, noscapine ICRS 1 and salbutamol ICRS 1 were received shortly before the meeting of the Expert Committee and were still under review.

With regard to tiabendazole ICRS 1, it was pointed out that the Secretariat intended to publish an International Infrared Reference Spectrum (IIRS) of tiabendazole. At the time of the meeting, the release of the ICRS was pending until laboratory tests to record a suitable spectrum had been finalized.

After reviewing the EDQM report on amiloride HCl ICRS 1, the ICRS Board decided to first revise the monograph on amiloride HCl and then to reevaluate the suitability of the characterized candidate material.

The ICRS Board reviewed the EDQM monitoring report on testosterone enantate ICRS which described a new impurity not found during previous monitoring. The standard was evaluated as still suitable for the intended use, as prescribed by the Ph.Int. The chapter on ICRS in the Supplementary information section clarifies that ICRS may also be used in tests and assays not described in the Ph.Int. However, the responsibility for assessing the suitability of the substances then rests with the user or with the pharmacopoeia commission or other authority that has prescribed this use. As it was not possible to exclude the possibility that customers might use the standard in a manner other than that intended, the ICRS Board decided to stop the distribution of testosterone enantate ICRS and to discard remaining vials. The monograph on testosterone enantate would need to be revised with a view to obviating the need for a reference substance (see section 3.2.7 Other medicines).

Following investigations into pseudopolymorphic and polymorphic forms and transformations of niclosamide the ICRS Board proposed to revise the monographs on niclosamide and niclosamide tablets (see section 3.2.5 Neglected tropical diseases medicines). The evaluation of the niclosamide ICRS candidate material was therefore pending until the proposed revisions were adopted.

The Expert Committee expressed its thanks to the members of the ICRS Board for their important contribution to the ICRS approval process.

4.1.4 Draft chapter on reference substances and reference spectra for the Supplementary information section of *The International Pharmacopoeia*

The draft chapter presented to the Expert Committee described principles to be applied during the establishment and use of ICRS, which guarantee that the reference substances are suitable for their intended purpose. The chapter, which was circulated for comments in 2012 and discussed at the forty-seventh meeting of the Expert Committee, was revised and circulated for further comments in 2013. It was then discussed at the informal consultation on new medicines, quality control and laboratory standards in June 2013. The text presented to the

Expert Committee incorporated all the changes the experts had agreed on. It was noted that the chapter would form part of the Supplementary information section of the Ph.Int., which provides the user with texts for guidance and information, and would not constitute part of the standards.

The Expert Committee adopted the chapter as revised.

4.1.5 International Chemical Reference Substances – miscellaneous topics

Distribution of ICRS no longer included in *The International Pharmacopoeia*

The Expert Committee was informed that the Ph.Int. distributed some ICRS which no longer had a pertinent monograph in the pharmacopoeia. It was therefore proposed to withdraw these ICRS and to stop their distribution. The ICRS in question were: carbenicillin monosodium ICRS, cortisone acetate ICRS, desoxycortone acetate ICRS, estradiol benzoate ICRS, ethisterone ICRS, lanatoside C ICRS, meticillin sodium ICRS, nafcillin sodium ICRS, quabain ICRS, oxacillin sodium ICRS, prednisone ICRS, prednisone acetate ICRS and tolnaftate ICRS.

The Expert Committee approved the proposal to withdraw these ICRS and to discontinue their distribution.

ICRS with new and additional intended uses

As a result of recent monograph revisions, the intended uses of some ICRS have been extended. Previously, assays were described using absolute methods which often did not require reference substances. However, because of the introduction of new separation techniques, in particular for assay or to test for related substances, several reference substances that were established only for identification purposes have to be requalified in comprehensive analytical investigations to adapt or to extend their previous intended uses.

Because of the time these laboratory studies can take, the publication of a revised monograph often precedes the requalification of the ICRS mentioned in it. While a monograph describes the use of an ICRS, the information about what purpose the standard is qualified for is found in the leaflet that accompanies the reference standard.

It was proposed to draw users' attention to this situation by publishing a relevant note on ICRS on the WHO and EDQM websites.

The Expert Committee concurred with the proposal and agreed that the following note should be posted on the websites of WHO and EDQM:

> **"Note from the Secretariat of *The International Pharmacopoeia* – Intended use of ICRS:**
>
> The International Pharmacopoeia *constantly develops new monographs and revises existing ones to stay abreast of advances in analytical science*

and regulatory affairs. Along with these changes the intended use of already established ICRS often needs to be adjusted, for example, because an ICRS previously used for identification only shall newly also be employed in quantitative tests.

The user of The International Pharmacopoeia *finds information on the actually established intended uses of an ICRS in the leaflet enclosed with the substance when distributed or accessible via the ICRS online database (http://www.edqm.eu/en/who-icrs-reference-standards-products-1384.html). The information found in current leaflets is applicable to all standards of the respective batch number."*

The Committee noted that similar phrases had already been included in the chapter on Reference substances and reference spectra for the Supplementary information section of *The International Pharmacopoeia*.

Priorities for establishing ICRS

In view of the need to prioritize the establishment of certain ICRS, the Expert Committee discussed a proposed priority list.

At its forty-seventh meeting in 2011, the Expert Committee decided to revise the monograph on artemisinin and to align it to the specification for artemisinin used as a starting material in line with the document *Recommendations for quality requirements when artemisinin is used as a starting material in the production of antimalarial active pharmaceutical ingredients* adopted by the Expert Committee at its forty-sixth meeting. At its forty-eighth meeting, the Expert Committee was informed that the revised monograph would be published in the next supplement of the Ph.Int. Artemisinin ICRS would be suitable for both specifications as they would differ only in their requirements but not in the methods prescribed.

The Expert Committee reviewed the priority list and agreed to assign high priority to capreomycin sulfate, tenofovir disoproxil fumarate, emtricitabine and artemisinin ICRS. The Expert Committee also took note of the additional information provided concerning artemisinin ICRS.

4.2 Report of the custodian centre for ICRS

4.2.1 Annual report

The Expert Committee received from EDQM the 2012 annual report on the establishment, storage, distribution and monitoring of ICRS for the Ph.Int. During the year 17 reports on new ICRS were adopted or proposed for adoption and regular teleconferences were held between EDQM and the WHO Secretariat. A total of 1087 ICRS were distributed, with 43% sent to the WHO European

Region, 21% to the African Region, 14% to the Region of the Americas, 9% to the Western Pacific Region, 9% to the South-East Asia Region and 5% to the Eastern Mediterranean Region. It was noted that the new system of approval of ICRS through the ICRS Board had accelerated the approval process.

The Expert Committee expressed its thanks to EDQM for the report and for establishing the ICRS. The extensive technical expertise and experience in providing primary reference standards is highly appreciated.

4.2.2 Update on the annual report

In a 2013 update on its annual report, EDQM noted that the establishment report on dextromethorphan hydrobromide had been issued and adopted by the ICRS Board, a further five ICRS reports had been issued, two establishment studies were under way and the adoption of four ICRS was pending. In addition, nine monitoring studies had been performed in 2013, bringing the total to 15. It was noted that some difficulties remained, but the system had improved considerably and collaboration between EDQM and WHO was good. During the year EDQM had been awarded international accreditation of ISO-17025.

The Expert Committee thanked EDQM for the update and expressed appreciation for the good collaboration.

5. Quality control – national laboratories

5.1 External Quality Assurance Assessment Scheme

The External Quality Assurance Assessment Scheme (EQAAS), which is a programme for the external evaluation of quality control management systems in chemical control laboratories, was established in 2000 at the request of the Global Fund and is conducted in collaboration with EDQM. Using interlaboratory comparisons, the programme determines the performance of participating laboratories in carrying out specific tests or measurements. The Scheme supplements laboratories' internal quality assurance procedures by providing an external measure for their testing capabilities. Some 60 laboratories participated in Phase 5 of EQAAS.

5.1.1 Final report on EQAAS 5.6

The Expert Committee received the final report on Procedure 6 (Dissolution test) of EQAAS Phase 5. Fifty-two participants submitted their results for this study in which each laboratory received the testing sample (10 capsules each labelled as containing 150 mg of rifampicin) and one vial of rifampicin reference substance RS (100 mg). The laboratories were required to determine the percentage of rifampicin released by the capsules after 30 minutes according to the analytical method described in the Ph.Int. monograph on rifampicin capsules.

The feasibility study carried out at the EDQM laboratory showed no problems, either with the method or with the sample. However, the individual values reported by the laboratories were not as expected and showed high variability, indicating a possible problem when performing the dissolution test that could be linked to the specific product tested in the study. It was noted that, as a consequence of these results, it was decided not to assess the performance of the laboratories. Rather, the proficiency testing would provide the participants with comparative material so that they could interpret their own data in the light of performance of other laboratories and draw their own conclusions for corrective actions where appropriate.

The Expert Committee noted the report.

5.1.2 Preliminary report on EQAAS 5.7

A preliminary report on Phase 5, Procedure 7 (Assay by titration) was presented to the Expert Committee. Forty-eight participants submitted their results for this study. Each laboratory received the testing sample (1 vial containing 100 mL of chloroquine sulfate oral solution with a declared content of 50 mg chloroquine/5 mL) and the protocol. They were requested to determine the amount of chloroquine in the sample according to the titration method described in the Ph.Int. monograph on chloroquine sulfate oral solution, but

using dichloromethane as the extraction reagent instead of chloroform. Forty of the 48 laboratories (83%) reported satisfactory results and three reported questionable results. It was judged that five laboratories needed to investigate their procedures and take action to improve their performance.

The Expert Committee noted the report.

5.1.3 EQAAS Phase 6 proposals

Phase 6 of EQAAS was planned to cover the years 2014 to 2016. The Expert Committee noted and supported the intended types of tests to be conducted in this phase.

The Expert Committee noted that there had been some consideration of proposals for changes to the EQAAS, such as the introduction of a user fee. The Committee supported the suggestion that the Secretariat should look into the necessary changes to ensure the continuation of this important programme.

5.2 Networking

The Secretariat had been using email as the means for communication with participants in the EQAAS but in view of the developments in communications technology it was felt that other means might be more efficient. The Expert Committee was requested to provide suggestions regarding effective means of electronic communications with partners and collaborators. Tools used by the *British Pharmacopoeia*, the Pan American Health Organization, the Association of South-East Asian Nations (ASEAN) and National Official Medicines Control Laboratories (NOMCoL) (for Africa) were mentioned as possible models for the Secretariat to consider for interlaboratory communication tools.

5.3 Training materials for quality control laboratories and microbiological laboratories

This issue is discussed in section 6.4.

The Expert Committee expressed its gratitude for the update.

6. Quality assurance – good manufacturing practices

6.1 Updates of WHO good manufacturing practices

Proposed updated text for WHO GMP for pharmaceutical products: main principles

At its forty-seventh meeting in 2012 the Expert Committee had noted that a number of European Union and US Food and Drug Administration (FDA) GMP guidelines had been updated. The Expert Committee had requested the Secretariat to make a proposal on how to revise the WHO GMP guidelines in the light of these other new guidelines. Following drafting in late 2012, the working document was circulated for comments in early 2013 and was discussed during the joint informal consultation with the prequalification inspection team and inspectors from national inspectorates. A subgroup of expert inspectors then finalized the new draft for further circulation. The feedback received was reviewed with the prequalification inspection team prior to submission of the document to the Expert Committee. The document put before the Expert Committee at its forty-eighth meeting comprised a table showing the newly proposed text of the WHO GMP guidelines beside the existing text. The proposed changes were explained and discussed by the members of the Committee.

The Expert Committee considered the proposed changes and approved the document subject to the amendments agreed (Annex 2).

GMP for biologicals

The GMP for biologicals were first published in 1992 and a WHO team had been updating the document. Drafting began in 2013, a consultation would be held in 2014, and the document would be presented to the Expert Committee on Specifications for Pharmaceutical Preparations and the Expert Committee on Biological Standardization in 2015, with a view to adoption.

GMP for excipients

There is an ongoing international effort to update the GMP for excipients but there had been no concrete proposal presented to WHO. In light of this, the Expert Committee encouraged the Secretariat to look into the need for revision of this text and to report its findings at its next meeting.

6.2 Update of WHO good manufacturing practices: validation

Proposal for revision of the supplementary guidelines on good manufacturing practices: validation, Appendix 7: non-sterile process validation

The need for revision of the published guidelines on validation of GMP had been identified by PQP. The main concern related to Appendix 7 (Non-sterile process validation) of the *Supplementary guidelines on good manufacturing*

practices: validation.[2] A draft document was circulated widely for comment in early 2013 and the feedback was discussed at an informal consultation on quality assurance guidelines held in July 2013. Comments from inspectors were being collated and reviewed by the Secretariat. A revision of the document would be circulated for comments in due course.

The principles described in the revised guidelines, which allow for different approaches in process validation, are applicable to non-sterile finished pharmaceutical dosage forms. Thorough knowledge of product and process development studies, previous manufacturing experience, and quality risk management principles are essential in all approaches to process validation as the focus is on the life-cycle approach which links product and process development, validation of the commercial manufacturing process and maintenance of the process during routine commercial production. The revised guidelines recommend a risk-based approach to validation, linked to in-line or online controls and monitoring to ensure that a process is properly controlled during routine manufacture.

It was noted that comments were also being sought as to whether Appendix 3 (Cleaning validation) should be revised in line with developments on setting health-based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities.

The Expert Committee asked the Secretariat to process the comments and circulate the document accordingly.

6.3 General guidance for inspectors on "hold-time" studies

Because the quality and stability of starting materials, intermediate products, bulk and finished products should be ensured at all stages of manufacture, GMP require that the maximum allowable "hold time" should be established to ensure that in-process and bulk product can be held, pending the next processing step, without any adverse effect on the quality of the material. Consequently a document providing guidance to inspectors on hold-time studies – which establish the time limits for holding the materials at different stages of production by assuring that the quality of the product does not deteriorate during the hold time – was drafted in late 2012. After circulation for comments in early 2013, the document was further reviewed by inspectors collaborating with WHO/PQP as well as during a joint informal consultation of the prequalification inspection team and inspectors from national inspectorates. Follow-up with expert inspectors led to a new draft of the document being circulated and

[2] The current text of the Supplementary guidelines (WHO Technical Report Series, No. 937, 2006, Annex 4) is available at: http://www.who.int/medicines/areas/quality_safety/quality_assurance/SupplementaryGMPValidationTRS937Annex4.pdf.

further feedback from the prequalification inspection team was provided. It was noted that hold times should normally be determined prior to marketing of a product and following any significant changes in processes, equipment, starting and packaging materials.

The Expert Committee reviewed the comments received on the document. A small working group was established to review all comments received and to prepare for the circulation of a revised document.

6.4 Training materials

The series of WHO GMP training modules was presented to the Expert Committee for information. The training materials on the basic principles of GMP consist of 10 modules, and there are supplementary modules on topics such as sterile pharmaceutical products, validation and water. In addition there are three training modules on quality control, as well as two-part modules on good practices for pharmaceutical microbiology laboratories and on transfer of technology. All training modules are available on CD-ROM and will be made available on the WHO website.

The Expert Committee welcomed the report.

7. Quality assurance – new initiatives

7.1 International meetings of world pharmacopoeias

Since the first meeting of the world pharmacopoeias, the Secretariat had been collating information on the different pharmacopoeias. The draft working document "Review of world pharmacopoeias" was presented to the Expert Committee. This document presented a summary of the answers to the "Questions to pharmacopoeias" provided by representatives of world pharmacopoeias participating in the international meeting and other related information received from representatives who were unable to actively participate in this meeting.

The Expert Committee considered the Review of world pharmacopoeias document to be very useful and requested the Secretariat to regularly review and maintain the document to ensure that it reflects current information.

7.2 Good pharmacopoeial practices

In 2012 several meetings – including the first international meeting of world pharmacopoeias, the FIP-WHO conference during the FIP Centennial Congress, the 15th ICDRA International Meeting, and the forty-seventh meeting of the Expert Committee – supported the idea of developing good pharmacopoeial practices to harmonize approaches and policies in establishing pharmacopoeial standards. A number of pharmacopoeias agreed to participate in an initial drafting group. It was agreed that development of the harmonized good pharmacopoeial practices would take place under the auspices of the Expert Committee, benefiting from its well-established international standard-setting processes and procedures. The final guidance would then be presented to WHO's 194 Member States and pharmacopoeial authorities.

The Expert Committee received a concept paper noting that the primary objective of the guidance contained in the WHO good pharmacopoeial practices (GPhP) is to harmonize approaches and policies for establishing pharmacopoeial standards, which will support regulatory authorities in controlling the quality of pharmaceutical ingredients and their finished products and other materials, and that will provide a tool by which the user or procurer can make an independent judgement regarding quality. While the implementation of GPhP by national and regional pharmaceutical authorities is voluntary, it is recommended and encouraged, since a high level of participation will result in greater benefit to stakeholders and ultimately to patients.

The draft table of contents of GPhP and the concept paper were reviewed by all the representatives of pharmacopoeias, leading to a first draft of the GPhP with a new structure thanks to the active contribution of the representatives of the world pharmacopoeias. This first draft of the GPhP was circulated to all world pharmacopoeias for comment. The feedback received was then further reviewed

during the second international meeting of world pharmacopoeias hosted by the Indian Pharmacopoeia Commission and WHO, with the support of FIP, in New Delhi in April 2013. The concept paper was also reviewed during the informal consultation to discuss new medicines, quality control and laboratory standards in June.

Encouraging positive feedback had been received on this new initiative, not only from pharmacopoeias, but also from industry, nongovernmental organizations and others.

Following receipt of the updated chapters of the GPhP from the world pharmacopoeias, the text would be shared with all world pharmacopoeias for further feedback and would be discussed at the third international meeting of world pharmacopoeias. It was noted that the representatives of the pharmacopoeias wished to prepare a draft that they could agree on, and this would then be subject to the usual WHO review process.

The Expert Committee thanked the Secretariat for the progress report.

7.3 FIP-WHO technical guidelines

In March 2011 the Expert Committee on the Selection and Use of Essential Medicines, which has a subcommittee on children's medicines, considered the preliminary draft guidance on extemporaneous preparation of medicines for children, which had been commissioned by WHO. This Expert Committee felt that extemporaneous preparation of medicines for children might be necessary in some situations but was concerned about the risks of inappropriate preparations. The Committee also considered the risks of diverting efforts aimed at the development of age-appropriate dosage forms for children and indicated that WHO's endorsement of extemporaneous use should not be seen as indicating a lack of need for commercially available paediatric dosage forms.

The comments of the Committee were discussed during the informal consultation on paediatric and generics guidelines development in May 2011, held under the auspices of the WHO Expert Committee on Specifications for Pharmaceutical Preparations. The experts agreed to prepare a time-limited version, to send out the working document widely for comments, and to report the outcome to the Expert Committee on Specifications for Pharmaceutical Preparations.

The revised document was considered at the forty-sixth and forty-seventh meetings of the Expert Committee. In early 2013 there was a further review of comments received and of the recommendations of the Expert Committee, and an in-depth discussion took place between the Secretaries of the FIP Expert Group and the WHO Expert Committee on Specifications for Pharmaceutical Preparations. This was followed by the preparation of a new

working document which was circulated for comments and then by discussion in the Expert Committee on the Selection and Use of Essential Medicines. Feedback was collated and further discussion between WHO and FIP ensued.

The document presented to the Expert Committee on Specifications for Pharmaceutical Preparations at its forty-eighth meeting was entitled *FIP-WHO Technical Guidelines: provision by health-care professionals of children-specific preparations that are not available as authorized products – points to consider*. This change was intended to indicate that extemporaneous preparations for children should be used only if children-specific preparations were not available. The document states that children should have access to authorized, age-appropriate preparations of medicines and that children with swallowing difficulties, or who are being fed by tube, should have access to formulations that facilitate the safe and effective administration of medication. Nothing in the document should detract from this objective; however, it was recognized that such preparations would not always be available and a safe and effective alternative must be sought. The document defined children broadly in order not to restrict applicability to a small age range. It was also pointed out that the document would be most applicable to use in resource-limited settings.

The Expert Committee considered the document and reviewed the comments received and proposed alternative text where appropriate. The Committee concluded that the document was not ready for adoption and recommended further consultation and review.

7.4 Screening technologies for "suspect" medicines

At its forty-seventh meeting in 2012, the Expert Committee was briefed on screening technologies that drew attention to the use of screening tests that had been deliberately prepared to produce positive results. In addition, it was reported that WHO was increasingly receiving requests from countries for assistance in dealing with suspect medicines. The Expert Committee expressed concern at this issue and a discussion took place about the possibility of preparing a guidance document describing the various screening technologies. In this regard the Secretariat presented an outline of the proposed content for a possible guidance document on rapid detection technologies, based on techniques currently used in most countries, with examples of rapid detection technologies in research and in use in China. It was noted that for some methods the main cost was the purchase of equipment but that once the equipment had been purchased the running costs would be low.

An oral report was received on screening in Singapore where a large database of substances and screening materials had been developed. Most of the spurious/falsely-labelled/falsified/counterfeit (SFFC) medical products identified were so-called "western drugs".

The Expert Committee supported the development of a guidance document on rapid detection technologies. The document should provide an overview and describe the different techniques available for use and their implementation.

7.5 Laboratory functions survey regarding testing of spurious/falsely-labelled/falsified/counterfeit medical products

In order to support WHO in the prevention and control of medical products of compromised quality, safety and efficacy, such as SFFC medical products, the WHO Collaborating Centre for the Quality Assurance of Medicines at North-West University, South Africa, conducted a survey to assess the extent and current practices used by pharmaceutical quality control laboratories to evaluate SFFC products. Responses from 39 laboratories from 39 countries revealed that the main activities of all the laboratories included the quality assurance/quality control testing of medicines and/or medical devices. Some 28 laboratories (72%) indicated that they were actively participating in the testing of SFFC products in their respective countries. Thirty-five of the 39 participants (90%) indicated that they considered SFFC products to be a problem in their country.

Various techniques are reported in the literature for the detection of SFFCs, although most of them are extremely intricate and require expensive equipment. The various methods used by the participant laboratories were classified into three categories, namely chromatography, spectrophotometry and other techniques. Ninety-seven per cent of the participant laboratories expressed a need for standard operating procedures (SOPs) for the testing of SFFCs and indicated that their laboratories would benefit both from such guidance and from training sessions. It was noted that permission from the laboratories concerned would be required before the final results of the survey could be made public.

The Expert Committee thanked the Secretariat for conducting the survey and noted the expressed need for SOPs for the testing of SFFCs. The Expert Committee recommended that the Secretariat should prepare a draft of such SOPs for consideration at its next meeting.

8. Quality assurance – distribution and trade of pharmaceuticals

8.1 WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce

8.1.1 Update

The WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce is an international voluntary agreement to provide information to countries which participate in the Scheme about the quality of pharmaceutical products moving in international commerce. The Scheme was first endorsed by the World Health Assembly in 1969 and had been revised several times since, with each revision being endorsed by the World Health Assembly.

In 2010, WHO made a request to its Member States for information regarding their use of the Scheme. Responses have so far been received from 12 Member States. Nevertheless, Member States consistently refer to the value of the Scheme and it had been reported that the pharmaceutical industry regarded the WHO Certification Scheme as an important tool. However, an extension of the Scheme on the certification of starting materials has evoked limited interest from Member States.

The Expert Committee took note of the report.

8.1.2 Proposed letter to Member States

The primary document of the Scheme is the Model Certificate of Pharmaceutical Product. It was proposed to send to Member States a circular letter regarding their use of the Certificate of Pharmaceutical Product, together with a questionnaire requesting basic information such as the contact addresses of the respective competent authorities.

The Expert Committee noted the letter and endorsed the new initiative to gather further information on the Scheme.

8.2 Monitoring and surveillance of the national supply chain

8.2.1 Project update

The Expert Committee received a report from WHO on a rapid alert system for suspect SSFFCs in the national pharmaceutical supply chains. WHO had developed an online reporting form for the systematic and structured reporting of incidents involving suspected SSFFC medical products in order to enable regulatory authorities to react rapidly to a problem situation. This system was developed following two consultative meetings with Member States and a four-month pilot study. In 2013 the system was rolled out to the African Region

and the Eastern Mediterranean Region, and staff from 57 countries had been trained. Some 133 regulatory inspectors, pharmacovigilance and laboratory experts attended three-day regional workshops.

When WHO receives an alert report, the originator is contacted by WHO to discuss the incident further – within 72 hours if no adverse reactions are reported and within 24 hours if adverse reactions are reported. WHO assesses each incident with a focus on risks to public health and geographical risks. The system automatically compares the incident with others in the database and provides a notification if matches are found. Analysis helps identify common weaknesses in the supply chain, the medicines most at risk and the regions concerned. The system had so far received reports relating to more than 190 different batches of medical products from all WHO regions. All therapeutic categories are affected, from inexpensive paracetamol through to expensive oncology products, generics and innovator products, and a range of dosage forms. They have been reported from hospitals, clinics, surgeries, pharmacies, street markets and the Internet.

The short-term objective of this project is to provide coordination and technical support, including facilitation of laboratory testing. The long-term objective is to reduce the harm caused to public health by SSFFC medical products by applying proportionate and sustainable measures to protect supply chains.

The Expert Committee noted the report.

8.2.2 Proposal for a procedure on sampling and market surveillance survey

Following the recommendation made by the Expert Committee at its forty-sixth and forty-seventh meetings in 2011 and 2012 the Secretariat commissioned the development of guidance for sampling procedures based on examples obtained from many countries as feedback to the Secretariat's proposal for a procedure on sampling and market surveillance and on a first proposal presented in 2012. This first proposal was based on an existing survey protocol developed by the WHO Prequalification Laboratory Programme, which had been extensively involved in the establishment of survey protocols for major studies for antimalarial and antituberculosis medicines.

The Expert Committee noted in 2012 that the document would be of particular importance in monitoring and post-marketing surveillance and agreed that it should be further developed as a general document to provide advice on sampling for various groups of medicines. The Expert Committee also noted the need for separate, specific guidance in relation to SFFC medical products.

A comprehensive draft working document, which would be prepared for public consultation in due course, was presented to the Expert Committee for comments.

The Expert Committee noted this information and thanked the Secretariat for the draft working document.

8.3 Proposal for revision of good trade and distribution practices for starting materials

8.3.1 Good trade and distribution practices for pharmaceutical starting materials

At its forty-seventh meeting in 2012 the Expert Committee discussed the possible revision of WHO's guide on Good trade and distribution practices for pharmaceutical starting materials. Due to new developments and concepts, it was felt that there was a need for further improvement of both the WHO guide and the good distribution practices (GDP) guide for pharmaceutical excipients, which was issued by the International Pharmaceutical Excipients Council (IPEC) and was aligned with the WHO document. The IPEC Federation proposed a revision and update of the WHO good trade and distribution practices guide and offered its support in providing a proposal which could be developed by member groups of the IPEC Federation. If adopted, following the usual process of review and consultation, the IPEC Federation would then update its own guide in line with that of WHO. It was reported that a variety of comments had been received with differing views about the extent of the revision, with some requesting the inclusion of further elements and others putting forward the view that the revision went beyond what was appropriate in many situations. The issue of repackaging and relabelling had been extensively discussed in previous consultations and a decision had been made that this aspect should remain in the revised document as this was a problematic area in the supply chain.

The IPEC proposal for revision of the WHO guide, including a comparison of the original and revised texts, was presented to the Expert Committee for its consideration. The Expert Committee asked that a subgroup of the Committee be formed to address the issues raised. The subsequent revision would be circulated for further comments.

8.4 Procurement agencies

8.4.1 Model quality assurance system for procurement agencies

Originally adopted by the Expert Committee in 2005, the model quality assurance system (MQAS) for procurement agencies has been widely used. In 2011 WHO and the Global Fund to Fight AIDS, Tuberculosis and Malaria agreed on the need for a revision of the MQAS and for an assessment tool for procurement agencies. The MQAS was revised and the assessment tool developed in a consultative process. In 2012, at its forty-seventh meeting, the Expert Committee endorsed the proposal for a revision of the MQAS and proposed a number of amendments to the draft. It was noted that the MQAS documentation was critical for the work of the Global Fund.

Further revision of the MQAS and drafting of the proposed assessment tool took place in early 2013. The working document was discussed at an

informal joint consultation of the Global Fund and the WHO Quality Assessment Programme. A newly revised draft was prepared on the basis of that discussion and was circulated for comments. The revision of the MQAS resulted in several documents, namely:

- the newly proposed revised text of the MQAS;
- a revised product questionnaire;
- an assessment tool, together with an inspection report format;
- an aide-memoire for the inspection.

These working documents were submitted to the Expert Committee for consideration.

8.4.2 Assessment tool for procurement agencies

General principles

Since the MQAS was adopted, several organizations have prepared tools to assess procurement agencies with regard to their level of implementation of and compliance with the MQAS.

In view of the variety of tools, WHO and the Global Fund agreed in 2011 to develop a harmonized tool that could be used by all organizations and agencies. Consequently, a working group consisting of representatives from the Committee for Medicinal Products for Human Use (CHMP), Crown Agents, Global Drug Facility (GDF), International Committee of the Red Cross (ICRC), International Development Association (IDA), Médecins Sans Frontières (MSF), Management Sciences for Health (MSH), Partnership for Supply Chain Management (PFSCM), Quality Medicines for All (QUAMED), International Union Against Tuberculosis and Lung Disease (The Union), United Nations Children's Fund (UNICEF), United Nations Office for Project Services (UNOPS) and the United States Agency for International Development (USAID), was created to develop a harmonized assessment tool. The Global Fund Secretariat, which coordinated the process, contracted a consultant through a competitive process to prepare a harmonized assessment tool based on the MQAS, WHO *Guidelines on good storage practices*, and WHO *Guidelines on good distribution practices*. The working group considered the assessment tool thoroughly.

The assessment tool follows the six modules of the MQAS. The logical flow considered is the quality system and infrastructure of the procurement agency under assessment, how the agency performed prequalification and then purchasing of the products followed by the receipt and storage thereof. The last two modules on the receiving of orders and dispatch of products are followed by the re-evaluation concept. This assessment tool is a typical example of a checklist that can be used by a procurement agency when carrying out a self-inspection (Annex 3).

Model inspection report

During the revision of the MQAS and the development of a harmonized assessment tool, the need for a model inspection report to ensure standardization of findings became clear. The draft inspection tool was submitted to the Expert Committee for consideration.

Aide-memoire for inspection

The aide-memoire for inspection, which was presented to the Expert Committee for consideration, is intended to be used when assessing a procurement agency for compliance with the MQAS. It was noted that the tool was intended for use by qualified and experienced persons when assessing procurement agencies (including wholesalers and distributors) (Annex 4).

8.4.3 Product questionnaire

Interagency finished pharmaceutical product questionnaire

The interagency finished pharmaceutical product questionnaire, which was presented to the Expert Committee for consideration, is part of the package of materials developed as a result of the revision of the MQAS for procurement agencies.

The Expert Committee reviewed the product questionnaire together with the comments received. Following discussion, it was agreed that a small subgroup of the Expert Committee should meet to discuss a number of specific technical issues and to finalize the document.

The Expert Committee adopted the revised MQAS, along with its annexes (assessment tool, model inspection report, aide-memoire, and product questionnaire), including further revisions of the product questionnaire by a subgroup of the Committee.

9. Prequalification of priority essential medicines

9.1 Update on the Prequalification Programme managed by WHO

9.1.1 Progress report

The Expert Committee was informed that, during restructuring, the three WHO Prequalification Programmes (for medicines, vaccines, and diagnostics) had been brought together in one administrative unit (Prequalification Team). However, it was noted that the product specificities will be retained. In addition to prequalification itself, the Programmes conduct training activities and have a fellowship programme whereby national regulatory staff spend time working with the Prequalification Team in Geneva.

The Committee was given an update on PQP, managed by WHO, a United Nations programme that aims to ensure that key health products are safe, appropriate and meet stringent quality standards for international procurement. It does so by assessing product dossiers, inspecting manufacturing and testing sites, organizing quality control testing of vaccines and medicines, validating the performance of diagnostics and verifying that the products are suitable for use in the destination countries. It was pointed out that the vaccines and diagnostics prequalification programmes have implemented a cost-recovery mechanism and a nominal fee is now also being introduced for the medicines programme.

As of June 2013, 397 finished pharmaceutical products (FPPs) had been prequalified since PQP began in 2001, and 44 of these FPPs were undergoing review for requalification. Some 150 products were currently under assessment and 82 new applications had been received in 2012. It was noted that the majority of the 9.7 million people currently on HIV treatment in low- and middle-income countries were taking prequalified antiretroviral medicines. More than 280 million treatment courses of prequalified artemisinin-based combination therapy (ACT) were sold in 2011 to treat malaria. It was stressed that the norms and standards developed and approved through the Expert Committee sustain all of PQP's activities.

The Expert Committee expressed its gratitude for the report and congratulated PQP on its continuing efforts to ensure the quality of medicines, vaccines and diagnostics.

9.2 Revision of guidelines for prequalification of finished pharmaceutical products approved by stringent regulatory authorities

9.2.1 Guidelines on submission of documentation for prequalification of finished pharmaceutical products approved by stringent regulatory authorities

WHO recognizes the scientific evaluation of FPPs by regulatory authorities which apply stringent standards for quality, safety and efficacy that are similar

to those recommended by WHO. Where an applicant and a stringent regulatory authority (SRA) agree to share with WHO certain specific information on an FPP, WHO is prepared to consider the FPP for inclusion in the list of WHO-prequalified products, as and when information about the product is made available to WHO and the applicant expresses an interest in the product being prequalified. In this regard the information required is listed in the guidelines.

The need for a revision of the published WHO *Guidelines on submission of documentation for prequalification of innovator finished pharmaceutical products approved by stringent regulatory authorities* was identified by PQP, and a draft revision was circulated for comments in May 2013. The revised draft was then discussed in a joint informal consultation of the Medicines Quality Assurance and Prequalification of Medicines Programmes on interchangeability of multisource products and prequalification guidance. The draft was subsequently further revised and circulated for further comments before being presented to the Expert Committee. It was noted that, because the guidelines for innovator products and multisource (generic) products were very similar, the revision of the guidelines on the former had been extended to include the latter. The title was accordingly changed to *Guidelines on submission of documentation for prequalification of finished pharmaceutical products approved by stringent regulatory authorities*.

The Expert Committee reviewed the revised guidelines together with the comments received and after further revision adopted the guidelines (Annex 5).

10. Prequalification of active pharmaceutical ingredients

10.1 Update on the prequalification of active pharmaceutical ingredients

The API prequalification procedure was begun in October 2010 with the intention of publishing a list of APIs that had been assessed by PQP for compliance with both quality and GMP requirements. Applications are made by API manufacturers independent of any application for prequalification of a medicine (similar to the certificate of suitability procedure). However, applications are restricted to those APIs listed in the current API invitation for EOI. This list reflects those APIs required to produce FPPs invited for FPP prequalification.

Both the numbers of APIs prequalified and the numbers of applications received continue to exceed expectations. Currently there are 48 APIs prequalified and a further 52 applications under assessment. By comparison, figures reported at the 2012 meeting of the Expert Committee were 23 APIs prequalified and 39 under evaluation. In addition, it was also notable that during 2012–2013 there was prequalification of the first Chinese-sourced API and of the first API used in the therapeutic area of reproductive health.

The Expert Committee expressed appreciation for the report.

11. Prequalification of quality control laboratories

11.1 Update on the prequalification of quality control laboratories

The prequalification procedure for quality control laboratories was established in 2004 for Africa only and has since expanded globally. Any quality control laboratory (whether public or private) may now participate in the programme. Participation is voluntary and 63 laboratories have asked to participate since 2004 (75% being national quality control laboratories). The focus is on pharmaceutical testing (testing of vaccines and biologicals is not included). Currently 27 laboratories have been prequalified, with at least one in each WHO region. The programme also includes capacity building, with training provided for national quality control laboratories in developing countries. Technical assistance has so far been provided to 36 laboratories (including 13 in 2013).

The benefits of prequalification to quality control laboratories include the possibility to provide testing services to United Nations agencies and other organizations, the recognition that comes from being listed as a WHO-prequalified laboratory, the learning process of improving laboratory standards and the possibility of being assisted by WHO expert consultants and of participating in WHO-organized training.

The Expert Committee expressed its appreciation for the report.

11.2 Update on WHO quality monitoring projects

PQP organizes quality monitoring of medicines projects to monitor the quality of prequalified products and of medicines procured by United Nations agencies. As these projects are organized in cooperation with national medicines regulatory authorities (NMRAs), they contribute to the quality control of medicines in WHO Member States and to capacity-building. The Expert Committee was informed that two such projects were ongoing.

In response to a complaint of poor quality, a survey of the quality of antimalarials supplied within phase 1 of the Affordable Medicines Facility malaria project, which is managed by the Global Fund, was being conducted. Complaint procedures were initiated by prequalification inspectors following random inspections of manufacturers and on the basis of samples and documentation. Samples were collected in Ghana, Nigeria and Uganda, including at delivery points and at pharmacies. The lowest artemisinin content was around 90%. Testing was carried out in accordance with manufacturers' methods and specifications and approved during the prequalification process. Suspicion of significantly substandard quality was not confirmed and the validity of the relevant monograph in the Ph.Int. was not called into question. A detailed report was being prepared.

A second quality survey was conducted within the project of the United Nations Commission on Life-Saving Commodities for Women and Children with the objective of identifying products of good quality, or of a quality that could be improved in a short period of time. One of the recommendations of the strategy (Recommendation 4) is that, by 2015, at least three manufacturers per commodity will be manufacturing and marketing quality-certified and affordable products in each of 49 Every Woman Every Child (EWEC) countries.

In this context, a survey was under way to identify products of good quality or of a quality that can be improved in a short period. Samples of 12 medicines identified by the Commission were being collected in 10 countries in Africa and Asia and would be sent to testing laboratories.

The Expert Committee expressed its appreciation for the report.

12. Regulatory guidance

12.1 Pharmacovigilance and "quality defect" reporting

The Expert Committee received a report on WHO's work on pharmacovigilance. Since SSFFC products can be difficult to detect in the supply chain, the report suggested that pharmacovigilance databases could be exploited to accumulate data on SSFFCs. The Medical Dictionary for Regulatory Activities (MedDRA) is a set of terminologies used to report adverse drug reactions (ADRs) and events to the WHO (global) and national pharmacovigilance databases. Twenty-four MedDRA terms refer to product "inadequacy", and clusters of reports of product "inadequacy" in the WHO global ADR database may reflect cases of SSFFC medicinal products. Currently, efforts are under way to identify further reporting terms that could be related to SSFFC products.

The WHO Collaborating Centre (the Uppsala Monitoring Centre (UMC)) and EMP have developed an algorithm to detect clusters of reports that are suggestive of SSFFCs within the 8 million ADR reports in WHO's global database. The algorithm identifies clusters of unexpectedly high reporting of specific events that may reflect product inadequacy, such as those that correspond to a lack of effect or an unintended effect. By comparing the relative reporting rates for the same medicine across the database, the algorithm identifies temporal and geographical deviations.

This algorithm was successfully piloted by WHO and UMC in 2012 on specific known events of SSFFC medical products, with several national pharmacovigilance centres. Future work will aim to further validate the algorithm for a proof of concept and its practical application in routine monitoring of pharmacovigilance data to detect SSFFCs, with the assistance of six national pharmacovigilance centres. The algorithm will be applied to all data in the WHO database with a view to finding suspected SSFFC cases in a specified period. Participating national centres will be invited to investigate whether the event highlighted in the WHO database corresponds to a real case of SSFFC in their country. In a proactive approach, the algorithm will also be used to create a "watch list" of products to be kept under surveillance for potential cases of SSFFCs.

The Expert Committee noted the report.

12.2 Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product: quality part

The document *Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product (FPP): quality part* was presented to the Expert Committee for consideration. The document, which provides recommendations on the quality information on APIs and FPPs that should be

submitted to NMRAs to support product dossiers, is technically and structurally related to the generic quality guidelines.[3] The resulting guidance document is proposed for wider use by NMRAs. The guidelines are intended to promote effective and efficient processes for the development of product dossiers by applicants and the subsequent assessment procedures by NMRAs. The document adopts the modular format of the Common Technical Document – Quality (M4Q) as developed by ICH.

Alternative approaches to the principles and practices described in this document could be acceptable provided they are supported by adequate scientific justification. It was also noted that NMRAs may request information or material, or define conditions, not specifically described in this guidance.

The development of the document was recommended at the forty-seventh meeting of the Expert Committee in 2012 and was drafted and circulated for comments in early 2013. Comments were reviewed in the joint informal consultation on interchangeability of multisource products and prequalification guidance of the Medicines Quality Assurance and Prequalification of Medicines Programmes. A revised draft was then recirculated and further comments received.

The Expert Committee adopted the document subject to the amendments agreed (Annex 6).

12.3 Proposal for general guidance on variations

The Expert Committee noted that the process of preparing general guidance on variations was under way.

12.4 Guidelines on registration requirements to establish interchangeability (bioequivalence)

WHO published *Multisource (generic) pharmaceutical products: Guidelines on registration requirements to establish interchangeability* in 2006.[4] In preparation for the revision of the WHO document, the Expert Committee received a report that compared the WHO guidance on interchangeability with that of the European Medicines Agency (EMA) and the United States Food and Drug Administration (US FDA). Guidance issues proposed for revision were highlighted. It was stated that a first draft of the revision would be available in due course. The Committee was also asked to consider to what extent WHO guidance should extend to non-

[3] WHO Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part. WHO Technical Report Series, No. 970 (Annex 4)

[4] Annex 7 in WHO Technical Report Series, No. 937.

biological complex drugs (NBCDs). The Committee agreed that guidance for this new group of products might be relevant if they were included in the EML and asked the Secretariat to look into it.

The Expert Committee noted the progress report.

12.5 Update of biowaiver list based on the WHO Model List of essential medicines

At its forty-seventh meeting in 2012, the Expert Committee encouraged efforts to update WHO's biowaiver guidance. At its forty-eighth meeting, the Committee received a report comparing the biowaiver guidance of WHO with that of EMA and US FDA. It was noted that the current list of the biopharmaceutics classification system (BCS) includes only medicines listed in the twelfth edition of the EML. It was emphasized that the BCS tables should be updated in line with the eighteenth edition of the EML and that the use of the BCS tables must be more clearly described in the accompanying text since there have been reports that the tables have been misinterpreted. Work on revision of the biowaiver document would be carried out in parallel with the update of the *Guidelines on registration requirements to establish interchangeability*.

The Expert Committee noted the report.

12.6 Update of International Comparator Products List and related guidance on selection of comparator products for equivalence assessment of interchangeable multisource (generic) products

The selection of an appropriate comparator pharmaceutical product is essential for assessment of the equivalence of interchangeable multisource (generic) products. WHO published its first guidance on comparator products in 2002.[5] At its forty-seventh meeting in 2012, the Expert Committee pointed out the need for updating this guidance and the WHO list of international comparator pharmaceutical products. At its forty-eighth meeting, the Committee received a progress report on the updating.

The guidance on selection of comparator products is being revised to harmonize it with the prequalification process and to give national regulatory authorities more and clearer options. In this regard it was proposed that the original decision-tree for use in identifying comparator pharmaceutical products, and intended as an information tool for national regulatory authorities and

[5] Annex 11, WHO Technical Report Series, No. 902.

pharmaceutical manufacturers, should also be changed. The Expert Committee reviewed two possible decision-trees – one for national regulatory authorities and one for PQP. It was also proposed to divide the list of comparators into two groups – oral products and other products – although it was noted that the collaborating centre would be able to update only the comparator list for oral products following each revision of the EML. Thus WHO would need to identify a group that would be willing to keep the list of non-oral products up to date.

The Expert Committee noted progress in the development of this guidance.

13. Nomenclature, terminology and databases

13.1 Quality assurance terminology

In October 2011 the Expert Committee created a subgroup to review the list of terms and definitions to ensure its standardization and potentially to reduce the number of definitions for each term. Progress in this area was slower than anticipated due to the departure of the staff member responsible. Work in this area would be restarted in the near future.

13.2 International Nonproprietary Names for pharmaceutical substances

The International Nonproprietary Names (INN) nomenclature scheme for cell therapy products, which was under development, was presented to the Expert Committee. In this scheme it was proposed that *–cel* would be the common stem with a preceding infix that would designate the cell type, in line with the United States Adopted Name (USAN) scheme. A variety of infixes for different cell types would be created. For genetically modified cells, a two-word name was proposed, with the first word indicating the nature of the gene involved and the second word indicating the cell.

The Expert Committee was informed that a discussion on an INN proposal for similar biotherapeutics products (SBPs) took place during the fifty-sixth INN Consultation as well as during an INN ad hoc meeting attended by biological experts of the INN Expert Committee and representatives of worldwide regulatory agencies. INN for SBPs follow general naming principles and there are no specific means of identifying them as SBPs within their INN. The current naming situation is such that non-glycosylated SBPs have the same INN while glycosylated SPBs are likely to have a different name from their reference product due to potential differences in their glycoforms, this being achieved by the use of a Greek letter, although in neither case is the reference product identified within the INN. Comparability studies are usually performed between an SBP and its reference product; two separate SBPs may be compared to the same reference but usually not to each other. Thus, switching between SBPs may not be desirable from a medical point of view and the INN experts therefore considered assigning INNs that may distinguish between one SBP and another and between the SBP and the reference product. It is the mandate of the WHO INN Programme to ensure clear identification of pharmaceutical substances, both chemical and biological. The INN experts felt that the best way to do this was through nomenclature, with involvement of the INN Programme in developing a unique global qualifier. The aim would be to try to avoid non-unified qualifiers being assigned to SBPs by individual regulatory bodies.

The Expert Committee heard that it is proposed that an SBP should have a two-part name; the first part would be the INN of the reference product while the second part would be a qualifier that would indicate that this is an SBP and would identify it as a particular SBP or biological substance. To achieve this WHO could assign the qualifier according to an agreed policy or could produce a policy document according to which regulatory authorities could produce the fantasy suffix or code. Alternatively WHO could issue an advice document laying out a naming convention for use by NMRAs. It was stressed, however, that all regulatory authorities would need to support a global system.

In response to a question, it was pointed out that INN are the responsibility of the Expert Committee on Specifications for Pharmaceutical Preparations. However, because of the wide-ranging nature of its work, the Programme also consults with other WHO Expert Committees when this is appropriate.

During its discussion the Expert Committee expressed concern about the risk of biotherapeutic products not being named in accordance with a unified global system and welcomed WHO's efforts to establish a global system.

The Expert Committee noted the report on the work of the INN Programme.

14. Miscellaneous

14.1 Strategy

14.1.1 References

Quality assurance of pharmaceuticals CD-ROM

The Expert Committee was informed that a CD-ROM was now available containing a compendium of all current WHO guidelines and related materials in quality assurance. The compendium was a replacement and update for the compendium issued in 2010. The new compendium includes a study pack of the WHO training modules on GMP, as well as a large set of training materials reflecting the various GMP texts. A flyer advertising the CD-ROM had also been produced.

The International Pharmacopoeia, Fourth edition, First, Second and Third Supplements

The Expert Committee was further informed that a CD-ROM was now available containing the First, Second and Third Supplements of the Fourth edition of *The International Pharmacopoeia*. The CD-ROM contains all monographs, amendments and additions, as adopted by the Expert Committee. This latest version of the Fourth edition will not be produced in print as the electronic version is intended to replace all previous versions in a user-friendly form. A flyer advertising this CD-ROM has also been produced.

Forty-seventh report of the Expert Committee

It was reported that the forty-seventh report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations had been published in 2013 and was now available in the WHO Technical Report Series, No. 981.

The Expert Committee welcomed the publication of the CD-ROMs and of the report of the previous meeting and thanked the Secretariat for the materials produced.

The meeting was closed by Dr L. Rägo with thanks to all participants.

15. Summary and recommendations

The WHO Expert Committee on Specifications for Pharmaceutical Preparations advises the Director-General of WHO in the area of medicines quality assurance. It provides recommendations and guidance to ensure that medicines meet identical standards of quality, safety and efficacy in all WHO Member States.

Since its creation in 1947, the Expert Committee's original role of developing *The International Pharmacopoeia* (Ph.Int.) has expanded in light of globalization and new technologies. Today it provides independent expert advice, developed through a broad consensus-building process, covering all areas of quality assurance of medicines from their development to their distribution to patients. The Committee's implementation-ready norms and standards enable countries to move forward towards universal access to safe, quality-assured medicines for their people.

At its forty-eighth meeting from 14 to 18 October 2013, the Expert Committee heard updates from the WHO Expert Committee on Biological Standardization and the WHO Expert Committee on the Selection and Use of Essential Medicines, as well as from international organizations and standard-setting bodies that form part of its collaboration network. Progress with jointly-developed standards and guidelines was reviewed, and areas for further collaboration were discussed. Noting the reports of the Global Fund to Fight AIDS, Tuberculosis and Malaria, the International Atomic Energy Agency (IAEA) and from the United Nations Children's Fund (UNICEF), the Expert Committee welcomed the commitment by these and other international organizations to implement WHO-recommended quality standards in medicines procurement.

The Expert Committee reviewed new and revised specifications and general texts for quality control testing of a wide range of medicines. It adopted a number of texts and monographs for inclusion in the Ph.Int. and endorsed the adoption and withdrawal of International Chemical Reference Substances (ICRS) as proposed by the ICRS Board. The Expert Committee noted the report on proficiency testing under Phase 5 of the External Quality Assurance Assessment Scheme (EQAAS) and supported proposals for the continuation of this important programme into Phase 6 and for continued funding. The Committee welcomed new initiatives for collaboration among world pharmacopoeias and noted the positive feedback received from industry, nongovernmental organizations and others on this work.

In the various quality assurance-related areas the Expert Committee adopted revised guidelines on manufacture, regulation and the WHO model quality assurance system (MQAS) for procurement agencies, including a harmonized assessment tool developed with input from a wide range of international procurement agencies. Guidance on good distribution practice and

on sampling and quality control testing in countries was discussed, including approaches to combat medicines of suspect quality. In this regard, the Committee heard a project update on the WHO rapid alert system for suspect medicines in national supply chains and noted the outcomes of a survey on quality control laboratory practices to detect such medicines. As part of the report on WHO's work on pharmacovigilance, the Expert Committee was informed of a proposed algorithm to generate warning signals of possible medicines' quality defects in countries, from WHO's global adverse events reporting database.

The Expert Committee heard an update from the new WHO unit that oversees the prequalification of vaccines, medicines, diagnostics and medical devices for procurement by international organizations. With regard to pharmaceuticals this work is based on the Expert Committee's norms and standards and is a source of important feedback for development of guidelines. The Committee welcomed the sustained rapid progress with prequalification of finished pharmaceutical products, APIs and quality control laboratories and the activities undertaken to monitor the quality of medicines procured by United Nations agencies. It noted that all prequalification work is conducted in close collaboration with regulators around the world, thus building regulatory capacity that will enable national authorities to implement unified, international quality standards for medicines across WHO Member States.

A full list of decisions and recommendations made by the Expert Committee at its forty-eighth meeting is given below.

The following guidelines were adopted and recommended for use:

- *The International Pharmacopoeia* – updating mechanism for the section on radiopharmaceuticals (Annex 1)
- WHO good manufacturing practices for pharmaceutical products: main principles (Annex 2)
- Model quality assurance system for procurement agencies, including appendices (model inspection report and product questionnaire) (Annex 3)
- Assessment tool based on the model quality assurance system for procurement agencies: aide-memoire for inspection (Annex 4)
- Guidelines on submission of documentation for prequalification of finished pharmaceutical products approved by stringent regulatory authorities (Annex 5)
- Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product: quality part (Annex 6)

For inclusion in *The International Pharmacopoeia*

The Expert Committee adopted the following monographs subject to the agreed amendments:

- *For maternal, newborn, child and adolescent health medicines:*
  - medroxyprogesterone acetate (revision)
  - medroxyprogesterone injection (revision)
- *For antimalarial medicines:*
  - chloroquine phosphate tablets (revision)
  - chloroquine sulfate tablets (revision)
  - chloroquine sulfate oral solution (revision)
- *For antiviral medicines:*
  - aciclovir API (new)
  - aciclovir tablets (new)
  - aciclovir for injection (new)
- *For antituberculosis medicines:*
  - streptomycin for injection (revision)
- *For neglected tropical diseases:*
  - albendazole chewable tablets (new), including the additional dissolution test as discussed during the meeting
  - niclosamide (revision)
  - niclosamide tablets (revision)
  - pentamidine isetionate (revision)
  - pentamidine isetionate for injection (revision)
  - sulfamethoxazole and trimethoprim intravenous infusion (new)
  - sulfamethoxazole and trimethoprim oral suspension (new)
- *For other anti-infective medicines:*
  - fluconazole (new)
- *For other medicines:*
  - testosterone enantate (revision)

- *General monographs for dosage forms and associated method texts:*
  - General chapter 1.2.1: Melting temperature and Melting range (revision)
  - Information on the strength of medicines in the Additional information section, subject to further clarification by the Secretariat
- *For inclusion in the Supplementary information section:*
  - Chapter on dissolution testing of tablets and capsules
  - Chapter on reference substances and reference spectra
- The Committee endorsed the adoption of the following International Chemical Reference Substances (ICRS) approved by the ICRS Board:
  - biperiden hydrochloride ICRS
  - clofazimine ICRS
  - cytarabine ICRS
  - dextromethorphan hydrobromide ICRS
  - gallamine triethiodide ICRS
  - glibenclamide ICRS
  - quinidine sulfate ICRS
  - salbutamol sulfate ICRS
  - timolol maleate ICRS
  - valproic acid ICRS
  - verapamil hydrochloride ICRS
- The Committee approved withdrawal of the following ICRS, which no longer had a pertinent monograph in *The International Pharmacopoeia*:
  - carbenicillin monosodium ICRS
  - cortisone acetate ICRS
  - desoxycortone acetate ICRS
  - estradiol benzoate ICRS
  - ethisterone ICRS
  - lanatoside C ICRS
  - meticillin sodium ICRS
  - nafcillin sodium ICRS

  - quabain ICRS
  - oxacillin sodium ICRS
  - prednisone ICRS
  - prednisone acetate ICRS
  - tolnaftate ICRS

- *The Expert Committee further approved:*
  - A new 13-step process and procedures for updating the section on radiopharmaceuticals in *The International Pharmacopoeia* in close collaboration with the IAEA (Annex 1)
  - An explanatory note on the intended uses of ICRS as proposed at the meeting, for publication on the websites of WHO and the ICRS custodian centre at the European Directorate for the Quality of Medicines and HealthCare (EDQM).

Recommendations

The Expert Committee made the recommendations listed below in the various quality assurance-related areas. Progress on the suggested actions should be reported to the Committee at its forty-ninth meeting.

Collaboration of pharmacopoeias and good pharmacopoeial practices

- Regularly review and maintain the information on the different pharmacopoeias published in the Review of World Pharmacopoeias on the WHO website.
- Invite input from all world pharmacopoeias to the draft text on *Good pharmacopoeial practices* prior to its submission to the usual consultative WHO review process.
- Work towards convergence of radiopharmaceutical texts in different pharmacopoeias through annual radiopharmaceutical pharmacopoeia update meetings convened by the IAEA.

The International Pharmacopoeia

- Continue development of monographs, general methods and texts and general supplementary information, including radiopharmaceutical monographs developed by IAEA, in accordance with the workplan and as decided at this meeting.
- Develop a policy on the naming of monographs.

- Develop a policy defining criteria for withdrawal of monographs.
- Establish ICRS for the priority substances agreed at the meeting.

External Quality Assurance Assessment Scheme (EQAAS)

- Continue the EQAAS for pharmaceutical quality control laboratories in Phase 6.
- Look into necessary changes to ensure continuation of the programme, including funding.

Good review practice

- Continue working with the Asia Pacific Economic Cooperation (APEC) Regulatory Harmonization Steering Committee (RHSC) on the draft WHO guidelines on Good review practices, for submission to WHO in early 2014 and subsequent consultative review for adoption by the Expert Committee on Specifications for Pharmaceutical Preparations and the Expert Committee on Biological Standardization.

Manufacturing

- Continue the revision of the *Supplementary guidelines on good manufacturing practices: validation*, *General guidance for inspectors on "hold-time" studies* and *Good manufacturing practices for biologicals*.
- Look into the need to revise the guidelines on *Good manufacturing practices for excipients*.
- In light of the outcome of current discussions on the ICH good manufacturing practices for active pharmaceutical ingredients, consider revision of the General notes: additional clarifications and explanations published together with the WHO good manufacturing practices (GMP) texts.

FIP-WHO technical guidance for health care professionals

- With the International Pharmaceutical Federation (FIP), continue the development of the joint technical guidance on points to consider in extemporaneous preparation of children's medicines that are not available as authorized finished products.

Good distribution and storage practices

- Further develop the revision proposed by the International Pharmaceutical Excipients Council (IPEC) Federation on WHO *Good trade and distribution practices for starting materials* through a Committee subgroup.
- Circulate the 18 technical supplements to the *Model guidance for storage and transport of time- and temperature-sensitive pharmaceutical products* for comment prior to submission to both the Expert Committee on Biological Standardization and this Expert Committee in 2014.

Post-marketing surveillance

- Develop a guidance document on rapid detection technology.
- Prepare draft standard operating procedures for quality control testing of "suspect" medicines in pharmaceutical quality control laboratories for consideration at the forty-ninth meeting of the Expert Committee.
- Develop a general guidance document on sampling of medicines types in countries.
- Develop separate, specific guidance on the sampling for detection of spurious/falsely-labelled/falsified and counterfeit (SFFC) products.
- Send a circular letter to WHO Member States with a questionnaire on their use of the certificate of pharmaceutical product.

Regulatory guidance

- Continue developing a general guideline on variations.
- Continue the revision of the *Multisource (generic) pharmaceutical products: Guidelines on registration requirements to establish interchangeability* and WHO guidance on biowaivers to align them with current regulatory practice and with the eighteenth edition of the WHO Model List of essential medicines (EML).
- Continue the revision of guidance on the selection of comparator products.

WHO databases

- Maintain the International Nonproprietary Names (INN) database and continue to make it available on the WHO website, ensure clear identification of chemical and biological pharmaceutical substances, including biotherapeutic products.
- Continue making WHO quality assurance guidelines and related materials available on CD-ROM and on the WHO website.
- Continue to further review the list of terms and definitions covered by this Expert Committee and to make it available on the website.

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Annex 1

The International Pharmacopoeia – Updating mechanism for the section on radiopharmaceuticals

Based on the official process for developing monographs for inclusion in *The International Pharmacopoeia* (Ph.Int.) as outlined in World Health Organization (WHO) Technical Report Series, No. 970 (Annex 1), the following process was elaborated to fit the specific purpose of development and update of radiopharmaceutical specifications, a joint project between the International Atomic Energy Agency (IAEA) and WHO, in close collaboration with the Council of Europe (CoE) and other parties prepared to join.

- Phase 1: Identify a specific radiopharmaceutical specification that needs to be revised and/or developed in a joint meeting of IAEA/WHO/CoE experts, following confirmation by the parties concerned (i.e. IAEA and WHO). Identify "radiopharmacy experts" to review material and suggest additions or deletions or modifications as appropriate. Include and update the current workplan on the Ph.Int. website accordingly.
- Phase 2: Identify the information on specifications available in the *European Pharmacopoeia*, other pharmacopoeias and nuclear medicine resources. Arrange for draft monographs to be prepared. This work supported by IAEA will be undertaken by individual experts and consultants through research contracts and/or supporting consultancy meetings. IAEA should invite suitable experts with pharmacopoeia experience to strengthen the process.
- Phase 3: Mail draft specifications to the IAEA Technical Officers and WHO Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations and to specialists, provide drafts on the Ph.Int. website, in accordance with the WHO Expert Committee on Specifications for Pharmaceutical Preparations and IAEA consultative processes.
- Phase 4: WHO will forward any feedback received to IAEA for review by IAEA experts.
- Phase 5: If applicable, discuss comments received during the consultation process with IAEA specialists, contract laboratories and, if relevant, with the International Chemical Reference Standards custodian centre (this arrangement to be confirmed by the European

Directorate for the Quality of Medicines & HealthCare (EDQM)) and a specialized agency, as necessary (to be further reviewed with IAEA and EDQM).

- Phase 6: The outcome of the IAEA review will be communicated to WHO.
- Phase 7: Recirculate draft monograph for comments as in Phase 3.
- Phase 8: Repeat Phases 3–7 until the agreed draft is suitable for adoption.
- Phase 9: Present the drafts to WHO for possible formal adoption. If not adopted repeat Phases 3–7 as often as necessary. If the draft is adopted, proceed to Phase 10.
- Phase 10: Incorporate all changes agreed during the discussion leading to adoption together with any editorial corrections.
- Phase 11: In all cases, confirm the amended text by correspondence with the IAEA experts before making it available on the Ph.Int. website.
- Phase 12: Make "final texts" available on the Ph.Int. website to provide users with the approved specifications in advance of the next publication date.
- Phase 13: Include in the Ph.Int.

Annex 2

WHO good manufacturing practices for pharmaceutical products: main principles[1]

[1] The current document is a revision of WHO Good manufacturing practices for pharmaceutical products: main principles, previously published in WHO Technical Report Series, No. 961, 2011, Annex 3.

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 medicines 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 1 and 2 are reproduced in this document (*1*). "Quality management in the medicines industry: philosophy and essential elements", outlines the general concepts of quality assurance (QA) 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 QA.

These two parts were subsequently supplemented by further guidelines which are integral parts of these GMP for pharmaceutical products. All these texts are available on the Medicines web page (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 (*2–5*). Thus there is a necessity to revise the main principles and incorporate the concept of validation.

Among other items of feedback discussed during the consultation on WHO guidelines for medicines quality assurance, quality control (QC) laboratories and transfer of technology on 27–31 July 2009, the need was identified to incorporate a new section on "Product quality review" under Chapter 1: "Quality assurance".

In addition, several updates were suggested to further enhance the guidelines. These included the concept of risk management, replacing "drugs" by the term "medicines" and introducing the concept of a "quality unit".

During 2012 the Secretariat was made aware that the current *Good manufacturing practices (GMP) for pharmaceutical products: main principles*, published as Annex 3 in the WHO Technical Report Series, No. 961, 2011, would need updating (http://www.who.int/medicines/areas/quality_safety/quality_assurance/production/en/index.html – Quality assurance of pharmaceuticals: a compendium of guidelines and related materials).

The WHO Expert Committee on Specifications for Pharmaceutical Preparations discussed the need for an update during its forty-seventh meeting and agreed to pursue the matter accordingly.

The following sections were updated in the newly revised version and, after the usual consultation process, were presented to the forty-eighth Expert Committee for adoption:

Section: **Pharmaceutical quality system**

Section 2: **2. Good manufacturing practices for pharmaceutical products**

Section 7: **Contract production, analysis and other activities**

Section 17: **17. Good practices in quality control**

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 medicines inspectors, as well as for production, QC and QA personnel in the industry.

The guide is applicable to operations for the manufacture of medicines 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 guides,[2] and they may be adapted to meet individual needs. The equivalence of alternative approaches to QA, 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 has also been recently recommended (WHO Technical Report Series, No. 961, 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 (INN) 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.

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

[2] The word "should" in the text means a strong recommendation.

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 or pharmaceuticals, 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 100 ml or more in one container of the finished dosage form.

manufacture. All operations of purchase of materials and products, production, quality control (QC), 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 medicines 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 1 (*6*).

quality control. See Part 1 (*6*).

quality unit(s). An organizational unit independent of production which fulfils both quality assurance (QA) and quality control (QC) responsibilities. This can be in the form of separate QA and QC units or a single individual or group, depending upon the size and structure of the organization.

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 medicine, bulk process intermediate (final biological bulk intermediate) or bulk product of a single batch or 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 medicines 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 medicines industry: philosophy and essential elements[3]

In the medicines industry at large, quality management is usually defined as the aspect of the 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 "QA". Within an organization, QA serves as a management tool. In contractual situations, QA also serves to generate confidence in the supplier. The concepts of QA, GMP, QC and quality risk management (QRM) are interrelated aspects of quality management and should be the responsibility of all personnel. They are described here in order to emphasize their relationship and their fundamental importance to the production and control of pharmaceutical products.

1. Pharmaceutical quality system

1.1 *Principle*. 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.

[3] 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); and in: *Quality assurance of pharmaceuticals. A compendium of guidelines and related materials. Volume 2*, 2nd updated edition. *Good manufacturing practices and inspection*. Geneva, World Health Organization, 2007; and in: *Quality assurance of pharmaceuticals. A compendium of guidelines and related materials*. Geneva, World Health Organization, 2010 (CD-ROM).

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 company, the company's suppliers and the distributors. To achieve this quality objective reliably there must be a comprehensively designed and correctly implemented pharmaceutical quality system (PQS) incorporating GMP and QRM

1.2 Senior management has the ultimate responsibility to ensure an effective PQS is in place, is adequately resourced, and that roles, responsibilities, and authorities are defined, communicated and implemented throughout the organization. Senior management's leadership and active participation in the PQS is essential. This leadership should ensure the support and commitment of staff at all levels and sites within the organization to the PQS.

1.3 Quality management 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 management, therefore, incorporates GMP and other factors, including those outside the scope of this guide, such as product design and development.

1.4 GMP applies to the life-cycle stages from the manufacture of investigational medicinal products, technology transfer, and commercial manufacturing, through to product discontinuation. The PQS can extend to the pharmaceutical development life-cycle stage and should facilitate innovation and continual improvement and strengthen the link between pharmaceutical development and manufacturing activities. All parts of the PQS should be adequately resourced and maintained, including being provided with sufficient competent personnel, suitable premises, equipment and facilities.

1.5 The PQS appropriate to the manufacture of pharmaceutical products should ensure that:

a) product realization is achieved by designing, qualifying, planning, implementing, maintaining and continuously improving a system that allows the consistent delivery of products with appropriate quality attributes;

b) product and process knowledge is managed throughout all life-cycle stages;

c) pharmaceutical products are designed and developed in a way that takes account of the requirements of GMP and other associated codes

such as those of good laboratory practice (GLP) and good clinical practice (GCP);

d) production and control operations are clearly specified in a written form and GMP requirements are adopted;

e) managerial responsibilities are clearly specified in job descriptions;

f) arrangements are made for the manufacture, supply and use of the correct starting and packaging materials, the selection and monitoring of suppliers and for verifying that each delivery is the correct material from the approved supply chain;

g) all necessary controls on starting materials, intermediate products, and bulk products and other in-process controls, calibrations and validations are carried out;

h) the finished product is correctly processed and checked, according to the defined procedures;

i) pharmaceutical products are not sold or supplied before the authorized persons (see also sections 9.11 and 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;

j) processes are in place to assure the management of outsourced activities;

k) satisfactory arrangements exist to ensure, as far as possible, that the pharmaceutical products are stored, distributed and subsequently handled so that quality is maintained throughout their shelf-life;

l) there is a procedure for self-inspection and/or quality audit that regularly appraises the effectiveness and applicability of the PQS;

m) product and processes are monitored and the results taken into account in batch release, in the investigation of deviations and, with a view to taking preventive action to avoid potential deviations occurring in the future;

n) arrangements are in place for the prospective evaluation and approval of planned changes and their approval prior to implementation taking into account regulatory notification and approval where required. After implementation of any change, an evaluation is undertaken to confirm that the quality objectives were achieved and that there was no unintended adverse impact on product quality;

o) regular reviews of the quality of pharmaceutical products are conducted with the objective of verifying the consistency of the process and identifying where there is a need for improvement;

p) a state of control is established and maintained by developing and using effective monitoring and control systems for process performance and product quality;

q) continual improvement is facilitated through the implementation of quality improvements appropriate to the current level of process and product knowledge;

r) there is a system for QRM;

s) deviations, suspected product defects and other problems are reported, investigated and recorded. An appropriate level of root cause analysis is applied during such investigations. The most likely root cause(s) should be identified and appropriate corrective actions and/or preventive actions (CAPAs) should be identified and taken. The effectiveness of CAPAs should be monitored.

1.6 There should be periodic management reviews, with the involvement of senior management, of the operation of the PQS to identify opportunities for continual improvement of products, processes and the system itself. Unless otherwise justified, such reviews should be conducted at least annually.

1.7 The PQS should be defined and documented. A quality manual or equivalent documentation should be established and should contain a description of the quality management system including management responsibilities.

Quality risk management

1.8 QRM is a systematic process for the assessment, control, communication and review of risks to the quality of the medicinal product. It can be applied both proactively and retrospectively.

1.9 QRM should ensure that:

- the evaluation of the risk to quality is based on scientific knowledge, experience with the process and ultimately links to the protection of the patient;
- the level of effort, formality and documentation of the QRM process is commensurate with the level of risk.

Product quality review

1.10 Regular, periodic or rolling quality reviews of all pharmaceutical products, including export-only products, should be conducted with the objective of verifying the consistency of the existing process and the appropriateness of current specifications for both starting materials and finished product, to highlight any trends and to identify product and process improvements.

Such reviews should normally be conducted and documented annually, taking into account previous reviews, and should include at least:

a) review of starting materials and packaging materials used for the product, especially those from new sources and in particular the review of supply chain traceability of active substances;
b) a review of critical in-process controls, and finished product results;
c) a review of all batches that failed to meet established specification(s) and their investigation;
d) a review of all significant deviations or non-conformances, the related investigations and the effectiveness of resultant CAPAs taken;
e) a review of all changes made to the processes or analytical methods;
f) a review of dossier variations submitted, granted or refused;
g) a review of the results of the stability monitoring programme and any adverse trends;
h) a review of all quality-related returns, complaints and recalls and the investigations performed at the time;
i) a review of adequacy of any other previous corrective actions on product processes or equipment;
j) post-marketing commitments for new dossiers and variations to the dossiers;
k) the qualification status of relevant equipment and utilities, e.g. heating, ventilation and air-conditioning (HVAC), water or compressed gases and a review of the results of monitoring the output of such equipment and utilities;
l) a review of technical agreements to ensure that they are up to date.

The manufacturer and, where different, marketing authorization holder, should evaluate the results of the review and an assessment should be made as to whether CAPA or any revalidation should be undertaken, under the PQS. CAPAs should be completed in a timely and effective manner, according to documented procedures. There should be procedures for the ongoing management and review of these actions, and the effectiveness of these procedures should be verified during self-inspection. Quality reviews may be grouped by product type, e.g. solid dosage forms, liquid dosage forms, or sterile products, where scientifically justified. Where the marketing authorization holder is not the manufacturer, there should be a technical agreement in place between the various parties that defines their respective responsibilities in producing the quality review. The authorized person responsible for final batch certification, together with the marketing authorization holder, should ensure that the quality review is performed in a timely manner and is accurate.

2. Good manufacturing practices for pharmaceutical products

2.1 GMP is that part of quality management which ensures that products are consistently produced and controlled according to the quality standards appropriate to their intended use and as required by the marketing authorization, clinical trial authorization or product specification. GMP is concerned with both production and QC. GMP is aimed primarily at managing and minimizing the risks inherent in pharmaceutical manufacture to ensure the quality, safety and efficacy of products. Under GMP:

a) all manufacturing processes are clearly defined, systematically reviewed for associated risks in the light of scientific knowledge and 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) sufficient and 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) procedures are carried out correctly and personnel are trained to do so;

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 with the objective of determining the root cause and appropriate corrective and preventive action is implemented;

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 and takes account of good distribution practices (GDP);

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 medicines. 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 ongoing 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 for 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 Particular attention should be 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 that the product that gave rise to a complaint was defective.

5.5 Any complaint concerning a product defect should be recorded with all the original details and thoroughly investigated. The person responsible for QC 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, a suspect product 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 or 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, analysis and other activities

7.1 *Principle*. Contract production, analysis and any other activity covered by GMP 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 production and analysis, including technology transfer and 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 and activities of the contract acceptor or mutually agreed subcontractors.

7.4 In the case of contract analysis, the final approval for release must be given by the authorized person in accordance with GMP and the marketing authorization as specified in the contract.

The contract giver

7.5 The PQS of the contract giver should include the control and review of any outsourced activities. The contract giver is responsible for assessing the legality, suitability and competence of the contract acceptor to successfully carry out the work or tests required, for approval for contract activities,

and for ensuring by means of the contract that the principles of GMP incorporating QRM principles 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 hazards associated with the product, work or tests that might pose a risk to premises, equipment, personnel, other materials or other products.

7.7 The contract giver should review and assess the records and results related to the outsourced activities. The contract giver should ensure that all products and materials delivered by the contract acceptor have been processed in accordance with GMP and the marketing authorization; comply with their specifications and that the product has been released by the authorized person in accordance with GMP and the marketing authorization.

7.8 The contract giver should monitor and review the performance of the contract acceptor including the implementation of any needed improvements and their effectiveness.

7.9 The contract giver is responsible for ensuring that the contract acceptor understands that his or her activities may be subject to inspection by competent authorities.

The contract acceptor

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

7.11 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 information and knowledge, including that from assessments of the suitability of the third party, are made available in the same way as between the original contract giver and contract acceptor.

7.12 The contract acceptor should refrain from any activity (including unauthorized changes outside the terms of the contract) that may adversely affect the quality of the product manufactured and/or analysed for the contract giver.

The contract

7.13 There must be a written contract between the contract giver and the contract acceptor which clearly establishes the responsibilities of each party, covering the outsourced activities, the products or operations to which they are related, communication processes relating to the outsourced activities and any technical arrangements made in connection with it.

7.14 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.

7.15 Technical aspects of the contract should be drawn up by competent persons with suitable knowledge of pharmaceutical technology, analysis and GMP.

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

7.17 The contract should clearly describe who is responsible for contracted activities, e.g. knowledge management, technology transfer, supply chain, subcontracting, testing and releasing materials and undertaking production and QC, 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.

7.18 Manufacturing, analytical and 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, or to investigating in the case of a suspected falsified product or laboratory fraud, must be accessible and specified in the procedures of the contract giver.

7.19 The contract should describe the handling of starting materials, intermediate, bulk 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, quality audits and suppliers' audits and approval

8.1 *Principle*. The purpose of self-inspection is to evaluate the manufacturer's compliance with GMP in all aspects of production and QC. 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) QC;
(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 who are 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 with 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 QC 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 suppliers' 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 QA 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 as to present any risk to quality.

9.3 Responsible staff should have its specific duties recorded in written descriptions and adequate authority to carry out its responsibilities. Its duties may be delegated to designated deputies with a satisfactory level of qualifications. 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 instruction, 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 QC areas. Personnel who do not work in these areas should not use them as a passageway.

Key personnel

9.6 Key personnel include the heads of production, the head(s) of quality unit(s) and the authorized person. The quality unit(s) typically comprise the quality assurance and quality control functions. In some cases, these could be combined in one department. The authorized person may also be responsible for one or more of these quality unit(s). Normally, key posts should be occupied by full-time personnel. The heads of production and

quality unit(s) 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 production and quality unit(s) for 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 QA of pharmaceutical products. In order to gain such experience, a preparatory period may be required, during which they should perform 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 QC of pharmaceutical products.

9.8 The heads of the production and the quality unit(s) 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 QA;
(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 production generally has the following responsibilities:

(a) to ensure that products are produced and stored in accordance with 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(s) of the quality unit(s) generally have the following responsibilities:

(a) to approve or reject starting materials, packaging materials, and intermediate, bulk and finished products in relation to 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 QC 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 unit personnel is carried out and adapted according to need;
(i) establishment, implementation and maintenance of the quality system;
(j) supervision of the regular internal audits or self-inspections;

(k) participation in external audit (vendor audit);

(l) participation in validation programmes.

Other duties of QC 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 or supply.

9.12 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.

9.13 No batch of product is to be released for sale or supply prior to certification by the authorized person(s). In certain countries, by law, the batch release is a task of the authorized person from production together with the authorized person from QC.

9.14 The authorized 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;

(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 QC 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 medicines 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 QC 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 QC;

(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).

9.15 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 QA by means of batch review.

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 QA 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 QC 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 complied with.

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 medicines 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 wearing 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, or 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 should protect materials and products from the weather. Receiving areas should be designed and equipped to allow containers of incoming materials to be cleaned, if necessary, before storage.

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 medicines, 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, contamination or cross-contamination.

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

Quality control areas

12.33 QC 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 QC 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 pipework 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 according to a fixed schedule.

13.6 Production equipment should be thoroughly cleaned according to a fixed schedule.

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 QC 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 being used for 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 beneficial for 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, to be contractually agreed between the manufacturer and the supplier.

14.9 For each consignment, at a minimum, the containers should be checked at least for 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 QC 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. in 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 QC 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 standards, 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 QC 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. This 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 QC 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 re-standardization 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 medicine 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 manufacturer. 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 be done in such a way as to 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 SOPs 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 system, 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, electronic discs, paper printouts 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 medicines should be identified by labelling, as required by the national legislation, bearing at least the following information:

(a) the name of the medicines;

(b) a list of the active ingredients (if applicable, with the INN), 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 the QC or QA units. Specifications for starting materials, intermediates, 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 QC 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 reexamination.

Packaging material should conform to specifications, and should be compatible with the material and/or with the medicines 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 programs 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 programs 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 if it is 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 and records

15.31 SOPs 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 SOPs 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 SOPs for the internal labelling, quarantine and storage of starting materials, packaging materials and other materials, as appropriate.

15.35 SOPs 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 SOPs 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 an SOP 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 SOPs 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 SOP 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, for example, 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 out these operations.

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 Deviation from instructions or procedures should be avoided as far as possible. If deviations occur, they should be 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 QC 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 also record 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 reentry 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 SOPs.

16.14 Production areas where susceptible products are processed should undergo periodic environmental monitoring (e.g. for microbiological 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 relevant 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 the 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 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. Online 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 online control of the product during packaging should include at a minimum 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.

16.36 Production records should be reviewed as part of the approval process of batch release before transfer to the authorized person. Any divergence or failure of a batch to meet production 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. Good practices in quality control

17.1 QC is the part of GMP concerned with sampling, specifications and testing, and with the organization and documentation 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 compliant with the requirements. QC is not confined to laboratory operations, but may be involved in many decisions concerning the quality of the product.

17.2 The independence of QC from production is considered fundamental.

17.3 Each manufacturer should have a QC function. The QC function should be independent of other departments and under the authority of a person with appropriate qualifications and experience. Adequate resources must be available to ensure that all the QC arrangements are effectively and reliably carried out. The basic requirements for QC 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 by the QC department;

(c) qualification and validation;

(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) 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 for the appropriate time in its final pack unless the pack is exceptionally large, in which case one that is equivalent to the marketed packaging system may be used.

17.4 Other QC responsibilities include:

(a) establishing, validating and implementing all QC procedures;
(b) evaluating, maintaining and storing reference standards for substances;
(c) ensuring the correct labelling of containers of materials and products;
(d) ensuring that the stability of the active pharmaceutical ingredients and products is monitored;
(e) participating in the investigation of complaints related to the quality of the product;
(f) participating in environmental monitoring;
(g) participation in QRM programmes.

These activities should be carried out in accordance with written procedures and, where necessary, recorded.

17.5 QC personnel must have access to production areas for sampling and investigation as appropriate.

Control of starting materials and intermediate, bulk and finished products

17.6 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.

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

17.8 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.

17.9 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.

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

17.11 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.

17.12 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

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

17.14 An identity test should be conducted on a sample from each container of starting material (see also section 14.14). It is permissible to sample only a proportion of the containers where a validated procedure has been established to ensure that no single container of starting material has been incorrectly labelled. This validation should take account of at least the following aspects:

- the nature and status of the manufacturer and of the supplier and their understanding of the GMP requirements;
- the QA system of the manufacturer of the starting material;
- the manufacturing conditions under which the starting material is produced and controlled;
- the nature of the starting material and the medicinal products in which it will be used.

Under such a system it is possible that a validated procedure for exemption from the requirement for identity testing of each incoming container of starting material could be accepted for the following:

- starting materials coming from a single product manufacturer or plant; or

– starting materials coming directly from a manufacturer, or in the manufacturer's sealed container where there is a history of reliability, and regular audits of the manufacturer's QA system are conducted by the purchaser (the manufacturer of the medicinal product) or by an officially accredited body.

It is improbable that such a procedure could be satisfactorily validated for either:

– starting materials supplied by intermediaries, such as brokers, where the source of manufacture is unknown or not audited; or
– starting materials for use in parenteral products.

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

17.16 In lieu of full 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 (*7*):

(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

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

Finished products

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

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

Batch record review

17.20 QC records should be reviewed as part of the approval process of batch release before transfer to the authorized person. 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.

17.21 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 reexaminations.

Stability studies

17.22 QC should evaluate the quality and stability of finished pharmaceutical products and, when necessary, of starting materials and intermediate products.

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

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

(a) a complete description of the medicine 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 medicine;
(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.

17.25 Stability should be determined prior to marketing and following any significant changes, for example, in processes, equipment or packaging materials.

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Annex 3

Model quality assurance system for procurement agencies

Background

The Expert Committee on Specifications for Pharmaceutical Preparations of the World Health Organization (WHO) adopted a Model quality assurance system for procurement agencies (MQAS) during a meeting in Geneva, Switzerland in 2005. This was subsequently published as Annex 6 in the Technical Report Series, No. 937 in 2006. Some procurement organizations have implemented the recommendations presented in the MQAS. Some donor organizations (including the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM)) have endorsed the MQAS as part of their quality assurance policy for the procurement of pharmaceutical products with their funds. Several organizations have also prepared a tool to assess procurement agencies to establish the level of implementation and compliance with the MQAS.

Participants at a WHO/GFATM joint stakeholders meeting on Quality Assurance for Essential Medicines held in August 2011 in Geneva agreed that a working group consisting of representatives from the Committee for Medicinal Products for Human Use (CHMP), Crown Agents, Global Drug Facility (GDF), International Committee of the Red Cross (ICRC), International Development Association (IDA), Médecins Sans Frontières (MSF), Management Sciences for Health (MSH), Partnership for Supply Chain Management (PFSCM), Quality Medicines for All (QUAMED), International Union Against Tuberculosis and Lung Disease (The Union), United Nations Children's Fund (UNICEF), United Nations Office for Project Services (UNOPS), and the United States Agency for International Development (USAID), be created to develop a harmonized Assessment Tool that could be used by all with the aim of better use of resources by coordinating procurement agency assessments and working towards mutual recognition of procurement agency assessment findings, and to participate in the revision of the MQAS.

The Global Fund Secretariat contracted a consultant through a competitive process in 2012 to review the existing MQAS and to make recommendations to WHO (in case the need was identified to change or update the MQAS), to review tools used by procurement agencies in the light of the existing MQAS and to prepare a harmonized tool for the assessment of procurement agencies, based on the MQAS, through a consultative process.

Four informal meetings were also held at the Global Fund between 2012 and 2013 to discuss the MQAS, the comments, the draft tool, progress made and the way forward.

Since the first publication of the MQAS and its use by many organizations, it appeared that a revision would be timely and could include current developments.

A first proposal for revision of the MQAS was presented at the forty-seventh meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations, in Amsterdam, Netherlands. The recommendations included in the report (WHO Technical Report Series, No. 981) of the forty-seventh meeting of the Expert Committee read as follows (excerpt):

> **8.1 Revision of model quality assurance system for procurement agencies**
>
> The model quality assurance system (MQAS) for procurement agencies was adopted by the Expert Committee in October 2005, since when it has been used by many organizations. … The revised MQAS and the proposed assessment tool were … circulated for comment in August 2012 by WHO following the usual Expert Committee consultation process. Comments were collated and the draft revised MQAS and the comments were presented to the Expert Committee for consideration.
>
> The Expert Committee considered the comments and proposed a number of amendments to the draft. The Expert Committee endorsed the proposal for a revision of the MQAS, and noted progress made to date.
>
> **8.2 Assessment tool based on the model quality assurance system**
>
> In August 2011, WHO and GFATM identified the need for a new assessment tool for procurement agencies in conjunction with the revision of the MQAS. The proposed assessment tool was based on the MQAS. A draft of the proposed tool was prepared during 2012 and was circulated for comment. The draft was being tested in a pilot process from August to December 2012, after which it would be further reviewed and revised according to the experience gained.

During 2012 the draft assessment tool was used in a pilot phase (July to December 2012) by different organizations procuring medicines. Comments received on the MQAS as well as additional comments based on the use of the draft assessment tool (to assess procurement agencies) were reviewed during a meeting of the working group arranged through the Global Fund, on 7 and 8 February 2013, at the Global Fund offices in Geneva.

The fourth informal consultation was held in June 2013 to discuss additional comments on the MQAS as well as the newly developed aide-memoire to be used in assessing procurement agencies. The objective of the revised MQAS and use of an aide-memoire is to promote and ensure that all procurement agencies follow the same standard. A model format for an inspection report was prepared. The product questionnaire was reviewed.

During its forty-eighth meeting, the WHO Expert Committee on Specifications for Pharmaceutical Preparations adopted the updated MQAS together with the replacement texts for Appendix 6 Interagency finished pharmaceutical product questionnaire and Appendix 14 Guidance on good manufacturing practices: model inspection report. In addition, the aide-memoire was recommended for use and is published as Annex 4 in the report of the forty-eighth Expert Committee meeting (WHO Technical Report Series, No. 986).

Glossary

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

accountability: The obligation to account for one's conduct and actions, usually to an individual or group, but ultimately to the public. Both individuals and organizations may be accountable. There is some overlap between accountability and *transparency* (see below).

active pharmaceutical ingredient (API): A substance or compound intended to be used in the manufacture of a pharmaceutical product as a therapeutically active compound (ingredient).

affordability: The extent to which pharmaceutical products are available to the people who need them at a price they can pay.

authorized person: A person (among key personnel of a manufacturing establishment) responsible for the release of batches of finished products for sale. In some *good manufacturing practice* (GMP) guides and legal texts, the term *qualified person* is used to describe analogous functions.

bioavailability: The rate and extent to which the active pharmaceutical ingredient or active moiety is absorbed from a pharmaceutical dosage form and becomes available at the site(s) of action.

bioequivalence: Two pharmaceutical products are bioequivalent if they are pharmaceutically equivalent or pharmaceutical alternatives and their bioavailabilities, in terms of peak (C_{max} and T_{max}) and total exposure (area under the curve (AUC)), after administration in the same molar dose under the same conditions, are similar to such a degree that their effects can be expected to be essentially the same.

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

competitive tender: A procedure for procuring pharmaceutical products which puts a number of suppliers into competition. Purchasing is done on the basis of quotations submitted by the suppliers in response to a public notice.

effectiveness: An expression of the degree to which activities have produced the effects planned.

efficiency: The relationship between the results of activities and the corresponding effort expended in terms of money, resources and time.

essential pharmaceutical products: Those pharmaceutical products that satisfy the health care needs of the majority of the population. WHO's Expert Committee on the Selection and Use of Essential Medicines updates the *WHO Model List of essential medicines* at two-year intervals. Each country may use this model to generate its own list of essential pharmaceutical products.

generic products: The term *generic product* has somewhat different meanings in different jurisdictions. The use of this term is therefore avoided as far as possible, and the term *multisource pharmaceutical product* (see below) is used instead. Generic products may be marketed either under the approved nonproprietary name or under a brand (proprietary) name. They may be marketed in dosage forms and/or strengths different from those of the *innovator products* (see below). Where the term *generic product* is used, it means a pharmaceutical product, usually intended to be interchangeable with the innovator product, which is usually manufactured without a licence from the innovator company and marketed after expiry of the patent or other exclusivity rights. The term should not be confused with generic names for APIs.

generic substitution: The practice of substituting a product, whether marketed under a trade name or generic name, with an equivalent product, usually a cheaper one, containing the same active ingredient(s).

good manufacturing practice (GMP): That part of quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization.

indicator: Criterion used to measure changes, directly or indirectly, and to assess the extent to which the targets or objectives of a programme or project are being attained. Indicators should meet the criteria of clarity, usefulness, measurability, *reliability*, *validity* (see below) and acceptance by key stakeholders.

innovator pharmaceutical product: Generally the pharmaceutical product which was first authorized for marketing (normally as a patented product) on the basis of documentation of efficacy, safety and quality according to requirements at the time of the authorization. When a substance has been available for many years, it may not be possible to identify an innovator pharmaceutical product.

inspection: An official examination, normally conducted on site, of the compliance with WHO good manufacturing practices as referred to in this document. In some cases, an off-site review of documentation may be done in lieu of the on-site examination.

interchangeability: An interchangeable pharmaceutical product is one that is therapeutically equivalent to a comparator (reference) product.

International Nonproprietary Name: The shortened scientific name based on the active ingredient. WHO is responsible for assigning INNs to pharmaceutical substances.

legislation: The first state of the legislative process, in which laws are passed by the legislative body of government with regard to a subject matter, e.g. control of pharmaceuticals. Laws define the roles, rights and obligations of all parties involved in the subject matter in general terms (see also *regulations* below).

licensing system: National legal provisions on who should manufacture, import or supply pharmaceutical products, what qualifications people in the supplying agency should have, and who should dispense and sell pharmaceutical products.

manufacture (manufacturing): All or any operations of purchase of materials and products, production, quality control, release, storage and distribution of finished products and the related controls.

marketing authorization: A legal document issued by the competent medicines regulatory authority for the purpose of marketing or free distribution of a product after evaluation for safety, efficacy and quality. It must set out, inter alia, the name of the product, the pharmaceutical dosage form, the quantitative formula (including excipients) per unit dose (using INNs or national generic names where they exist), the shelf-life and storage conditions, and packaging characteristics. It specifies the information on which authorization is based (e.g. "The product(s) must conform to all the details provided in your application and as modified in subsequent correspondence."). It also contains the product information approved for health professionals and the public, the sales category, the name and address of the holder of the authorization, and the period of validity of the authorization. Once a product has been given marketing authorization, it is included on a list of authorized products – the register – and is often said to be "registered" or to "have registration". Market authorization may occasionally also be referred to as a "licence" or "product licence".

medicine: Any substance or pharmaceutical product for human or veterinary use that is intended to modify or explore physiological systems or pathological states for the benefit of the recipient. In this document, the terms *medicine* and *pharmaceutical product* (see below) are used interchangeably.

medicines regulatory authority: A national body that administers the full spectrum of medicine regulatory activities, including at least all of the following functions in conformity with national medicine legislation:

- marketing authorization of new products and variations of existing products;
- quality control laboratory testing;
- monitoring of adverse drug reactions;
- provision of information on medicines and promotion of rational use of medicines;
- *good manufacturing practice* (GMP) inspections and licensing of manufacturers, wholesalers and distribution channels;
- enforcement operations;
- monitoring of drug utilization.

medicines legislation: The legal conditions under which pharmaceutical activities should be organized (see also *legislation* above).

multisource (generic) pharmaceutical product: Pharmaceutically equivalent or pharmaceutically alternative products that may or may not be therapeutically equivalent. Multisource pharmaceutical products that are therapeutically equivalent are interchangeable.

national list of essential pharmaceutical products: The list of *essential pharmaceutical products* (see above) that has been defined, adopted and published at country level. It is normally used by all health facilities, including the main hospitals.

pharmaceutical product: See *medicine*.

prequalification: The activities undertaken in defining a product or service need, seeking expressions of interest from enterprises to supply the product or service, and examining the product or service offered against the specification and the facility where the product or service is prepared against common standards of *good manufacturing practice* (GMP). The examination of the product or service and of the facility where it is manufactured is performed by trained and qualified inspectors against common standards. Once the product is approved, and the facility is approved for the delivery of the specified product or service, other procurement agencies are informed of the decision. Prequalification is required for all pharmaceutical products regardless of their composition and place of manufacture/registration, but the amount and type of information requested from the supplier for assessment by the procurement agency may differ.

procurement: The process of purchasing or otherwise acquiring any pharmaceutical product, vaccine or nutraceutical for human use. For the purpose of this document, *procurement* means the pre-selection of products and manufacturers through a procedure of qualification, including *prequalification* (see above) and continuous monitoring thereafter, purchase of the prequalified products from prequalified manufacturers (linked to the specific product) through defined purchasing mechanisms, storage and distribution.

procurement agency: A procurement agency in the context of this document is defined as any organization purchasing pharmaceutical products, vaccines, or other health products or otherwise involved in their *prequalification* (see above), purchasing, storage and distribution.

product information: Information on pharmaceutical products submitted by manufacturers or suppliers in any of the formats specified in the procurement agency's guidelines (including product dossiers, product questionnaires or other formats) to obtain prequalification for the products.

qualification: Action of proving and documenting that any premises, systems and equipment are properly installed and/or work correctly and lead to the expected results. Qualification is often a part (the initial stage) of validation,

but the individual qualification steps alone do not constitute process validation. It is the work done to prove that the supply system will deliver products of the quality required and specified on a routine basis, meeting all the applicable quality requirements.

quality assurance: Quality assurance is a wide-ranging concept covering all matters that individually or collectively influence the quality of a product. It is the totality of the arrangements made with the object of ensuring that pharmaceutical products are of the quality required for their intended use.

quality control: Quality control is concerned with sampling, specifications and testing, and with the procurement agency's documentation and acceptance/rejection procedures which ensure that the necessary and relevant tests are actually carried out and that starting materials, intermediates and finished products are not accepted for use, sale or supply until their quality has been judged to be satisfactory.

regulations: The second stage of the legislative process (the first stage being legislation, see above). Regulations are specifically designed to provide the legal machinery to achieve the administrative and technical goals of legislation.

reliability: An expression of the degree to which a measurement performed by different people at different times and under different circumstances produces the same results (see also *validity*).

reliable quantification of medicines needs: A careful evaluation of the quantities needed of each medicine, based on either adjusted past consumption or anticipated pattern of diseases and standard treatment, which can be expected to match actual needs reasonably well.

stringent regulatory authority (SRA): A regulatory authority which is:

a. a member of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) (as specified on www.ich.org); or
b. an ICH observer, being the European Free Trade Association (EFTA), as represented by Swissmedic and Health Canada (as may be updated from time to time); or
c. a regulatory authority associated with an ICH member through a legally-binding, mutual recognition agreement including Australia, Iceland, Liechtenstein and Norway (as may be updated from time to time).

transparency: The term transparency means:

– defining policies and procedures in writing and publishing the written documentation; and
– giving reasons for decisions to the public (see also *accountability* above).

validation: Action of proving and documenting, in accordance with the principles of good manufacturing practice, that any procedure, process, or method actually and consistently leads to the expected results (see also *qualification* above).

validity: An expression of the degree to which a measurement performed actually measures the characteristic which the investigator wishes to measure (see also *reliability* above).

variation: Variation to an approved product questionnaire or product dossier that includes, for example, changes in formulation, specifications, or manufacturing process.

WHO-type certificate: A certificate of pharmaceutical product of the type defined in the WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce.[1]

[1] World Health Organization. *WHO Certification Scheme on the quality of pharmaceuticals products moving in international commerce*. Geneva, World Health Organization, 2000. WHO/EDM/QSM/2000.2 (http://www.who.int/medicines/organization/qsm/activities/drugregul/certification/certifschemes.html).

MODULE I

General requirements for procurement agencies

I.1 Introduction

Procurement agencies often have to purchase and supply pharmaceutical and other health products using scarce resources. In many cases, product quality is compromised when products are obtained from unqualified sources. Procurement agencies may deal with various types of organizations, suppliers and customers, including medicines regulatory authorities, manufacturers, quality control laboratories, contract manufacturers, contract laboratories, traders, brokers, distributors and pharmacies. A quality assurance system should be in place to ensure that transactions with these partners ultimately result in procuring pharmaceutical products and other health products (hereafter referred to collectively as products) of the best possible quality.

This module addresses the general requirements for such a system, including physical resources such as premises, equipment and personnel, as well as the documented policies, standards and procedures required to ensure consistency in all the key activities of procurement. The general requirements described in this module are, therefore, applicable to all procurement agencies and general principles may apply to the activities covered in subsequent modules.

I.2 Physical resources

I.2.1 Premises

I.2.1.1 Offices

The procurement agency should have sufficient office space to accommodate the personnel required and the activities to be performed.

I.2.1.2 Storage

The procurement agency should have sufficient space for storage and retention of products, product documentation, product samples, stock, reports, files and other records relating to all key activities of procurement. Samples and products should be stored under suitable conditions which are specified on product labels, e.g. with regard to temperature, humidity or protection from light. Details of storage requirements are given in Module IV. There should be sufficient space for storage of equipment, stationery and materials for proper distribution. Details of distribution requirements are given in Module V.

I.2.2 Equipment

I.2.2.1 Computers

The use of computers can facilitate, but not replace, efficient procedures in pharmaceutical procurement. When implemented appropriately, computerization will speed up complex tasks, increase accuracy and automate repetitive tasks. Staff must be trained adequately in the use of computerized systems.

Many aspects of procurement are suitable for computerization, including planning of requirements, budget management, financial analysis, preparation of documentation, traceability of batches supplied to customers, and reports and inventory control. Hard copies (printouts) should be produced as required to provide documentary evidence of the activities.

I.2.2.2 Software

The software selected should be suitable for the intended use. The programs used should be able to provide the required quality and management information reliably and accurately. They should be user-friendly and staff should be trained adequately in their use. Where possible, different programs used should be compatible so that data can be transferred between them without having to be re-entered. Where information is exchanged between the procurement agency and the manufacturer(s) by electronic means, appropriate programs should be in place. Suitable security systems should be in place to prevent unauthorized access or changes to computer records and reports. Back-up systems must be in place to prevent loss of data. A good-quality virus protection program and firewall must be installed, configured, used and updated regularly to prevent unauthorized access and loss of data.

Technical support should be available to ensure that software and security systems are kept functional and up-to-date.

Standard operating procedures (SOPs) should be implemented to ensure that back up of data is made at defined, regular intervals.

Back-up data should be stored in a secure place with access control, under suitable conditions (e.g. protected from fire hazard).

Systems should be in place to ensure that back-up data are accessible and will be readable in the future, when required.

I.2.2.3 Hardware

The hardware selected should be able to handle the required software efficiently. The system should have sufficient capacity and memory for the intended use, as well as adequate input and output devices, including good-quality printers. Access to the Internet and possibly to an internal network (LAN) should be provided to facilitate exchange of information.

A maintenance plan should be in place to ensure that the system remains functional.

I.2.2.4 Telecommunications

There should be access to telephone and email systems to ensure instant communication.

I.2.2.5 Furniture

Suitable office furniture should be provided, including desks, chairs, shelves, cupboards, filing cabinets and other items as required.

I.2.2.6 Office equipment

Office equipment should be provided and kept in working order.

I.2.2.7 Stationery and consumables

The procurement agency should provide stationery to enable staff to perform the relevant tasks, including paper, letterheads, business cards and pre-printed forms as required. Computer consumables, including printer cartridges and printing paper, as well as any replacement parts not covered by a maintenance contract, should be provided.

I.2.3 Vehicles and transport

As the procurement agency is responsible for transportation and distribution of products, appropriate transport should be provided to ensure that the quality of the products is maintained. (For details see Module V.)

I.2.4 Financial systems

The procurement agency should be able to effect national and international financial transactions as required. Funds must be available to ensure continued operations.

Adequate banking facilities must be available. Signatories of bank accounts should be appointed to ensure control on one hand, and continuity of operations during the absence of key personnel on the other hand.

An accounting system should be in place. Regular financial audits should be performed.

If the procurement agency is part of a larger organization, it should have sufficient autonomy and/or effective systems in place to enable it to conduct all its financial transactions without delay.

I.2.5 Human resources

I.2.5.1 Personnel

There should be a sufficient number of appropriately trained, educated and experienced personnel to perform the key activities. The number of members of

staff required in the department responsible for the key activities will depend on the activities and volume of products sourced and to be supplied.

Sufficient support staff for secretarial, organizational and accounting duties as well as legal support should also be available.

Key personnel should include those responsible for quality assurance, prequalification, purchasing, storage and distribution. The person responsible for quality assurance could also be responsible for prequalification. The personnel responsible for quality assurance/prequalification and the personnel responsible for purchasing should be independent of one another. One should not report to the other.

National legislation should be complied with, for example, requirements for a responsible person for purchasing, storage and distribution of pharmaceutical products.

The responsibilities of the staff in charge of the different key activities are described in Modules II–V.

I.2.5.2 Qualifications and experience

Personnel responsible for quality assurance, prequalification, purchasing, storage and distribution should have sufficient qualifications, knowledge and experience in their respective fields (see Modules II–V).

I.2.5.3 Code of conduct

All staff members should comply with a code of conduct which should guide all their professional activities. More detail on codes of conduct is given in section I.2.4. An example of a code of conduct is shown in Appendix 1.

I.2.5.4 Confidentiality

It is essential that all information obtained by any person working for the procurement agency is treated as confidential. Most of the information obtained from companies and manufacturers is product-specific, may be patented and will be commercially sensitive. Personnel must treat all information submitted and observed during the assessment of product dossiers and inspections at manufacturing sites, and otherwise in connection with the discharge of their responsibilities as strictly confidential and proprietary to the party collaborating with the procurement agency.

Confidentiality agreements should be considered where necessary. An example of such an agreement is attached in Appendix 2. Additional information may be found in Appendix 3 (example of a guideline on conflict of interest).

I.2.5.5 Conflict of interest

Before undertaking any work, key personnel in key activities (e.g. quality assurance, prequalification, purchasing, specification setting – including contracted

personnel) should sign a declaration of interest. If, based on their declaration of interest, it is deemed appropriate for them to undertake the work specified, they agree to carry out their functions exclusively for the agency.

They should confirm that the information disclosed by them in the declaration of interest is correct, that no situation of real, potential or apparent conflict of interest is known to them and that they have no financial or other interest in, and/or relationship with a party which:

- may have vested commercial interest in obtaining access to any confidential information disclosed to them in the course of the evaluation activities described in the declaration;
- may have a vested interest in the outcome of the evaluation activities including, but not limited to, parties such as the manufacturers whose products are subject to evaluation or manufacturers of competing products.

Personnel should undertake to advise the procurement agency promptly of any change in their circumstances, for instance if an issue arises leading to a conflict of interest during the course of their work for the procurement agency.

I.2.5.6 Job descriptions

There should be written job descriptions, with definitions of responsibilities, for all key personnel. Personnel and their supervisor should sign and date the job description.

I.2.5.7 Organization chart

The procurement agency should have an authorized, current organization chart indicating the positions, names of responsible persons and reporting lines.

The organization chart should reflect the responsibilities and reporting lines in accordance with the job descriptions.

I.3 Documentation of policies and standards

Documentation is an essential part of a quality assurance system. The procurement agency should have a comprehensive documentation infrastructure, which should include policies, guidelines, norms, standards, manuals, procedures, records and related documents.

All activities of each section or department should be performed and documented in a standardized manner, following approved written procedures.

The main elements of the documentation system of this MQAS are described below.

I.3.1 Quality manual

The procurement agency should have a quality manual. The purpose of such a manual is to document the quality policy as defined by management in relation to the various activities undertaken by the procurement agency. There should be policy statements and a quality policy in terms of the agency's activities and objectives, as well as documents describing the policy of each section or department with regard to all activities in prequalification and subsequent purchasing, storage and distribution.

The quality manual should contain as a minimum:

(a) a quality policy statement, including at least the following:

  (i) a statement of the management's intentions with respect to the standard of service it will provide,
  (ii) a commitment to establishing, implementing and maintaining an effective quality management system,
  (iii) the management's commitment to good professional practice and quality of activities and services,
  (iv) the management's commitment to compliance with the content of these guidelines,
  (v) a requirement that all personnel concerned with the activities within the procurement agency familiarize themselves with the documentation concerning quality and the implementation of the policies and procedures in their work;

(b) the structure of the procurement agency (organization chart);
(c) the operational and functional activities so that the extent and the limits of the responsibilities are clearly defined;
(d) outline of the structure of documentation used in the procurement agency quality management system;
(e) the general internal quality management procedures;
(f) references to specific procedures, conflict of interest and code of conduct;
(g) information on the appropriate qualifications, experience and competencies that personnel are required to possess;
(h) information on initial and in-service training of staff;
(i) a policy for internal and external audit;
(j) a policy for implementing and verifying corrective and preventive actions;

(k) a policy for dealing with complaints;

(l) a policy for performing management reviews of the quality management system;

(m) a policy for the handling of out-of-specification (OOS) results;

(n) policy to select service providers and suppliers including reference to prequalification;

(o) a policy for storage and distribution of products.

Once this quality policy is defined, it should be implemented, maintained, reviewed and amended as necessary at regular intervals by the procurement agency.

I.3.2 Standard operating procedures

The procurement agency should have written, clear and detailed SOPs for all the activities to be performed in the procurement agency. Quality risk management (QRM) principles may be applied in determining the scope and extent of SOPs. The content of each SOP, particularly the step-by-step descriptions of activities and approved recording or reporting formats attached as addenda (see below), should reflect the operations of the particular procurement agency.

SOPs should be drafted by the person responsible for the procedure. An SOP for writing an SOP should be followed to ensure consistency of design, format and layout. An SOP on how to write an SOP is attached as Appendix 4.

SOPs should be reviewed periodically.

I.3.2.1 Style and layout

SOPs should be written in the procurement agency's approved format, and be formally approved (signed and dated) by the authorized person(s). SOPs should be written in clear, unambiguous language. The name and/or logo of the procurement agency should be included on the front page of each SOP.

I.3.2.2 Elements of standard operating procedures

The SOP should contain at least the following elements.

Title and number

Each SOP should have a title. The title should give a clear indication of the activity which it describes. A numbering system is useful to identify to which activity or department the SOP refers.

Objective

This section should describe what is to be accomplished and/or achieved with the SOP.

Scope

This section should describe to what level or depth, or how widely, the SOP is applicable.

Policy (optional section, if not included elsewhere)

This section should reflect the procurement agency's policy regarding this particular activity.

Responsibility

This section should list the person(s) and/or departments responsible for performing the activities listed in the procedure. It may be useful to refer to the position and/or department rather than the name of the person.

Action

This section should describe the sequence of action steps to be followed, from the beginning to the end of the process, to perform the activity. The action steps should be written in the imperative and should be numbered. It is advisable to indicate who is responsible for each step. This could be done by putting the position (job title) of the responsible person in brackets next to each step, or by indicating the numbers of the relevant steps next to the positions listed under the heading "Responsibility". Where a step leads to another procedure to be followed, the applicable SOP should be referred to in that particular step.

Distribution and retrieval

Documentation should be distributed with care. No superseded or obsolete SOPs should be available at user points. The sections and/or responsible persons (positions) to whom the SOP was distributed should be listed.

Revisions

In a section which could be headed "History", the date of each change to the SOP, the person responsible for the review, the change itself and the reason for the change should be recorded. This section will provide the procurement agency with the history of the amendments to the SOP.

Addenda

Any records to be completed or maintained as part of the activity should have a standardized format. It is useful to define and approve these formats in advance. The approved standard format should be part of the SOP and can be attached as an addendum to the SOP.

I.3.2.3 Activities to be covered by standard operating procedures

There should be written SOPs that reflect the activities of the procurement agency and ensure consistency in the execution of the operation, task or activity.

The following list gives examples of activities which could be covered by SOPs. A more specific list is provided at the end of each Module of these guidelines:

- how to write an SOP (see Appendix 4),
- handling of complaints,
- document/record control,
- self-inspection,
- handling of recalls,
- monitoring of environmental conditions (e.g. temperature),
- monitoring supplier performance,
- identifying and reporting substandard/spurious/falsely-labelled/falsified/counterfeit (SSFFC) products,
- evaluating offers received,
- ordering product(s) from supplier or manufacturer,
- retention of products,
- retention of product documentation,
- handling of product samples,
- stock management and inventory control,
- control, monitoring and recording of temperature and relative humidity,
- handling of materials and/or products requiring special storage conditions,
- budget management,
- financial analysis,
- traceability of batches supplied to customers,
- password control for personnel working with computers,
- how to make back-ups, and storage of data,
- ordering, storage and handling of consumables,
- managing signatories of bank accounts,
- management of the accounting system,
- performing financial audits,
- preparation and management of the code of conduct,
- establishment and maintenance of confidentiality agreements,
- preparation and maintenance of conflict of interest declarations,
- preparation of job descriptions,
- preparation of organization charts,

- preparation of the quality manual,
- distribution and retrieval of SOPs,
- change control,
- handling of variations,
- managing records and archives,
- establishing and maintaining contracts.

Each time the SOP is reviewed and amended, superseded versions of the SOPs should be removed from all user points listed and replaced with the updated version. The retrieval should be documented. The section and/or responsible person who receives the SOP should acknowledge the receipt thereof. Personnel should be trained appropriately in using the revised SOP.

I.3.3 Change control policy and handling of variations

I.3.3.1 Change control

The procurement agency should have a policy and procedure for change control. This policy should be designed to manage changes in the agency, e.g. changes to procedures, internal processes, or premises. The procedure should describe the process that will be followed to initiate the change, and the routing of the request for approvals to effect or reject the change. The review of the change request should include an assessment of the risk and impact of the change.

I.3.3.2 Variations

There should also be a procedure for handling variations to a prequalified product. Examples of variations include those that affect active pharmaceutical ingredients (APIs), formulation, manufacturing processes, analytical testing methods or packaging of prequalified products. The procedure should ensure that these variations are reported to the procurement agency before new batches are manufactured or before they are delivered and released for distribution.

Details of managing variations in product information are given in Module VI.

I.3.4 Code of conduct

The procurement agency should design, authorize and implement a written code of conduct.

The code of conduct should describe the policy of the procurement agency regarding the conduct of staff with respect to their activities. It should be followed by all personnel.

The code of conduct should give guidance to staff members on appropriate conduct in various situations. The following topics could be covered in the code:

- introduction and objectives
- key responsibilities
- personal responsibilities
- safety
- professional competence
- qualifications and experience
- conduct
- integrity and attitude
- attire, health and hygiene
- management relationship
- SOPs
- travel and accommodation
- confidentiality and conflict of interest
- documentation and records
- contracts and terms of reference (TOR)
- product files, evaluation and inspection
- samples
- evaluation and inspection reports
- provision of information and advice.

I.3.5 Guidelines on conflict of interest

The procurement agency should have a policy on conflict of interest which all personnel (including external experts, and consultants) should observe. An example of a guideline on conflict of interest is provided in Appendix 3.

The document should address at least the following points:

- introduction and objectives
- definitions and principles
- responsibilities
- confidentiality
- impartiality.

I.3.6 List of prequalified products, manufacturers and suppliers

The procurement agency should have a procedure for preparing and maintaining a list of prequalified products, manufacturers and suppliers, based on the outcome of the evaluation of product data and information and of manufacturing site inspections. The list should be product- and manufacturing site-specific,

i.e. sites are prequalified for one or more specified products, and products are prequalified as manufactured at specified sites.

The key person responsible for prequalification should be responsible for additions to and deletions from the list.

Once the evaluation of a product dossier is complete, and the inspection has been performed to assess compliance with GMP, good storage practices (GSP) and GDP as appropriate, the procurement agency should prepare a list reflecting the status of the prequalified products and manufacturers.

A current, authorized, access-controlled list of prequalified products and suppliers should be available. The list should be maintained by authorized personnel.

The list should contain at least the following information:

- name and physical address of manufacturer, including the approved site(s) of manufacture linked to each product;
- product details, including the brand name, International Nonproprietary Name (INN), dosage form, strength per dose and pack size;
- date of last (pre)qualification.

I.3.7 Maintenance of records

Records of all operations should be maintained and kept in a suitably organized manner.

Sufficient areas for the storage of records, including product information, manufacturers' information and inspection reports, should be available for a defined period of time. Access to these areas should be restricted to authorized personnel, as confidential information may be filed (including records of manufacture, testing and/or storage).

Records pertaining to batches of product procured should be retained for at least one year beyond the expiry date of the product or in accordance with customer requirements and national legislation, whichever is longer.

I.3.8 Contract arrangements

Where any activity is delegated to another organization (e.g. procurement agency, quality control laboratory, or distributor), this should be done by means of a written agreement between the two parties. The contract giver should ensure that the contract acceptor meets the requirements as recommended in these guidelines.

Module II

Prequalification

II.1 Introduction

Prequalification is one of the key elements in ensuring purchase and supply of pharmaceutical products of acceptable quality. The prequalification process can be subdivided into two major parts, i.e. product-related assessment and manufacturer-related inspection.

Product-related assessment should ensure that the correct product is specified by the procurement agency. The procurement agency should then assess whether the manufacturer is offering a product that meets the predetermined norms and standards in terms of safety, quality and efficacy.

Manufacturer-related inspection should ensure that the manufacturer is able to manufacture the product as specified in the product information questionnaire/dossier and in accordance with GMP as recommended by WHO. The manufacturer must be capable of routinely carrying out the activities to the specified standards to ensure batch-to-batch consistency of the product.

Assessment of contracted-out services, e.g. by storage and distribution agents, contract research organizations (CROs) and quality control laboratories for compliance with GMP, good clinical practices (GCP) and good laboratory practices (GLP), are further elements that may supplement the prequalification process.

The procurement agency is responsible for ensuring that all steps in the prequalification process are carried out in accordance with this MQAS. This should ensure that the manufacturers will be providing products as specified that meet all predetermined norms and standards. Full prequalification may not be required when products are already prequalified by the WHO Prequalification Programme, or registered by SRAs. It will assist procurement agencies in maximizing the use of resources and will avoid duplication of prequalification. Prequalification also reduces the risk of procurement agencies purchasing and supplying substandard products.

This module sets out recommendations which procurement agencies should implement when evaluating their product needs and when assessing the products and the manufacturing and supply arrangements offered by the manufacturers.

II.2 Principles for prequalification

Prequalification procedures should be based on the following principles:

- reliance on the information supplied by the national medicines regulatory authorities (NMRAs);

- evaluation of product data and information submitted by manufacturers, including product formulation, manufacture and test data and results;
- a general understanding of the production and quality control activities of the manufacturers and suppliers and of their commitment to the principles of good manufacturing practices (GMP);
- assessment of consistency in production and quality control through compliance with GMP as described in the latest update of the WHO publication *Quality assurance of pharmaceuticals* (*1*) and supplementary WHO GMP guidelines.

The procurement agency should have a document describing the policy and procedures for prequalification, including the assessment of product information and of manufacturers for compliance with standards.

Where prequalification is delegated to another party, this should be done by means of a written agreement between the two parties. The contract giver should ensure that the contract acceptor meets the requirements as recommended in this module.

II.2.1 WHO Model List of essential medicines

Procurement agencies may find that many of the products they require are on WHO's Model List of essential medicines, which is updated periodically (*2*). They will find this list a useful reference for establishing specifications for the medicines needed for their purposes.

II.2.2 Standards for prequalification

Current standards for prequalification can be found at: http://apps.who.int/prequal/default.htm

In principle, products should meet the recommendations made by WHO in *Marketing authorization of pharmaceutical products with special reference to multisource (generic) products – a manual for medicines regulatory authorities* (*3*). Manufacturing sites should comply with WHO GMP.

II.2.3 Key persons and responsibilities

All key personnel responsible for prequalification should have appropriate training.

II.2.3.1 Staff responsible for prequalification

The person responsible for prequalification should be independent from the person responsible for purchasing.

The key responsibilities of the unit responsible for prequalification activities should include the following:

- establishing specifications for products;
- publication of invitations for expressions of interest (EOI) (if this mechanism is used). An example of an EOI is provided in Appendix 5;
- preparation of a questionnaire for collecting product data and information and/or guidelines for the compilation of product information;
- assessment of product data and information for compliance with norms and standards;
- assessment of manufacturing sites, for compliance with WHO GMP;
- the list of prequalified products and manufacturers.

II.2.3.2 Staff responsible for evaluation of product information

Where possible, the person responsible for the evaluation of the product information should be independent from the person evaluating the manufacturing site.

The key responsibilities of the unit or appointed individual responsible for evaluating product information should include:

- preparing and implementing SOPs and guidelines for evaluation of product information;
- receipt of product information;
- screening of product information (for completeness on initial receipt);
- evaluation of product information (full evaluation to assess compliance with standards);
- informing manufacturers of the outcome of the evaluation of the product information;
- communicating with the person responsible for inspections of manufacturing sites.

The people assigned to evaluate product information should have relevant qualifications and experience, which may include a background in pharmaceuticals, pharmaceutical chemistry and pharmacology. Ideally they should be from a regulatory background, or have regulatory experience.

II.2.3.3 Staff responsible for inspection of manufacturing sites

The key responsibilities of the unit or appointed person responsible for inspection of manufacturing sites should include the following:

- preparation and implementation of guidelines and SOPs;
- coordination of inspections to be performed;
- recruiting or appointing inspectors with appropriate qualifications and experience, when necessary;
- conducting inspections;
- preparation of inspection report;
- follow-up of CAPA after inspections;
- finalizing inspection reports;
- informing manufacturers of the outcome of the inspection.

As a minimum, the personnel/appointed person responsible for inspecting manufacturing sites should have relevant qualifications and experience in pharmaceutical manufacturing, quality assurance, GMP and good distribution practices (GDP), performing inspections and audits, chemistry and quality control. Ideally they should have an inspection background from working with a regulatory authority or experience in managing manufacturing sites.

Although decision-making should be independent, there should be communication between the person responsible for evaluation of product information and the person responsible for inspection of manufacturing sites, as some information on the product may have to be verified during the site inspection.

II.2.4 Key steps in prequalification

The key steps in prequalification include soliciting and receiving product data and information, screening and assessment of the data and information, and assessment for compliance with standards for manufacture such as GMP.

The preparatory steps of drafting a documentation system, including confidentiality agreements, declaration of conflict of interest, SOPs and guidelines, are described in Module I.

II.2.4.1 Step 1: Soliciting information

Prepare product specifications for prequalification

Specifications for the product(s) to be prequalified should be prepared.

The specifications should be detailed, clear and unambiguous to avoid unnecessary submission and processing of documentation not relevant to the product to be sourced.

The specification should state at least:

- the name of the API(s)/INN;
- strength per dose;
- dosage form (route of administration).

Other aspects to consider include pack size, primary packaging materials and labelling requirements.

Once the specification is finalized, the information can be published widely to all manufacturers, or targeted to prequalified manufacturers according to the internal rules of the procurement agency. The information communicated should include at least:

- the purpose of the invitation;
- the list of products, including specifications for each product;
- information on quantities required (if available);
- details of the information to be submitted;
- procedure for submission, including information on details to be submitted, on the focal point for the submission and on the format for the submission;
- contact details (name, address, telephone number, fax, email and postal address) for submission;
- the closing date for receipt of the information by the procurement agency.

Procedure for submitting product information

The procedure for submitting product information should be publicly available and accessible. In cases where this is not the case, reasons for the decision should be given and documented.

The procedure should be written in clear, unambiguous language and should contain information detailing at least:

- the content and format of submission, including the type and format of information required (e.g. the procedure for submission of information for a product registered in a country recognized as having an effective medicines regulatory agency, and instructions for cross-referencing an existing dossier with the prescribed submission format);
- the process of submission, including the address to which the documentation should be sent and a statement of any fees payable for cost recovery.

Content and format of submission

For each product to be prequalified, interested manufacturers should be asked to submit product information, together with a sample of sufficient quantity to allow analyses of the product against its finished product specification as stated

in the product information. A covering letter and a checklist for the product information may be added (optional).

Depending on the active ingredients, country of manufacture and registration of products to be prequalified, different formats for submission will be required.

Detailed information should be submitted for products for which bioavailability may be altered by chirality, isomerism, controlled release formulation, polymorphism or other properties which may affect the therapeutic outcome.

In this document, the term "product information" refers to any of the following three formats in which submissions should be made:

1. For products manufactured and registered in countries where regulatory requirements are in line with international regulations for assessment of safety, efficacy and quality, the following information should be submitted:

   – a WHO-type certificate of a pharmaceutical product (CPP) (*4*) issued by a stringent regulatory authority, together with a summary of product characteristics (SmPC), or proof of the official registration of the product;
   – if the product is different to the one registered by the SRA, arguments and/or data to support the application should be submitted. This may include differences in formulation, strength or other specifications including packaging.

   Products registered for export purposes only, should be fully assessed unless these were approved or subject to a positive opinion under the Canada S.C. 2004, c. 23 (Bill C-9) procedure, or Article 58 of European Union Regulation (EC) No. 726/2004 or United States Food and Drug Administration (US FDA) tentative approval.
2. A standard product dossier as prepared for a national medicine regulatory authority should be submitted, provided it contains the appropriate information as required in the WHO guidelines, e.g. common technical document (CTD). In such cases, the supplier should provide a covering letter which indicates where the required information can be found in the standard product dossier.
3. A completed questionnaire with information on the product should be submitted. An example of a pharmaceutical product questionnaire is shown in Appendix 6.

Process of submission

Suppliers should be allowed at least 60 days for the compilation and submission of product information.

Manufacturers should be requested to state that the information submitted is true and correct.

The procurement agency should reserve the right to terminate the prequalification procedure of a product and manufacturer if the manufacturer fails to provide the required information within a specified time period, or if the information supplied is inadequate to complete the prequalification effectively.

II.2.4.2 Step 2: Receive product information

Receipt of information

The procurement agency should have the necessary infrastructure to receive and process the product information submitted by manufacturers. It will require personnel for processing the documentation; written procedures for receiving, identification and marking of files, containers and samples, and sufficient space for unpacking and storage.

Containers with product information should be received at the specified address before a specified date as determined by the procurement agency.

The procurement agency should have a clear policy regarding the acceptance of information after the specified closing date. Processing of late submissions should not normally be allowed. Only in exceptional instances should late information be considered, e.g. when a manufacturer is the only one to express an interest in supplying a specific product. It would be appropriate to express concern at the late arrival of the information, and manufacturers should give reasons for late submission.

Each product should be allocated a unique reference number to ensure traceability of the product information.

A record of all the information received from each manufacturer should be maintained.

II.2.4.3 Step 3: Screen product information

Each product information package submitted by the manufacturer should be screened for completeness. The screening should be done in accordance with a written procedure. If the product information submitted fails to meet the requirements, it should be excluded from the evaluation procedure and inspection process.

A screening form should be used to ensure consistency of screening. There should be a written record of the screening of each product information package.

Information to be recorded should include:

- date of receipt
- name of the interested manufacturer(s)
- address of the manufacturer

- name of the product
- country of manufacture
- product number
- outcome of the screening.

An example of an SOP for screening and assessing product information, including a sample screening form, is shown in Appendix 7.

Incomplete information should not be kept for evaluation purposes. The manufacturer should be informed that an incomplete information package was received, and be requested to supply the missing information within a specified period. If this request is not complied with, the application should be rejected on grounds of incompleteness.

Product information packages which meet the requirements of the screening procedure should be retained for full evaluation.

A summary should be made of each product information package received, stating any reference number allocated to the product by the procurement agency, the INN, strength, dosage form and pack size of the product, the name of the supplier, the name and address of the manufacturing site(s), whether a sample has been submitted, and if so, the sample size.

II.2.4.4 Step 4: Evaluate product information

Evaluators

Evaluators with suitable qualifications and experience in the evaluation of product data and information should be available to conduct the assessment. Suitably qualified external evaluators may be appointed. Appointment of external evaluators should be subject to compliance with the policy of the procurement agency regarding aspects such as confidentiality, conflicts of interest and financial resources. Examination of potential conflicts of interest and confidentiality must go beyond the potential evaluator signing a declaration. Checks on references should also be made.

A formal agreement for the performance of work and terms of reference for contracted evaluators should be in place before commencement of work.

A summary list of names, addresses, dates of appointment, qualifications and experience of evaluators should be maintained. Copies of signed agreements should be kept in a central file.

Evaluation

Time frames should be set for evaluation of product information. Product information should be evaluated within a reasonable period after the closing date for submission.

A written procedure for evaluation should be followed. An example of an SOP for screening and assessing product information is attached as Appendix 7.

The person responsible for evaluation should monitor the process to ensure that each product information package is evaluated in compliance with these requirements.

Evaluation reports

Each evaluator should prepare a formal evaluation report for each product, including a recommendation for acceptance or rejection. The evaluation report should be communicated to the manufacturer.

A response should be invited from the manufacturer in cases where data and information are found to be incomplete or do not meet the guidelines.

A reasonable period should be allowed for submission of additional data and information.

This additional information should be assessed and the final outcome of the evaluation should be communicated to the manufacturer.

The evaluation report should be filed with the product evaluation documentation for reference purposes and follow-up where relevant.

Analysis of samples

Samples submitted together with product information packages should be analysed – if deemed necessary based on risk assessment – in accordance with the finished product specification. Certificates of analysis of product samples should be made available to the procurement agency.

The procurement agency should have access to a quality control laboratory to perform the analyses. The WHO *Guide for a quality systems manual in a control laboratory* (*5*) seeks to establish a practical basis for the quality systems manual of a control laboratory which each country can adopt and adapt when preparing its own more detailed manual to meet the required level of specificity and complexity.

A laboratory may be contracted to perform the analyses. In that case, the procurement agency should ensure that the laboratory complies with GMP and good practices for control laboratories (*6*). The use of a WHO-prequalified quality control laboratory or an accredited laboratory is, therefore, recommended. The procurement agency should verify the accreditation. There should be a written contract or agreement between the procurement agency and the contract laboratory. The wording of the contract should be clear and it should specify the responsibilities of the contract giver and the contract acceptor.

The procurement agency is responsible for ensuring access to raw data.

The procurement agency should have a procedure for investigating, handling and reporting out-of-specification results when these are obtained

from laboratories. If a sample fails to meet the specifications, the procurement agency should investigate the problem and communicate the outcome to the manufacturer.

II.2.4.5 Step 5: Plan, prepare and perform inspections

Each batch of every product procured by a procurement agency should be manufactured in compliance with WHO GMP to ensure batch-to-batch consistency.

The actual site of manufacture of the product should be known and specified.

In some cases, a contract manufacturer may manufacture the product on behalf of the supplier or agent. Each manufacturing site specified in the product information should be inspected to assess compliance with WHO GMP.

Manufacturers of the APIs may be inspected, based on risk assessment, as part of the assessment procedure to ensure that the APIs were manufactured in accordance with WHO GMP.

Existing certificates

ISO certification is not an assurance of compliance with WHO GMP and is not a replacement or substitute for verification of compliance with WHO GMP.

Similarly, a CPP is not a guarantee of compliance with GMP. Participation in the WHO Certification Scheme (*7*) is a voluntary process, and there is no formal assessment or evaluation of medicines regulatory authorities entering the scheme. In some cases, reliance on the CPP alone is therefore not recommended.

The certification scheme is an administrative tool and is reliable only where the relevant national medicines regulatory authority has an established system which is known to comply with acceptable standards for evaluation and registration or licensing of products and manufacturers, including products for export markets. Information in addition to the CPP, e.g. a copy of the inspection report and corrective action plan from the manufacturer, may be requested. These documents, in addition to other documentation, may be considered useful in the prequalification process and in follow-up assessment or evaluation at a later stage.

The procurement agency should still verify compliance with WHO GMP as part of the prequalification procedure, and an inspection of the manufacturing site must be considered in every case. An example of requirements applicable to quality systems for the operation of inspection services can be found in Appendix 8.

Inspectors

Inspections should be performed by a suitably qualified, experienced inspector or team of inspectors with relevant qualifications, training and experience in

performing inspections in foreign countries. Inspectors should have sound knowledge of quality assurance and GMP in production and quality control of pharmaceutical products. A sufficient number of inspectors should be appointed to carry out inspections within predetermined time frames.

Where possible, a representative from the procurement agency (the person responsible for prequalification with knowledge of GMP) should be part of the inspection team.

In exceptional cases, consultants from the private sector may be appointed to perform inspections, provided that there is no conflict of interests and that all confidentiality undertakings are agreed upon and maintained. For these reasons, persons working in a manufacturing company may not be considered suitable. Interested external inspectors should submit their letters of interest and curricula vitae to the procurement agency. The agency should review the documentation before deciding to appoint any inspectors. A formal agreement for the performance of work and terms of reference should be in place before commencement of work by contracted inspectors.

A summary list of names, addresses, dates of appointment, qualifications and experience of inspectors should be maintained.

Planning and preparation of inspections

In preparation for the inspection, the procurement agency should ensure that the manufacturers who have submitted EOIs to supply products are listed in a recording system for inspection planning purposes.

To facilitate planning and to save costs, manufacturers should be grouped together by country. In some countries, one manufacturer may have different manufacturing sites in addition to the submitted address of the headquarters.

Manufacturers should be informed of tentative inspection dates, and should be requested to submit information about each manufacturing site to be inspected.

This information should normally be provided in a site master file (SMF). An example of a technical questionnaire for pharmaceutical manufacturers is attached as Appendix 9.

This information will be used during the preparation for the inspection and during the inspection itself to verify information supplied by the manufacturer to the procurement agency.

An example of an SOP for planning an inspection is shown in Appendix 10.

As the manufacturer will be inspected as part of the process of prequalification for the supply of specific products to the procurement agency, inspectors should prepare for inspections by studying the product information submitted by the manufacturer.

Appendix 11 contains an example of an SOP for preparing for an inspection.

A site visit before deciding whether a GMP inspection should be performed may in some cases be appropriate. This visit is optional and does not lead to the requirement for the performance of the inspection being waived.

Performing inspections

Inspections should be performed in accordance with a written procedure.

The inspection should cover all aspects of WHO GMP. An example of an SOP for performing an inspection is shown in Appendix 12.

Information submitted in relation to the supply of the API, formulation of the product, manufacturing method and stability data should also be verified during the inspection.

The inspection should cover the evaluation and assessment of the documentation, premises, equipment, utilities and materials. It should also cover verification of data and documentation such as results, batch records, compliance with an SOP and information submitted on the manufacturing method, equipment and aspects including (but not limited to) validation of the manufacturing process, validation of utilities and support systems, and validation of equipment.

If checklists are used, these should be drawn up and agreed upon for use by collaborating procurement agencies implementing this MQAS. An example of a GMP checklist is shown in Appendix 13.

Waiving of inspections

The need for an inspection may be waived where there is evidence that the site was inspected and approved by an inspection authority which is a member of PIC/S; an ICH member or its associated country; or from the WHO Prequalification Programme for the manufacturing site under consideration, covering activities for the product(s) being prequalified, provided that:

- all aspects of GMP for the relevant product(s) have been covered;
- the approval was within the last 36 months;
- there is a statement from the manufacturer that no major changes have been made to premises, equipment and key personnel since the inspection by the medicines regulatory authority.

Inspection report

Each inspector or inspection team (where inspection teams are performing inspections) should prepare a formal inspection report for each manufacturing site inspected.

The inspector or inspection team should make a recommendation on the status of the manufacturer in relation to compliance with WHO GMP. According to the findings, the recommendation following the inspection may for example be one of the following.

- The manufacturer is considered not to be operating at an acceptable level of compliance with WHO GMP and a follow-up inspection is recommended to verify implementation and acceptability of corrective actions.
- The manufacturer is considered not to be operating at an acceptable level of compliance with WHO GMP and a compliance report is needed to verify implementation and acceptability of corrective actions.
- The manufacturer is considered to be operating at an acceptable level of compliance with WHO GMP.
- The manufacturer is considered not to be operating at an acceptable level of compliance with WHO GMP.

The inspector or inspection team(s) will finalize a report according to the recommended format published in WHO *Guidance on good manufacturing practices (GMP): inspection report* (*8*) (see Appendix 14 for a model inspection report).

A copy of the inspection report should be filed in a central manufacturer's file that is unique to that manufacturer.

The inspection report should be communicated to the manufacturer. Where noncompliance was observed, corrective actions and timelines for completing them should be suggested. A response with supporting documentation should be invited from the manufacturer.

If any additional information is required, or if corrective action has to be taken, a final recommendation as to the acceptability of the product and manufacturer should be made only after such information has been evaluated, or the corrective action has been verified. In the event of any dispute, a standard procedure should be followed for discussing and resolving the issue.

The ownership of the report should be with the procurement agency, as it is responsible for the prequalification.

II.2.4.6 Step 6: Finalize assessment process

Decision-making process for acceptance or rejection of a manufacturer

The procurement agency should follow a written procedure to collate the outcomes of the evaluation of product information, laboratory results for samples analysed and inspection reports.

This SOP should also identify the people responsible for taking the decision to accept or reject a product and/or manufacturer, including the grounds for the decision. It may be helpful to refer to the responsible person by position, rather than by name.

The procurement agency should inform the manufacturer in writing of the outcome of the prequalification of each product manufactured at each specified site.

Recording of outcomes

The person responsible for prequalification should record the outcome of the prequalification process in a list of prequalified products and manufacturers.

The list should include only those products evaluated as indicated by the manufacturer. It should be product- and manufacturing-site-specific.

The list may be published in the public domain.

Information on prequalified sources should be transparent and made available to customers when required.

The procurement agency should have an agreement with the supplier to ensure compliance with the prequalification principles and that the products supplied are the same products as were prequalified (e.g. they are manufactured at the same site and the same processes are adhered to).

The list should be reviewed and updated at regular intervals. Newly prequalified manufacturers should be added to the list as they become qualified, and non-compliant manufacturers should be removed from the list as soon as they are recognized as such.

Where possible, more than one supplier of a product should be included on the list to ensure open and transparent procurement through competitive procurement procedures (see Module III).

II.2.5 Requalification and monitoring

Requalification should occur at regular intervals. Routine re-inspection of manufacturers should take place as required based on risk assessment but at least every five years. Routine reevaluation of product information or questionnaires should be done every five years. Non-routine reevaluation and/or inspection should be done when necessary, e.g. when the manufacturer implements any change to the formula, manufacturing method or manufacturing site; if any product supplied is considered not to be in compliance with the agreed specification of the product; or if a serious complaint has been received. For more details on reassessment see Module VI.

II.2.6 Monitoring of complaints

Complaints should be handled in accordance with a written procedure.

A written report of the complaint, investigation, effective implementation of corrective and preventive action (CAPA) and outcome should be available.

Any complaint concerning a pharmaceutical product or batch of products supplied should be thoroughly investigated and include a root cause analysis, risk assessment and effective CAPA to avoid recurrence. The nature of the complaint should be communicated to the manufacturer.

The outcome of the investigation should be communicated to the complainant.

II.2.7 Cost recovery

It is recommended that the costs of prequalification should be covered by the procurement agency. If costs are to be recovered, defined transparent procedures should be established and manufacturers should be notified of these procedures in advance.

Cost recovery should be based on a fee-for-services structure.

II.3 List of suggested SOPs

- communication between the procurement agency and national medicines regulatory authority
- assessment of product data and information for compliance with norms and standards
- assessment of manufacturing sites for compliance with WHO GMP
- assessment of product data and information submitted by manufacturers
- assessment report writing
- planning of inspection
- inspection report writing
- procedure for prequalification
- delegation of prequalification to another procurement agency
- establishing specifications for products
- publication of invitations for expressions of interest (EOI)
- preparation and maintenance of the guidelines for the compilation of product information
- preparation and maintenance of the list of prequalified products and manufacturers
- receipt of product information
- screening of product information (for completeness on initial receipt)

- informing manufacturers of the outcome of the evaluation of the product information
- communicating with the person responsible for inspections of manufacturing sites
- recruiting or appointing inspectors with appropriate qualifications and experience when necessary
- follow-up of CAPA after inspections
- training of inspectors when necessary
- informing manufacturers of the outcome of the inspection
- preparation of product specifications for prequalification
- publication of product specifications for prequalification
- receipt of information (including late arrivals) and record-keeping
- contracting of a quality control laboratory
- submission of samples to a contract laboratory
- investigating, handling and reporting out-of-specification results
- waiving of inspections
- decision-making process for acceptance or rejection of a manufacturer
- requalification
- handling of complaints
- cost recovery on a fee-for-services basis.

MODULE III

Purchasing

III.1 Introduction

Procurement should be done with the aim of purchasing effective, quality assured products, and should not be focused on price alone.

Prequalification of products and manufacturers as described in Module II contributes to ensuring in advance that manufacturers and suppliers can deliver quality products on a sustained basis.

This Module gives an overview of the strategies and methods used in pharmaceutical procurement. The term "procurement" in this Module relates specifically to the purchase of health sector goods from manufacturers or suppliers. The Module goes on to describe the key activities in purchasing pharmaceutical products, as well as the recommended organizational structure of the procurement agencies which carry out these key activities.

See also *Operational principles for good pharmaceutical procurement* as recommended by the Interagency Pharmaceutical Coordination Group (IPC) (*9*).

III.2 Procurement strategies

Strategic objectives for good pharmaceutical procurement include:

- selection of reliable suppliers of quality products;
- procurement of the most cost-effective pharmaceutical products in the right quantities and meeting the quality standards;
- mitigating possible risks;
- timely delivery;
- achievement of the lowest possible total cost (which includes but is not limited to the price, cost of analysis, and transportation).

Where the supplier is an entity other than the manufacturer, such a supplier should meet the standards recommended in this MQAS.

These objectives should be achieved through efficient and transparent management reflected in an appropriate division of the different activities and responsibilities; appropriate standardization, selection, specification and quantification of pharmaceutical products; the use of good financial management procedures and competitive procurement methods; and a quality system that involves the selection and monitoring of qualified suppliers and their products.

It is recommended that a standard procedure be prepared to assist in the calculation of the lowest possible total cost. This approach aims to ensure that costs are calculated in a consistent manner, with a consistent weight given to each of the factors taken into account.

To be effective, a procurement agency should ensure that the following principles are applied:

- prequalified products are purchased from approved manufacturers or suppliers;
- procurement and purchasing procedures are transparent;
- activities follow formal written procedures throughout the process, including explicit criteria for awarding contracts;
- independent contract review;
- purchasing is based on the defined procurement policy of the procurement agency;
- purchasing and tender documents list all pharmaceutical products by their INN or national generic names;
- suppliers are selected and monitored through a process that takes into account product quality, service reliability and performance, delivery time, ethics, legal status, financial viability and minimum order quantities;
- intellectual property rights are respected in accordance with best practice and national law.

III.3 Procurement methods

Although there are different methods of procurement, they all involve a number of common activities that must take place beforehand. These activities are the establishment of technical specifications, quantification of requirements, and selection of product(s) and manufacturer(s) preferably based on prequalification.

Whatever the procurement method, responses should be examined to ensure that offers have been received from invited suppliers and that the offers are substantially responsive to the defined terms and conditions. Awards should be made to the maker of the lowest acceptable offer for the prequalified product that meets the terms and conditions. The companies should be informed of the outcome.

A brief description of different procurement methods is given below. (See also *Operational principles for good pharmaceutical procurement* (IPC) (*9*); and *Managing drug supply* (MSH)) (*10*).

III.3.1 Restricted tender

In a restricted tender, also called a "closed bid" or "selective tender", interested suppliers are approved in advance through a prequalification process. This type

of procurement is often referred to as "limited international bidding" (LIB) which is an "invitation to competitive bids" conducted by direct invitation to all prequalified suppliers. Procurement agencies should use restricted tenders to invite bids from prequalified suppliers for all health products and services whenever possible.

III.3.2 Competitive negotiation

This method is also referred to as "international/national shopping". The basis of this method is the comparison of price quotations obtained from several local or foreign suppliers. Usually, quotations are solicited from a minimum of three suppliers to ensure competitive prices.

This method is appropriate for procuring small amounts of readily available products. However, its use should be explicitly justified, and approval should be obtained from senior management. Only prequalified products and suppliers should be used.

III.3.3 Direct procurement

In direct procurement, products are obtained directly from a single source without applying the requirements of a tender process or comparing price quotations.

Normally direct procurement is not recommended, but it may be used when there is only one prequalified source for the product to be procured. A history of "reasonable" prices for the product in question should be assessed to negotiate the price with the supplier.

III.3.4 Open tender

Open tender is the formal procedure by which all manufacturers, national and international, are invited to bid for the sale of goods. The term "international competitive bidding" (ICB), which is an open tender to all manufacturers, is often used.

Open tendering is not appropriate for health products, because it may be difficult to establish, before a contract is awarded, whether unknown bidders will be able to supply products of the required quality in the required quantities on a sustained basis.

III.4 Quality assurance in purchasing

The procurement agency should have a documented infrastructure for purchase and procurement of health products and services, which should aim to ensure that products are of the quality required for their intended use.

III.5 Key activities in purchasing

III.5.1 Develop a list

The procurement agency should develop a list or catalogue of products, listed by INN, that are identified for purchasing based on need, the national list of essential medicines, and the WHO Model List of essential medicines (*2*).

The procurement agency should develop specifications for the products in accordance with what has been prequalified and the terms and conditions for procurement. These may include pack size, remaining shelf-life, and lead time, among others.

III.5.2 Quantification

All requests for products should include quantities. Accurate quantification of needs is essential to avoid shortages or excess stocks. Quantities purchased should be based on a reliable estimate of actual need.

The possible methods of product quantification include the consumption method, the morbidity method and the adjusted or extrapolated consumption method.

III.5.3 Procurement method

The procurement agency should apply the procurement method according to their policy and procedures (see also section III.3 above).

III.6 Organization and responsibilities

Purchasing should be done by personnel with appropriate qualifications and training, following established procedures.

Each staff member who undertakes purchasing or provides support to purchasing should have a job description which clearly describes his or her tasks and responsibilities.

The personnel responsible for purchasing should be independent from those responsible for prequalification and quality assurance.

Key responsibilities may include:

- preparing requests for quotations or tender documents
- publishing and handling tenders (when applicable) according to best practices
- handling contracts
- price negotiations
- placing orders
- market research
- monitoring suppliers' performance.

The personnel should follow transparent, written procedures throughout the process of purchasing and should use explicit criteria for deciding to whom to award contracts.

All staff in the purchasing group must sign confidentiality agreements and declarations of conflict of interest.

There should be mechanisms in place to ensure reliable financing for procurement. Good financial management procedures should be followed to ensure that financial resources are used with maximum efficiency. Funds should be allocated before the tender is issued, and should be released in accordance with the purchase contract.

Procurement should be planned properly, and procurement performance should be monitored regularly.

III.7 Monitoring of performance of prequalified manufacturers

There should be a procedure for continuous monitoring of the performance of the manufacturers and suppliers. This may be a joint responsibility of different sections/units and include quality assurance and purchasing, among others. If a decision is taken to remove a product, manufacturer or supplier from the list, the supplier or manufacturer should be notified and a mechanism should be in place to prevent purchasing from this supplier or manufacturer.

Monitoring may include:

- review of quality control results;
- verification that the product batches supplied have been manufactured in compliance with standards and specifications accepted in the product dossier through inspection;
- pharmacovigilance (e.g. management of adverse event reporting);
- monitoring of complaints;
- outcome of inspection of manufacturing sites;
- outcome of reassessment of product information;
- monitoring of direct and indirect product costs;
- monitoring of adherence to delivery schedules.

Random samples of batches of pharmaceutical product(s) supplied by prequalified manufacturers, taken in accordance with a predefined sampling procedure (based on risk assessment), should be sent for independent testing at a reliable quality control laboratory (e.g. a WHO-prequalified laboratory) for compliance with final product specifications as part of the continuous monitoring programme.

The monitoring process should include continuous commercial monitoring that includes tracking of lead-time and monitoring for compliance with all of the contract terms and conditions.

There should be an information system that keeps track of the value of contracts awarded, the value of total purchases from each supplier per year and the performance for each tender (e.g. speed of delivery and compliance with specifications).

III.8 Country legislation

Customers requesting products from procurement agencies should be responsible for ensuring that the products supplied comply with the destination country's legislation on registration and licensing status and intellectual property rights.

III.9 Donations

Any procurement agency receiving donations should handle donated medicines in accordance with a written procedure to ensure that patients receive products of known, appropriate quality. The WHO *Guidelines for drug donations* (*11*) outline the key issues. The principles established in these guidelines should be followed.

III.10 List of suggested SOPs

- selection of suppliers and products
- quantification of products
- calculation of the lowest possible total cost
- ensuring that prequalified products are purchased from approved manufacturers
- awarding contracts
- independent contract review
- purchasing of products
- considering intellectual property rights
- preparation of requests for quotations or tender documents
- publishing and handling tenders
- handling contracts
- price negotiations
- market research
- monitoring suppliers' performance
- pharmacovigilance
- monitoring of direct and indirect product costs
- monitoring of adherence to delivery schedules
- donations.

MODULE IV

Receipt and storage of purchased products

IV.1 Introduction

The procurement agency should ensure that the pharmaceutical products purchased are received and stored correctly and in compliance with applicable legislation and regulations. Products should be received and stored in such a way that their quality and integrity is preserved, batch traceability is maintained and stock can be rotated.

It is recommended that premises are designed in such a manner that products will follow a unidirectional flow from receiving to dispatch, to avoid any possible mix ups.

Effective measures should be in place to ensure the security of materials and products.

This Module focuses on quality assurance and quality control during receipt and storage of products.

Quality control is concerned with sampling, specifications and testing as well as with the organization, documentation and release procedures which ensure that the necessary and relevant tests are carried out, and that materials or products are not released for use until their quality has been judged satisfactory for their intended purpose.

Each procurement agency should have access to a quality control laboratory, which should meet the general requirements for facilities, policies and procedures, staff expertise, experience and training as specified in Module I, as well as the requirements outlined in Module II under "Analysis of samples".

The quality control laboratory must be capable of undertaking the full range of tests required. Any subcontracting of such work to third parties should be managed correctly and the responsibility for the quality of the work done should be clearly defined.

The principles established in the WHO guide to good storage practices for pharmaceuticals (*12*) (see Appendix 15) should be followed throughout the steps described in this module.

IV.2 Pre-shipment quality control

Note: Pre-shipment is considered at manufacturer level prior to sending the product(s) to the procurement agency or customer.

Each batch of finished product should be tested by the manufacturer to determine that it conforms satisfactorily to its finished product specification, prior to supply.

The procurement agency may decide, using a risk-based approach, to test selected batches.

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

IV.3 Receipt of stock

Receiving and dispatch bays should protect materials and products from the weather. Receiving areas should be designed and equipped to allow containers of incoming materials to be cleaned if necessary before storage.

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

Products should be quarantined until test results confirm that the products meet all of the requirements, specifications, terms and conditions of the purchase order. It is strongly recommended that a review of certificates of analysis be made to confirm that what has been delivered is what was ordered and is certified by the manufacturer to meet specifications.

Upon receipt, each incoming delivery should be checked for correspondence between the order, the delivery note, the supplier's labels and transport conditions (e.g. temperature and relative humidity as appropriate). The consignment should be examined for integrity of packages and seals, and for uniformity of the containers. Should the delivery comprise more than one batch, it should be subdivided according to the supplier's batch number.

Containers should be cleaned where necessary and labelled, if required, with the prescribed data, e.g. label description, batch number, type and quantity.

Containers and products should be visually inspected for possible contamination, tampering and damage, expiry date, compliance with labelling and packaging instructions, and any suspect containers, or the entire delivery, should be quarantined. Damage to containers and any other problem that might adversely affect the quality of the material should be recorded and investigated.

The person responsible for receiving the goods should be independent of the person responsible for purchasing the goods.

V.4 Post-procurement quality control

Note: Post-procurement is considered at procurement agency level or at the level of the customer.

IV.4.1 Sampling

The procedures for receipt of supplies should include random sampling for independent laboratory analysis by the procurement agency to ensure that pharmaceutical products meet the required standards. Sampling should be performed in accordance with a written procedure and with national legislation. Products may also be randomly sampled at the end of the distribution chain

and sent for independent analysis. Representative samples should be taken from containers in the consignment. The samples should be analysed for compliance with the product specification.

Samples should be taken only by appropriately trained and qualified personnel and strictly in accordance with written sampling plans and sampling instructions that are based on risk assessment. (See also WHO guidelines on sampling and International Organization for Standardization (ISO)/American National Standards Institute (ANSI) guidelines on sampling (*13–15*).) Containers from which samples have been taken should be labelled accordingly.

Following sampling, goods should be quarantined. Batch segregation should be maintained during quarantine and all subsequent storage. Materials and pharmaceutical products should remain in quarantine until an authorized written release or rejection is obtained.

IV.4.2 Rejected materials

Stringent precautions should be taken to ensure that rejected materials and pharmaceutical products cannot be used. This can be achieved through separate storage or by means of a validated computerized system. Rejected materials may await destruction or return to the supplier. Whatever action is taken should be approved by authorized personnel and recorded. Rejected materials should be handled in accordance with a written procedure.

IV.5 Storage of materials and products

IV.5.1 Staff

All members of staff should be trained to observe high levels of personal hygiene and sanitation. The duties and responsibilities of all members of staff should be available in the form of a written job description.

Personnel employed in storage areas should wear protective or working garments appropriate for the activities they perform.

IV.5.2 Storage areas

Storage areas should be of sufficient capacity to allow orderly storage of the various categories of materials and products, including space for segregation of rejected, expired, recalled or returned stock. This includes appropriate measures for narcotics and psychotropic medicines which should be kept locked up and controlled under specific procedures as required by national legislation.

Adequate ventilation should be in place to control temperature and relative humidity. Where special storage conditions are required (e.g. for temperature and humidity) these should be provided, checked, monitored and records maintained.

Precautions should be taken to prevent unauthorized entry into the storage areas. A security system sufficient to safeguard all areas of the warehouse and offices should be in place.

A written procedure for fire control measures should be in place, including prevention of fire, fire detection and fire drills. Fire detection and fire-fighting equipment should be serviced regularly.

Smoking and eating should not be permitted in the storage areas.

Toilet and washing facilities should be sufficiently separated from storage areas.

IV.5.3 Storage conditions

All materials and products should be stored under the appropriate conditions established by the manufacturer and in an orderly fashion to permit batch segregation and stock rotation according to the first-expiry, first-out (FEFO) rule.

Stock should be stored off the floor and suitably spaced to permit cleaning and inspection. Pallets should be kept in a good state of cleanliness and repair and contents on pallets should be stacked in a manner that ensures that there is no damage to containers on the lower level.

Storage areas should be kept clean and free of vermin and accumulated waste. A written sanitation programme should be available indicating the cleaning and pest-control methods used, and their frequency of use. Safe pest-control agents should be used which will not contaminate materials and pharmaceutical products. There should be appropriate procedures for the cleaning up of any spillage to eliminate any risk of contamination.

Storage conditions used for pharmaceutical products and materials should comply with the instructions on the label, which are based on the results of stability testing.

In general, the instructions on the label have the meanings given in WHO GSP (http://www.who.int/medicines/areas/quality_safety/quality_assurance/GuideGoodStoragePracticesTRS908Annex9.pdf).

Cold rooms should be provided for storage of materials and products requiring storage under specified conditions between 2 and 8 °C. Cold rooms should be qualified, which includes temperature mapping. The temperature should be controlled, monitored and recorded with results reviewed for compliance with the specified limits. Where electronic systems are used for data collection, provision should be made for back-up of data at regular and defined intervals. Cold rooms should be fitted with alarm systems that will alert personnel of out of limit conditions.

In certain cases, e.g. with freeze-sensitive vaccines, products that have been stored below the temperature specified on the label should be destroyed.

Freeze-sensitive products should be equipped with an appropriate monitoring device.

IV.5.3.1 Monitoring of storage conditions

Temperature mapping of the facility should be well designed to support assurance of uniformity of the temperature across the storage facility. It is recommended that temperature monitors should be placed in the worst-case areas of the facility. Recorded temperature monitoring data should be available for review.

The equipment used for continuous monitoring should be calibrated at suitable predetermined intervals and the results should be recorded, reviewed and retained. Out of limit and out of trend results should be investigated in accordance with an SOP and appropriate action should be taken. All monitoring records should be kept for at least one year after the end of the shelf-life of the stored material or product, or as long as required by national legislation.

IV.5.4 Repackaging and relabelling

Where repackaging or relabelling is done, compliance with the requirements of national legislation and WHO GMP will be considered mandatory.

IV.5.5 Miscellaneous and hazardous materials

Materials which may affect other materials stored in their vicinity should be handled in accordance with a written procedure. Rodenticides, insecticides, fumigating agents and sanitizing materials should not be permitted to contaminate equipment, materials, or products. Toxic substances and flammable materials should be clearly marked as such and should be stored in suitably designed, separate, enclosed areas as required by national legislation. Flammable substances should be kept away from corrosive or oxidant substances at all times.

IV.5.6 Stock control

Stock rotation and control is best maintained by the use of a validated stock control system. Care must be taken to select a system that can manage the rigid requirements for batch number control and expiry dating, which are essential for handling pharmaceutical products.

Periodic stock reconciliation should be performed comparing actual and recorded stock levels.

All significant stock discrepancies should be subjected to investigation as a check against inadvertent mix ups and/or incorrect issue. Records should be maintained.

Damaged containers should not be issued unless it is certain that the quality of the material inside is unaffected. Any damaged containers should be reported without delay to the person responsible for quality assurance. Any action taken should be in accordance with an SOP and documented.

IV.5.6.1 Control of obsolete and outdated materials and products

All stock should be checked regularly for obsolete and outdated materials and pharmaceutical products. All due precautions should be observed to prevent issue of outdated materials and pharmaceutical products. The handling of such materials should be subject to a written procedure.

IV.5.6.2 Recalled materials and products

Recalled products should be identified, recorded, reconciled, and stored separately in a secure area until a decision has been taken on their fate. The decision should be made as soon as possible in coordination with the manufacturer. An assessment should be made by an appropriately qualified and experienced member of staff.

IV.5.6.3 Returned goods

Returned goods should be handled in accordance with a written procedure.

They should be placed in quarantine until a decision has been taken on their fate. Products returned from the customer should be destroyed in compliance with national requirements unless it is certain that their quality is satisfactory. In that case, they may be considered for resale. The nature of the product, any special storage requirements, its condition and history, and the time elapsed since it was issued should all be taken into account in this assessment. Where any doubt arises over the quality of the product, it should not be considered suitable for reissue. Any action taken should be recorded.

IV.5.6.4 Waste materials

Waste materials should be handled in accordance with a written procedure. Provision should be made for the proper and safe storage of waste materials awaiting disposal. Toxic substances and flammable materials should be stored in suitably designed, separate, enclosed cupboards, as required by national legislation.

Waste material should not be allowed to accumulate. It should be collected in suitable receptacles for removal to collection points outside the buildings and disposed of safely and in a sanitary manner at regular and frequent intervals in accordance with national regulations.

IV.5.7 Documentation: written instructions and records

Written instructions and records should be kept which describe the storage procedures and define the routes of materials, pharmaceutical products and information through the procurement agency, including handling of expired stock. Batch traceability is essential in the event of a product recall.

Permanent information, written or electronic, should exist for each stored material or product to indicate recommended storage conditions, any precautions to be observed and retest/expiry dates. National regulations concerning labels and containers should be respected at all times.

Records should be retained for each delivery. They should include the description of the goods, quality, quantity, supplier, supplier's batch number, the date of receipt, assigned batch number and the expiry date. National regulations which state a period for retention of records must be observed.

Where no such regulations exist, records should be retained for one year after the end of the shelf-life of incoming products. Comprehensive records should be maintained of all receipts and issues of materials and pharmaceutical products according to a specified system, e.g. by batch number.

IV.6 List of suggested SOPs

- receipt of products
- storage of products
- access control to areas
- handling of damaged containers
- preshipment sampling and testing
- postshipment sampling and testing
- handling of rejected products
- handling of returned products
- procedure for gowning
- fire control
- environmental monitoring
- cleaning of storage areas
- FEFO
- rodent and pest control
- packaging of freeze-sensitive materials
- temperature mapping studies
- handling of toxic and flammable goods
- handling of spillages
- stock reconciliation
- control of obsolete materials and products
- handling of waste materials.

MODULE V

Distribution

V.1 Introduction

A well-managed distribution system should achieve the following objectives:

- maintain a constant supply of medicines;
- keep medicines in good condition throughout the distribution process;
- ensure controlled transport conditions;
- minimize losses of medicines due to spoilage and expiry;
- maintain accurate inventory records;
- rationalize medicine storage points;
- use available transportation resources as efficiently as possible;
- reduce theft and fraud;
- provide information for forecasting medicine needs.

This Module focuses on measures to be taken to ensure product integrity and quality during distribution, and outlines the main points. The principles established in the WHO *Guidelines for good trade and distribution practices for pharmaceutical starting materials* (*16*) (see Appendix 16) should be followed.

V.2 Transport conditions

Materials and pharmaceutical products should be transported in such a way that the integrity of the material or pharmaceutical product is not adversely affected and that appropriate storage conditions are maintained.

Where temperature excursions occur during transport, risk assessment should be done to ensure that an informed decision is taken as to the fate of the products.

Every precaution should be taken to minimize the risk of theft and fraud.

V.3 Cold chain

Special care should be exercised when using a cold chain. If goods are distributed under controlled cool or cold conditions, appropriate containers should be used. Containers should be packed following established standard procedures to ensure that products are not negatively affected.

When a cooling agent, such as dry ice, is used in cold chains, it is necessary to ensure that the material or product does not come in contact with the cooling agent as this may adversely affect the quality of the product, e.g. as a result of freezing.

The process should be validated to cover the expected transport time, taking into account expected environmental conditions.

V.4 Temperature monitoring and records

Calibrated devices should be used to monitor conditions such as temperature during transportation. Records should be available for review.

V.5 Delivery order

The dispatch and transport of materials and pharmaceutical products should be carried out only after receipt of a delivery order, which has to be documented. There should be a procedure to ensure that products are supplied to authorized recipients only.

V.6 Dispatch procedures and policies

Rules for dispatch procedures should be established according to the nature of the materials and pharmaceutical products being dispatched and after taking into account any special precautions to be observed. Any special packaging requirements for movement of goods must be met. Some goods may require special protection before they can be shipped by sea or by air.

All legislation that may affect these requirements must be complied with.

V.7 Dispatch containers

The outside container should offer adequate protection from all external influences and should be indelibly and clearly labelled.

Products should be packed in such a way as to minimize the risk of theft, e.g. by using locked containers or by shrink-wrapping entire pallets in plastic.

V.8 Dispatch records

Records for dispatch should be retained, stating at least the following:

- date of dispatch;
- customer's name and address;
- product description, e.g. name, dosage form and strength (if appropriate), batch number and quantity;
- transport and storage conditions.

V.9 Traceability

Records of distribution should contain sufficient information to enable traceability of the product from the point of supply to the point of delivery.

Traceability of goods is crucial in case of the need for product recalls. It will also help to detect theft and fraud. Any discrepancies should be investigated and followed up by appropriate measures to tackle possible security breaches.

V.9.1 Recalled materials and products

When required, materials and products should be recalled following a written procedure. Written records of all major actions signed by the person responsible for carrying out each action should be maintained.

Recalled products should be identified, recorded, and reconciled.

The effectiveness of the arrangements for recalls should be evaluated at regular intervals.

V.10 Port of entry

All conditions required for storage should be achievable at the port of entry of goods. This is particularly important for all temperature-sensitive products shipped to ports where temperatures may be less well controlled. Specific arrangements may need to be made with local handling agents and customs to ensure speedy handling and clearance.

Security measures to prevent theft, fraud and bribery should be in place during storage at the port of entry.

V.11 List of suggested SOPs

- packaging of products in containers
- maintaining appropriate storage conditions during transport
- maintaining the cold chain
- calibration of temperature sensors and devices
- verification of authorized recipients
- labelling of outer containers
- maintaining dispatch records.

MODULE VI

Reassessment

VI.1 Introduction

The quality of all products and services procured in accordance with this MQAS should be continuously monitored. Reassessment will be required to ensure that the products procured continue to meet the norms and standards defined. This module briefly outlines the principles of routine and non-routine assessment of manufacturers, products and contracted-out services.

II.2.5 Requalification and monitoring

Requalification should occur at regular intervals. Routine reinspection of manufacturers should take place as required based on risk assessment but at least every five years. Routine reevaluation of product information or questionnaires should be done every five years. Non-routine reevaluation and/or inspection should be done when necessary, e.g. when the manufacturer implements any change to the formula, manufacturing method or manufacturing site; if any product supplied is considered not to be in compliance with the agreed specification of the product; or if a serious complaint has been received. For more details on reassessment see Module VI.

Random samples of batches of pharmaceutical product(s) supplied by prequalified manufacturers, taken in accordance with a predefined sampling procedure (based on risk assessment), should be sent for independent testing at a reliable quality control laboratory (e.g. a WHO-prequalified laboratory) for compliance with final product specifications as part of the continuous monitoring programme.

VI.2 Reevaluation of manufacturers

Reinspection of manufacturers should take place at regular intervals based on risk assessment, but no less often than every five years.

Procurement agencies should have a mechanism in place that ensures that manufacturers inform them immediately of any changes to the manufacturing site, manufacturing process or equipment that may have an impact on its prequalification. Non-routine requalification may be required in the following situations:

- in case of any omission of information in the initial assessment;
- if false or misleading information is suspected during the follow-up assessment;

- if changes are implemented that may have an impact on the prequalification of the manufacturing site, such as changes to key personnel or organizational structure, changes to equipment, apparatus or the manufacturing process, or the renovation or addition of facilities that need validation, commissioning or reinspection; or
- if a complaint considered to be serious in nature has been received.

The procurement agency should suspend or withdraw a prequalified facility from the prequalification list if there is evidence of noncompliance with the requirements for prequalification.

VI.3 Reevaluation of products

Product information should be reviewed every five years or sooner if major changes occur in the meantime.

Procurement agencies should have a mechanism in place that ensures that manufacturers inform them of any contemplated changes to the product that may affect its safety, efficacy or quality. With regard to the product, manufacturers should, for instance, report the following:

- change of manufacturing process, site or equipment relating to the product;
- change of contract manufacturers;
- change of pharmaceutical product release control laboratories;
- change of suppliers of starting materials or container or closure;
- changes to the formulation or composition of the product;
- new analytical method in the testing of starting material, intermediate or final product;
- change of specifications;
- change in shelf-life.

Based on the information submitted, the person responsible for prequalification should decide whether to approve the changes or whether to request additional data.

The section or department responsible for prequalification of products and manufacturers should inform the purchasing office about the changes and the result of the evaluation of such changes.

Non-routine reevaluation of products should be done in the following cases:

- if any omission by the manufacturer in the initial evaluation procedure, or during the follow-up activities, is evident in relation

to the requirements, including compliance with quality system standards and failure to notify complaints;

- if any batch or batches of supplied product(s) are documented by the procurement agency as not being in compliance with the agreed specifications of the product or as revealing failure(s) regarding safety, performance or quality of the product;
- if the investigation of a complaint considered leads to the conclusion that the quality and/or safety of the product is in question;
- if any fraud or misconduct by the manufacturer is evident;
- if any batch or batches of product(s) was supplied and is considered not to be in compliance with the agreed specification of the product;
- if a complaint considered to be serious in nature had been received by the organization;
- in cases of changes or variations to products, the WHO publication *Marketing authorization of pharmaceutical products with special reference to multisource (generic) products: a manual for medicines regulatory authorities* (*3*) gives guidance on when to proceed with which type of reevaluation;
- if, in the opinion of the organization, changes made in the sourcing of the API, formulation, manufacturing method, facility or other production aspects require that a reassessment be made;
- if supply has been suspended for one year or longer.

VI.4 Monitoring of contracted services

Monitoring of the performance of contractors (e.g. prequalification, quality control, storage, transport and distribution) and follow-up of noncompliance should be carried out according to a written procedure. It should include continuous monitoring, as well as periodic review and renewal of the contract.

The procurement agency should document any reported problems with service and inform the contractor of each problem. Continuous monitoring should also cover compliance of the contract-giver with contract conditions, and correction of any factors that prevent the contract-acceptor from fulfilling the specified duties.

Periodic review of the contract should be based on an assessment of the contractor's overall performance. The criteria outlined for monitoring of prequalified products and manufacturers (see section III.6) also apply to monitoring of contract acceptors who store and distribute pharmaceutical products.

Contracted laboratories should comply with the principles of GLP (*17*). The accreditation status alone does not guarantee compliance with GLP. The performance of contracted laboratories should be continuously monitored.

VI.5 List of suggested SOPs

- reassessment of product data and information
- reinspection of suppliers and manufacturers
- handling variations
- monitoring of the performance of contractors
- review of agreements.

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Further reading

Guidelines for good clinical practice for trials on pharmaceutical products. In: *WHO Expert Committee on the use of Essential Drugs, sixth report*. Geneva, World Health Organization, 2002 (WHO Technical Report Series, No. 902), Annex 8 (http://www.googlesyndicatedsearch.com/u/who?q=Good+clinical+practice+for+trials+on+pharmaceutical+products&sa=Go&sitesearch=who.int&domains=who.int

Model application form for new marketing authorizations, periodic reviews and variations, with notes to the applicant (http://apps.who.int/medicinedocs/en/d/Js2273e/13.6.html#Js2273e.13.6).

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WHO Model Formulary (http://www.who.int/selection_medicines/list/en/).

Appendix 1

Example of a Code of Conduct

1. Introduction

This Code of Conduct must be followed by appointed staff members as well as all other staff involved.

All members of staff including temporary advisers and experts appointed to carry out evaluations and inspection on behalf of WHO should keep in mind at all times the image of WHO.

(In the context of this Code of Conduct, staff and members of staff include contract appointments, short-term staff, advisers and experts appointed for the performance of work.)

2. Key responsibilities

Each member of staff, expert and temporary adviser has key responsibilities to fulfil. The overall objective is to perform these key responsibilities within the framework of this Code of Conduct.

An internal oversight framework has existed within WHO since the early days of the Organization. It is necessary periodically to ensure that all staff understand this function. The WHO summary statement on WHO's Office of Internal Audit and Oversight (IAO) which describes its purpose, authority and scope of work, should be read by each member of staff. This document summarizes the expectations for IAO and it furnishes direction for internal audit at WHO.

By accepting appointment, staff members pledge themselves to discharge their functions and to regulate their conduct to serve the best interests of WHO.

In the performance of their duties staff members shall neither seek nor accept instructions from any government or from any other authority external to the Organization.

No staff member shall accept, hold or engage in any office or occupation, which is incompatible with the proper discharge of his duties with WHO.

Staff members shall conduct themselves at all times in a manner compatible with their status as international civil servants.

Staff shall avoid any action and in particular any kind of public pronouncement which may adversely reflect on their status. While they are not expected to give up their national sentiments or their political and religious convictions, they shall at all times bear in mind the reserve and tact incumbent upon them by reason of their international status.

Staff members shall exercise the utmost discretion in regard to all matters of official business. They shall not communicate to any person any information

known to them by reason of their official position, which has not been made public, except in the course of their duties or by authorization of the Director-General. At no time shall they in any way use to private advantage information known to them by reason of their official position. These obligations do not cease with separation from service.

Any staff member who becomes a candidate for a public office of a political character shall resign from the Secretariat.

The immunities and privileges attaching to WHO by virtue of Article 67 of the Constitution are conferred in the interests of the Organization. These privileges and immunities furnish no excuse to staff members for nonperformance of their private obligations or failure to observe laws and police regulations. The decision whether to waive any privileges or immunities of the staff in any case that arises shall rest with the Director-General.

All staff members shall subscribe to the oath or declaration as set out in WHO Staff Regulations.

A staff member may not act as a delegate or observer for, or adviser to, his or her government.

A staff member may participate in international or national societies when such participation is not in conflict with the standards referred to in WHO Staff Rules and may represent such societies at an international meeting with the Director-General's authorization.

A staff member shall obtain the Director-General's permission before publishing articles whose contents reflect work performed for the Organization or information obtained arising out of such work.

All rights, including title, copyright and patent rights, in any work or invention produced or developed by a staff member as part of his official duties shall be vested in the Organization.

"Misconduct" means:

- any improper action by a staff member in his official capacity;
- any conduct by a staff member, unconnected with his official duties, tending to bring the Organization into public discredit;
- any improper use or attempt to make use of his or her position as an official for his or her personal advantage.

Any conduct contrary to the terms of his oath or declaration.

2.1 Personal responsibilities

Staff members must be committed to a strong oversight environment and must give IAO their full cooperation.

Staff must observe, implement and maintain the responsibilities in relation to the position in which they have been appointed.

Staff must perform the work they have been allocated to the best of their ability and finalize tasks in accordance with the timeframes set by WHO.

2.2 Safety

Safety is the responsibility of WHO staff, supervisors and WHO management. It includes reporting of possible hazards and suspected hazards and taking the necessary precautions and implementing safeguards to minimize safety problems.

Staff involved in activities where safety problems may arise, e.g. the inspection of a manufacturing site, should observe safety rules and regulations as recommended by WHO, the manufacturer and national legislation.

Staff must wear protective devices such as protective clothing, shields, eye covers (glasses), earplugs, where relevant, to protect the body, organs and extremities from possible harm. Staff must use their professional knowledge to ensure that they take appropriate care of their own safety. This means that should a manufacturer not provide what is deemed to be adequate personal protection, then the inspectors should refuse to enter an area on the grounds of lack of safety.

Staff must observe national regulations when driving vehicles.

Staff must be aware of, and take, the necessary precautions when collecting samples.

Special attention to safety requirements is necessary when performing site inspections. These include aspects in relation to the dosage form and activities observed (e.g. radioactive pharmaceuticals, hazardous materials, laboratory reagents, equipment and apparatus, explosions, personnel lifts, ladders, glassware, freezers, steam, radiation, microbiological hazards, viral and biological products and waste, and other relevant possible hazards).

3. Professional competence

3.1 Qualifications and experience

The staff appointed must have the required qualifications and experience to perform the tasks required. Any person appointed to perform work for or on behalf of WHO must indicate if he/she is not suitably qualified to perform the task, or does not have the relevant experience, before taking on the work or being appointed.

When people are approached to perform work on behalf of WHO, they must be truthful in providing evidence of their qualifications and experience.

Staff must not mislead WHO or procurement agencies in relation to their qualifications and/or experience. Any case of misrepresentation of qualifications or experience will be treated as fraud and may eventually lead to prosecution. No future employment in any capacity by any WHO or United Nations organization will be possible at any time.

4. Conduct

During daily activities, staff must maintain high standards of ethical conduct.

Staff must observe the WHO constitution and are responsible for complying with the WHO regulations and guidelines.

4.1 Integrity and attitude

To ensure that the business of WHO is conducted effectively, and without improper influence, all staff members must be persons of integrity and observe the highest standards of conduct.

- WHO must be able to rely upon staff to do the right things.
- Staff must be honest and dependable.
- Staff must be devoted to accuracy, truthfulness, objectiveness and fairness.
- Staff must not use restricted information not available to the general public for gain or to advance private interests.
- Staff must report findings such as presentation of false, misleading and fraudulent information provided to WHO.
- Staff should maintain a positive attitude towards WHO and its policies and projects.
- Staff must be dignified, diplomatic, tactful and courteous. Strong-arm tactics must be avoided.
- Staff must not act with an air of superiority or special authority.
- Staff must use a firm approach when requesting necessary and authorized information.
- Staff members are the contact persons of WHO and their action will be the basis upon which the public will judge the organization. Staff must exhibit exemplary behaviour at all times.

A staff member who has any financial interest in any business concern with which he may be required, directly or indirectly, to have official dealings on behalf of the procurement agency shall report such interests to the Director-General, who shall decide on the applicability of Staff Regulations. Staff may not have financial interests in companies to be evaluated or inspected. Shareholdings through pension schemes and other such "arm's length" arrangements will not normally be taken as a financial interest in this context. Any doubts on this matter should be referred to the WHO Internal Audit Office for clarification.

4.2 Attire, health and hygiene

Good public relations require that all members of staff dress appropriately for the activities to be performed. Staff should observe WHO guidelines regarding appropriate dress code.

Staff should normally wear protective clothing for inspections. Inspectors must wear protective clothing at least equivalent to that worn by employees of manufacturing sites (e.g. head covering or masks, when appropriate). Staff should conform to company procedures at all times. However, if company procedures are considered inappropriate then this fact should be recorded.

Staff involved in inspections must inform supervisors or managers of their health status when this could have impact on inspections, as persons with communicable diseases, wounds and open lesions may not be allowed in areas where products and material are exposed.

Staffs are responsible for taking the necessary precautions when travelling (e.g. having the appropriate inoculations).

Staff must practice good hygiene at all times.

4.3 Gifts, meals and favours

No staff member shall accept any honour, decoration, favour, gift or remuneration from any government, or from any other source external to the Organization, if such acceptance is incompatible with his status as an international civil servant.

A staff member who is offered any honour, decoration or gift from sources external to the Organization shall report this offer to the Director-General who shall decide on the applicability of Staff Regulations.

No member of staff shall receive or accept anything of value from any manufacturer for or because of any official act that has been performed or is to be performed.

Staff will not solicit or accept directly or indirectly any gift, gratuity, favour, entertainment loan or any other item of monetary value from members of the public with whom staff members have official relationships.

When performing inspections, staff must pay for their own meals whenever possible and must make an effort to pay for their own meals even when invited by the manufacturer, unless the situation is such that it will provoke a scene or create an embarrassment to WHO.

4.4 Management relationship

Staff must promote a positive relationship with supervisors and managers.

4.5 Standard operating procedures

Staff must follow authorized standard operating procedures (SOPs) for the performance of tasks.

4.6 Travel and accommodation

Staff must observe WHO regulations, guidelines and SOPs when travelling. The relevant procedures shall be followed for planning of visits, meetings, inspections and other activities such as making reservations and paying for accommodation.

4.7 Confidentiality and confl ict of interest

Staff must observe the WHO policy, country rules and regulations, and company policy with respect to confidentiality.

Staff must sign and abide by the conflict of interest and confidentiality undertaking.

4.8 Documentation and records

Staff shall follow SOPs and maintain appropriate records as required in the procedures.

All information provided by staff members must be truthful and correct, including reports and related documentation.

4.9 Contracts and terms of reference

Staff shall perform activities as stipulated in the contract or agreement for performance of work (APW) and terms of reference (TOR).

4.10 Product files, evaluation and inspection

Staff shall handle product files with care and treat all information as confidential relating to the task to be performed.

All data submitted initially and as a result of the evaluation, shall be dealt with in accordance with SOPs and be considered as confidential information between WHO and the manufacturer.

All aspects relating to the inspection performed shall be considered as confidential between WHO and the manufacturer.

Staff members shall observe the requirements and undertaking with regard to confidentiality and conflict of interest.

4.11 Samples

Samples taken during inspections shall be in accordance with a WHO SOP, with the approval of the manufacturer.

4.12 Evaluation and inspection reports

There shall be written evaluation and inspection reports for every product evaluated, and every manufacturing site inspected.

The reports shall be a true reflection of the findings of the evaluation and inspection.

4.13 Provision of information and advice

Staff shall not act as consultants to individual companies or manufacturers when appointed for the purposes of evaluation or inspection for a particular project, where the company can in particular benefit from such advice, unless the information is in the public domain or given to all manufacturers.

Appendix 2

Example of a guideline on confidentiality

The evaluators and inspectors will treat all information submitted and observed during the inspections and otherwise in connection with the discharge of their responsibilities with regard to the above-mentioned project, as strictly confidential and proprietary to WHO or parties collaborating with WHO in accordance with the terms set forth below and those contained in the attached provisions for team members participating in site visits within the scope of the prequalification procedure of pharmaceutical products. An example of a confidentiality undertaking is shown at the end of Appendix 3.

Evaluators and inspectors will take all reasonable measures to ensure:

- that the confidential information is not used for any purpose other than the evaluation activities described in this document;
- that confidential information is not disclosed or provided to any person who is not bound by similar obligations of confidentiality and non-use as contained herein.

Evaluators and inspectors will not, however, be bound by any obligations of confidentiality and non-use to the extent they are clearly able to demonstrate that any part of the confidential information:

- was known to them prior to any disclosure by or on behalf of WHO (including by manufacturers); or
- was in the public domain at the time of disclosure by or on behalf of WHO (including by manufacturers); or
- has become part of the public domain through no fault of theirs; or
- has become available to them from a third party not in breach of any legal obligations of confidentiality.

All personnel involved in prequalification and related matters, having access to confidential information regarding products and manufacturers, should treat all information submitted and observed during the inspections and otherwise in connection with the discharge of their responsibilities with regard to these activities, as strictly confidential and proprietary to the procurement agency or the parties collaborating with the procurement agency.

Appendix 3

Example of a guideline on conflict of interest

Introduction

This document presents policy on "conflict of interest" as it applies to external evaluators and members of advisory committees. These two categories are together referred to as "consultants" for the purposes of these guidelines. An example of a signed statement on conflict of interest is shown at the end of this Appendix.

Definitions and principles

The common meaning of "conflict of interest" is a conflict between an individual's private or personal interest and his or her duty. However, it may also refer to a situation where an individual has several duties which conflict without involvement of any private or personal interests.

A conflicting private or personal interest may be financial or non-financial as explained below.

When a decision-maker or consultant has a direct financial interest, however slight, in the matter to be decided, there is a conclusive presumption of bias and the decision-maker or consultant will thus be disqualified from acting.

Where a decision-maker or consultant has a *non-financial* interest, which gives rise to a reasonable presumption of bias, the decision-maker or consultant will be disqualified from acting. The test here is whether a reasonable observer would suspect that there is a possibility of bias, not whether that bias actually exists. A relevant non-financial interest may arise, for example, out of personal or family involvement between a decision-maker or consultant and a party whose interests are affected by the decision or recommendations. Such an interest may also arise where a decision-maker or consultant is seen to have prejudged the issues, either through preconceived opinions or prior involvement with the facts of a case on which he or she is required to make a decision on recommendations.

Conflict of interest in relation to consultants

There are a variety of situations in which consultants may find themselves in a situation of conflict of interest between their professional activities (e.g. preparation of objective and independent evaluations or membership of independent committees) and personal and private interest (e.g. private consultancies, grants to cover travel and accommodation at company-sponsored conferences, share holdings, research grants or honoraria). It is recognized that

almost all consultants have some *potential* conflict of interest because of their present or past association with the pharmaceutical industry.

Some situations of conflict of interest are clear-cut and some are more difficult to determine. If an individual is an employee of, or a retained consultant to, a pharmaceutical company, there is a clear possibility of conflict of interest. If an individual is an employee of a government organization, does no work on behalf of pharmaceutical companies, and is not in receipt of gratuities or funding, there is a minimal risk. Between these two situations is a spectrum of possibilities where the decision as to whether there is a conflict of interest may be less obvious.

Contracts are unlikely to be offered to consultants in any one of categories 1 to 6 listed below.

1. The consultant works in the pharmaceutical industry, either as an employee or as an owner or part owner (e.g. shareholder in the pharmaceutical company to be assessed).
2. The consultant receives a retainer (fee) from one or more of the pharmaceutical companies whose products she or he has to assess or which the new product is likely to replace.
3. The consultants have a *significant* direct current relationship with one or more companies. This may take the form of (a) financial support for a current research project or projects; (b) sponsorship of graduate or postgraduate students; or (c) company employees who are under the direct responsibility of the consultant.
4. He or she receives *substantial* financial assistance or expensive equipment to conduct research on behalf of the pharmaceutical company.
5. The consultant acts or has acted as a consultant for a pharmaceutical company *on the product she or he has agreed to assess*. Such a consultancy may include sponsorship as a speaker, or appointment as chairperson at professional meetings concerning the product, or attendance on behalf of the sponsoring company at national or international professional meetings concerning the product.
6. The consultant has provided significant input to the planning or conduct of a clinical trial of the product to be assessed, for example as a principal investigator, signatory to the study report, or author of any published or unpublished paper or other report of the study. Participation limited to the inclusion of patients in a large-scale multicentre study is *not* considered a significant conflict of interest.

A conflict of interest is less likely to be seen in situations 7 to 10 (see below).

7. The consultant has occasional contracts with one or more companies for particular projects, but does not have a signifi cant relationship with any one company. She or he has not been directly involved with the product in question.
8. The consultant owns or works for a consultancy, which does not provide advice to the pharmaceutical industry but may provide advice to other industries, such as the devices, food or paint industries. However it is unlikely that such consultants will have the technical knowledge or experience to qualify as a consultant in the pharmaceuticals field.
9. The consultant occasionally provides advice to one or more companies on the design of clinical trials to be conducted prior to submission of an application for marketing authorization, but does not have a significant current relationship with any one company (e.g. points 1 to 6 above).
10. The consultant has been invited to attend and contribute to national or international meetings organized by professional or academic associations.

The responsibility of consultants

A drug regulatory authority cannot be aware of all of the consultant's involvements and their ramifications when a contract is offered. The onus is therefore on the consultant to declare in writing any potential conflict or what may be seen as a potential conflict to the staff member of the drug regulatory authority who negotiated the contract or committee membership. If there is any doubt, the potential conflict must be declared. The consultant may only proceed with the evaluation of the data or take up committee membership after any potential conflict has been discussed with the drug regulatory authority and found not to be significant.

For this reason, each evaluation contract requires the evaluator to sign a statement to the effect that she or he has no current conflict of interest and that, if the risk of such a conflict arises during the evaluation, the drug regulatory authority will be notified immediately in writing.

The evaluator is expected to cease reading the application *immediately she or he becomes aware of a conflict of interest*, and return it promptly to the drug regulatory authority. This clause applies also to those involved in the inspection of facilities.

Confidentiality

Any data concerning a company's product which are supplied by the drug regulatory authority to a consultant for review are strictly confidential. As stated in the contract, all materials related to or referred to in the contract must be accepted in strict confidence and held in safe and secure custody at all times. An application may be discussed only with the staff members of the drug regulatory authority.

Consultants must be aware of and avoid the possibility of indirect breaches of confidence. There is clearly a potential, consciously or subconsciously, to misuse information gained from a consultancy in other papers or scientific presentations on the product in question. Such a case would also constitute a conflict of interest. The consultant must not use information gained in this way in future scientific papers or presentations without the agreement of the company or individual that submitted the data.

Impartiality

To protect impartiality, the company concerned is not informed by the drug regulatory authority of the identity of the consultant to whom applications, data or committee papers are forwarded. For this reason, the consultant should have no direct communication with the company concerning the product. The consultant may not disclose his or her role to the company, even after a decision on the application has been completed. This is clearly not possible in the case of an inspector of the manufacturing facility.

Subcontracting the evaluation

A consultant is not allowed to subcontract part or all of an evaluation to any second person without written permission from the drug regulatory authority. If the drug regulatory authority agrees to such an arrangement, the consultant must ensure that the subcontractor is fully aware of the provisions on conflict of interest, confidentiality and impartiality set out in these notes.

If any part of an evaluation is subcontracted, the person who actually undertakes the work must also sign all the reports to which she or he has contributed.

Example of a confidentiality undertaking and declaration of Conflict of Interest

World Health Organization Organisation Mondiale de la Santé

PROVISIONS FOR EVALUATORS OF PRODUCT INFORMATION AND FOR INSPECTORS (TEAM MEMBER PARTICIPATING IN SITE VISITS) WITHIN THE SCOPE OF THE QUALITY ASSESSMENT PROCEDURE OF PHARMACEUTICAL PRODUCTS

In the course of discharging your functions as an expert adviser to WHO under the attached agreement for performance of work (APW), you will gain access to certain information, which is proprietary to WHO or entities collaborating with WHO, including the manufacturers of the product(s) which need to be assessed as part of the quality assessment procedure by WHO. You undertake to treat such information (hereinafter referred to as "the Information") as confidential and proprietary to WHO or the aforesaid parties collaborating with WHO. In this connection, you agree:

(a) not to use the Information for any other purpose than discharging your obligations under the above-mentioned APW; and

(b) not to disclose or provide the Information to any person who is not bound by similar obligations of confidentiality and non-use as contained herein.

However, you will not be bound by any obligations of confidentiality and non-use to the extent that you are clearly able to demonstrate that any part of the Information:

(i) was known to you prior to any disclosure by or on behalf of WHO (including by the manufacturer(s)); or

(ii) was in the public domain at the time of disclosure by or on 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) _____

Organization _____

Place _____ Date _____

Appendix 4

Example of a standard operating procedure (SOP) for writing an SOP

1. Title

Standard procedure for writing a standard operating procedure (SOP)

	Signature	Date
Prepared by		9 May 2005
Authorized by		

2. Policy and objective

2.1 The procurement agency should have an SOP for each activity performed by the procurement agency. All SOPs should be in the required format and distributed with care to a predetermined list of personnel. SOPs should be authorized, implemented and kept up to date.

2.2 All SOPs should be written in English if any international use is expected, or in the local language if required only by local staff,

2.3 Documentation is a prime necessity in quality assurance. Its purpose is to define the system of control, to reduce the risk of error inherent in oral communication, to ensure that personnel are instructed in the details of, and follow the procedures concerned in a logical, reproducible manner.

2.4 There should be a written SOP for every critical or important activity in the procurement agency. SOPs should be written in the standardized format as attached.

2.5 A list should be kept of all SOPs required by the procurement agency.

2.6 Management should authorize SOPs prior to their distribution and implementation.

3. Responsibility

All members of staff should adhere to the SOP when drawing up the SOP. The project manager should supervise its implementation.

4. Action

4.1 Any person may initiate the first draft of an SOP. The headings (listed below) should conform to the attached format and should be used when writing the relevant sections of the SOP.

4.2 The SOP should include at least the following headings:

A. Title
B. Policy and objective
C. Responsibility
D. Action
E. Addenda
F. Distribution
G. Review date
H. Revision history

The following information should appear under each heading.

A. Title

Write in clear language the title of the procedure to ensure understanding of the process that the SOP will be describing. The procedure should also contain a clear indication of who was responsible for the preparation, review and approval of the procedure.

B. Policy and objective

Describe the WHO or procurement agency policy regarding the matter to be dealt with under the SOP. Describe the objective to be reached in following the SOP.

C. Responsibility

Describe and list the people responsible for performing the activities listed in the SOP. Wherever possible, it is preferable to use job descriptions or position names for these people rather than names of individuals. Use of the personal names of staff members means the SOP has to be changed every time personnel changes occur.

D. Action

4.1 Describe the sequence of actions needed to perform the task.

4.2 List the actions in the order in which they need to be performed and number them from 1 to the end.

4.3 Explain all the steps in detail in clear, unambiguous, language.

4.4 Put the initials of the responsible person in brackets next to the action step if a specific person is responsible for the action step.

4.5 Read the completed SOP to determine whether it describes all the action steps to be followed from the start of the process to the end.

4.6 If a step leads to another SOP, then refer to the relevant SOP in that step.

4.7 If the SOP requires any records to be kept, draft the required format of the document to be completed and attach it to the SOP as an addendum.

4.8 Forward the SOP to the supervisor or person responsible for documentation and quality assurance.

4.9 Read the SOP and assess its suitability and applicability.

4.10 If any changes are to be made, make amendments to the SOP in ink and return it to the person who wrote the SOP for their comments.

4.11 Return the SOP to the supervisor.

4.12 Sign and date the SOP if satisfied with its contents.

4.13 Forward the SOP to the second person who is responsible for approving documentation.

4.14 The SOP should be signed and dated by the second person who is responsible for approving the documentation if he or she is in agreement with the contents.

4.15 Return the SOP to the person responsible for maintaining the documentation infrastructure.

4.16 If applicable, proceed with the steps for distribution and retrieval of the previous version of the SOP.

4.17 File the original SOP in the SOP file.

E. Addenda

4.18 Draft each addendum in such a manner that it leads the person responsible for completing the addendum to document all the required information.

4.19 Each addendum shall form part of the authorized SOP and shall be reviewed when the SOP is reviewed, or when necessary.

F. Distribution

4.20 Records shall be maintained of the distribution and retrieval of SOPs to ensure that superseded SOPs are not still in use anywhere.

4.21 Complete the table (see Addendum A, point 6) to indicate the name of the person to whom the SOP will be sent.

4.22 Make a copy of the original SOP and stamp it in red ink as "official copy".

4.23 Only official copies of SOPs shall be controlled. SOPs not having a red stamp will be considered non-official and uncontrolled SOPs.

4.24 The person shall sign and date (in the appropriate space in the table (see Addendum A, point 6) on the original SOP), as proof of receipt of the SOP.

4.25 When the SOP is reviewed and amended, copies of the superseded SOP should be retrieved from all those who hold a copy when the new version is distributed.

4.26 When replacing the superseded SOP, the persons from whom it has been retrieved should sign (and date) the appropriate space on the distribution table in the original SOP.

4.27 Mark the original SOP as "superseded" on each page and file in the "superseded SOP" file.

4.28 Destroy all retrieved copies of superseded SOPs.

G. Review date

A date should be assigned on which the SOP will be reviewed to determine whether any changes are required to keep it up to date.

H. Revision history

4.29 To maintain a record of the history of the information on the SOP, complete the table regarding the history of the changes to the SOP (see Addendum A, point 7).

4.30 Each SOP should have a time limit for validity and should be reviewed before the end of the period of validity. This is an opportunity to consider whether the SOP still meets all its objectives and is appropriate for the work to be done and the methods of working. The updated SOP should go through the same writing and revision process.

5. Addenda

Addendum A contains an outline of the format of an SOP.

6. Distribution and retrieval

	Distribution		Retrieval	
Name	Signature	Date	Signature	Date

7. History

Date	Reason for change
	New SOP

Addendum A: Format of a standard operating procedure

WHO Logo Review date: 2006 **Standard operating procedure**	Document no.

1. Title

(indicate title)

	Signature	Date
Prepared by		9 May 2006
Authorized by		

2. Policy and objective

3. Responsibility

4. Action

4.1
4.2
4.3

5. Addenda

6. Distribution and retrieval

	Distribution		Retrieval	
Name	Signature	Date	Signature	Date

7. History

Date	Reason for change

Appendix 5

Example of an invitation for expression of interest

SIXTH INVITATION FOR EXPRESSION OF INTEREST (EOI)

In the context of dramatically increasing the access to, and affordability of, HIV/AIDS-related care and treatment, WHO, together with UNICEF, UNAIDS and UNFPA are inviting **expressions of interest** from manufacturers of pharmaceutical products in respect to the provision of drugs for the management of HIV-related diseases. The World Bank is in support of this effort.

This sixth invitation is published in order to increase the range of possible products and sources as a follow up to the interest that was expressed as a result of the first, second, third, fourth and fifth invitations published in 2000, 2001, 2002, 2003 and 2004.

Manufacturers should be committed to providing the above-mentioned products at **preferential prices** to **developing countries**. Interested manufacturers are encouraged to submit documentation and samples as specified below for various dosage forms and strengths of the products in the following categories:

I) Antiretrovirals as single-ingredient formulations for use in adults and adolescents:

- **Nucleoside/Nucleotide Reverse Transcriptase Inhibitors, including**
  Abacavir
  Didanosine
  Lamivudine
  Stavudine
  Tenofovir
  Zidovudine
- **Non-Nucleoside Reverse Transcriptase Inhibitors, including**
  Efavirenz
  Nevirapine
- **Protease Inhibitors, including**
  Indinavir
  Nelfinavir
  Ritonavir
  Saquinavir

Applications are also encouraged for single-ingredient formulations suitable **for use in paediatric populations**, that support existing international and or national treatment guidelines for paediatric antiretroviral therapy (ART).

As solid dosage formulations are the preferred formulations for treating children except for in the very young infant, manufacturers should also apply for reduced and/or scored solid dosage formulations of:

Zidovudine
Abacavir
Lamivudine
Nevirapine
Efavirenz

Also sought are syrups, solutions or dissolvable nucleoside/nucleotide and non-nucleoside formulations of the following products:

Zidovudine
Abacavir
Lamivudine
Nevirapine

For further information on paediatric formulations please consult: http://www.who.int/3by5/paediatric/en/

II) Antiretrovirals as fixed-dose combinations (FDC):

Applications are also encouraged for fixed-dose combinations of any first-line ARV regimens as described in the *WHO Guidelines for Scaling Up Antiretroviral Therapy in Resource Limited Settings – 2003* Revision. For further information please consult: http://webitpreview.who.int/entity/3by5/publicatons/documents/arv_guidelines/en/

Fixed-dose combinations listed below:

For use in adults and adolescents:

- **Reverse Transcriptase Inhibitors**

  Lamivudine + Stavudine
  Lamivudine + Zidovudine
  Lamivudine + Stavudine + Efavirenz
  Lamivudine + Stavudine + Nevirapine
  Lamivudine + Zidovudine + Efavirenz
  Lamivudine + Zidovudine + Nevirapine
  Lamivudine + Zidovudine + Abacavir
  Tenofovir + Emtricitabine

- **Protease Inhibitors**
  Lopinavir + Ritonavir

For paediatric use, reduced and/or scored solid dosage formulations of:

- **Reverse Transcriptase Inhibitors**
  Lamivudine + Stavudine
  Lamivudine + Zidovudine
  Lamivudine + Stavudine + Nevirapine
  Lamivudine + Zidovudine + Nevirapine
  Lamivudine + Zidovudine + Abacavir

- **Protease Inhibitors**
  Lopinavir + Ritonavir

Co-packaged preparations of the standard ARV combinations, for adult, adolescent and paediatric use are also sought. for further information on paediatric fixed dose and/or co-packaged formulations please consult: http://www.who.int/3by5/paediatric/en/

- **Anti-infective drugs listed below:**

  Antibacterial and antimycobacterial agents (other than MTB)
  Azithromycin
  Ceftriaxone
  Cefixime
  Ciprofloxacin
  Clarithromycin
  Clindamycin
  Rifabutin
  Spectinomycin

  Antiprotozoal and Antifungal agents
  Amphotericin B
  Dapsone
  Folinic acid
  Fluconazole
  Itraconazole
  Pentamidine
  Pyrimethamine
  Sulfadiazine
  Trimethoprim/Sulphamethoxazole

Antiviral agents
Acyclovir
Ganciclovir

- **Anti-cancer drugs**
  Bleomycin
  Etoposide
  Vinblastine
  Vincristine

- **Palliative care drugs**
  Amitriptyline
  Codeine
  Chlorpheniramine
  Ibuprophen
  Loperamide
  Morphine (oral formulation)

The medicines listed in this Invitation for Expression of Interest are those for which a need has been identified by the HIV/AIDS department, WHO. The submitted products should be of assured pharmaceutical quality and relevant data to support efficacy should be provided.

Procedure for submission of EOI

1. Submit a covering letter expressing the interest in participating in the project, confirming that the information submitted in the product dossiers is correct.

2. Submit a product dossier in the recommended format* as specified in the Guideline for submission of a product file which can be obtained by electronic mail from oakesl@who.int, also available on the the web page http://mednet3.who.int/prequal. The dossier should be accompanied by a sample of the product to enable analyses (e.g. 1 × 100 tablets).

   Submitted documentation reaching UNICEF Supply Division will be evaluated during March, May, July, September and November 2005. Documentation should be provided in English.

* If the dossier is compiled in a different format (e.g. EU), then such a dossier can be submitted with a covering letter cross-referencing the pages where the relevant data can be found in accordance with the above-mentioned Guideline

Interested manufacturers should submit the above-mentioned information to:
UNICEF Supply Division
Reference: Accelerated Access to HIV/AIDS Care
SIXTH EOI
UNICEF Plads - Freeport DK-2100 Copenhagen, Denmark
Email: supply@unicef.org
Tel: (45) 35 27 35 27 Fax: (45) 35 26 50 48

3. Submit a site master file for each manufacturing site as listed in the product dossier, in the recommended format, also available by electronic mail and on the web page http://mednet3.who.int/prequal/ to:
The Secretary
WHO/HTP/PSM/QSM
20 Ave Appia
1211 Geneva 27
Switzerland

   Products and manufacturing sites assessed for acceptability and meeting the specified standards will be added to the list published on the project web page (http://mednet3.who.int/prequal/). Products and manufacturers included in this list may be invited to bid for the supply of products, individually or collectively, directly by member governments, by the aforesaid United Nations agencies and/or by associated NGOs.

The following criteria will be taken into account in the quality assessment process.

- Valid manufacturer's licence for production.
- Product registered or licensed in accordance with national requirements.
- Products manufactured in compliance with GMP as certified by the national regulatory authority and/or certified GMP inspectors.
- Product certificates exist in accordance with the WHO Certification scheme on the quality of pharmaceutical products moving in international commerce.
- Product dossiers of acceptable quality submitted and outcome of the assessment in respect of the prequalification procedure.
- Outcome of the inspection performed by or on behalf of the above-mentioned agencies.
- Manufacturer demonstrates sound financial standing.

Only manufacturers THAT CAN SUPPLY APPROPRIATE PRODUCTS OF ACCEPTABLE QUALITY COMPLIANT WITH APPLICABLE REGULATORY REQUIREMENTS, WHO GUIDELINES AND LEGISLATION will be considered.

The United Nations procurement agencies reserve the right to determine specific conditions, as for example the exclusion of companies using child labour, or engaged in the manufacture of land mines or parts thereof.

Further references

For background information on drugs for the treatment of opportunistic infections in HIV/AIDS, please refer to www.aidsinfo.nih.gov/guidelines

For background information on palliative care drugs, please refer to http://www.who.int/3by5/publications/documents/en/genericpalliativecare082004.pdf

Appendix 6

Interagency finished pharmaceutical product questionnaire based on the model quality assurance system for procurement agencies

Please fill out one separate form for each pharmaceutical product

Section 1: Administrative section

1.1 **Product identification**

1.1.1 Active pharmaceutical ingredient(s) (use INN if any):

_____

1.1.2 Generic name of the product:

_____

1.1.3 Trade (proprietary) name (if any):

_____

1.1.4 Dosage form:

☐ Tablets ☐ Capsules ☐ Injectable ☐ Syrups/oral liquids

☐ Other: (Please specify)

_____

1.1.5 Strength per dosage unit: _____

1.1.6 Route of administration:

☐ Oral ☐ I.M. ☐ I.V. ☐ S.C.

☐ Other (Please specify)

_____

1.1.7 Please provide the formulation of the product (complete qualitative and quantitative composition including active ingredient(s), overages if any and excipients). Please also indicate the standard for each ingredient (e.g. BP, USP, in-house). Mention specifically if the product is a fixed-dose combination (FDC) or co-packaged: Annex A

_____

_____

_____

1.1.8 Please state inactive ingredients (excipients) of medical/pharmaceutical relevance, amount in dosage form or per dosage unit (e.g. contains alcohol 10%, paraben…….)

1.2 Packaging

1.2.1 Description and materials used for primary packaging[1] and pack size (quantity of dosage-form units per pack): Annex B

1.2.2 Description, pack size and material used for secondary packaging materials: Annex C

Contact details

1.3 Manufacturer identification

Name, address and activities of the manufacturer and manufacturing site(s) (or contract manufacturer(s):

Name of manufacturer, contract manufacturer if any	Reference of manufacturing licence, date and expiry date, if any	Physical address. Please specify units, and block if existing	Telephone number, facsimile number and email contact details	Activity (e.g. packaging)

1.4 Supplier identification

(to be filled in if not identical to that indicated in 1.3)

Name of company: _____

Physical address (complete details required): _____

_____

Telephone number: _____

Fax: _____

Website: _____

Email: _____

[1] For example, HDPE bottle, Alu-Alu strip, neutral glass vial.

Link with the product

☐ Marketing licence holder ☐ Manufacturer
☐ Distributor/wholesaler ☐ Other

1.5 Note for the applicant

Please note that the information in this questionnaire can be shared confidentially among ICRC, MSF, WHO procurement centre, UNFPA and UNICEF for procurement purposes. If you have any objection, please indicate this to the relevant agency that you are dealing with.

Has the dossier been submitted to any of the following agencies: ERP, ICRC, MSF, WHO procurement centre, UNFPA, UNICEF?

Please provide the date of the submission: _____

1.6 Regulatory (licencing) status

1.6.1 In the country of manufacture

☐ Product registered and currently marketed

Licence no.: _____

Provide a copy in Annex D

☐ Product registered for marketing in the country of manufacturing but not currently marketed

Licence no.: _____

☐ Product registered for export only

Licence no.: _____

☐ Product not registered *(please clarify)*: _____

- Please attach a certificate of pharmaceutical product (CPP) according to the WHO Certification Scheme (WHO Technical Report Series, No. 863) in Annex E. An earlier version is not acceptable).
- If a CPP cannot be obtained from the national medicines regulatory authority (NMRA), please state the reason and send an equivalent document if any.
- Submit recent as well as historical deficiency letters issued by the WHO Prequalification Programme (PQP)/SRA in relation to the specific product dossier in Annex F.

1.6.2 In other countries

List other countries where the product is registered and is currently marketed *(please provide registration number)*

_____

_____

1.6.3 WHO prequalification status, if applicable

This product is prequalified by WHO/PQP.[2]

☐ Yes ☐ No

If yes, please attach a copy of the relevant WHO/PQP acceptance letter signed by your company (Annex G).

1.6.4 Submitted for prequalification: indicate date of submission, WHO acceptance letter for product dossier review mentioning the WHO reference number assigned by WHO for this specific product (Annex H)

_____

1.7 Samples for technical evaluation

1.7.1 Samples of finished product and insert information

You are required to please provide a sample of the finished product(s) offered, and relevant inserts/leaflets. (If you cannot submit any of the above with the questionnaire, please state why not and when you will do so.) (Annex I)

1.7.2 Label language (attach a copy): primary packaging

☐ Bilingual English/French ☐ English ☐ French

☐ Other (specify) _____

1.7.3 Label language (attach a copy): secondary packaging

☐ Bilingual English/French ☐ English ☐ French

☐ Other (specify) _____

For oral powder for suspension and powder for injection, in-use periods and storage conditions after reconstitution should be stated on the product label.

1.7.4 Patient information leaflet (Annex J)

☐ Yes (attach a copy) ☐ No

[2] WHO Prequalification website: http://apps.who.int/prequal/.

Section 2: Active pharmaceutical ingredients

(If there is more than one active ingredient or more than one manufacturer is used, please replicate this section.)

2.1 Details of API used (INN if any):

_____

_____

2.1.1 Manufacturer

Manufacturer (name, physical address and country)/manufacturing site (please list all alternative sources):

_____

_____

GMP certificate from the country of origin: attach a copy of the GMP certificate, if available, in Annex K.

Last inspection of API manufacturing sites performed, when available, (please attach GMP certificate or relevant letter) by:

- ☐ Finished product manufacturer
- ☐ WHO Prequalification Programme, Geneva
- ☐ EDQM
- ☐ US FDA
- ☐ PIC/S members
- ☐ Others (specify)
- ☐ None of above

Outcomes and date:

_____

_____

Is/are the API(s) used to manufacture this product WHO-prequalified?

☐ Yes ☐ No

2.1.2 API specifications

- ➢ API specifications:
  - ☐ British Pharmacopoeia (BP) (edition/year):
  - ☐ United States Pharmacopeia (USP) (edition/year):

☐ *The International Pharmacopoeia* (Ph.Int.) (edition/year)

☐ Others (specify): _____

☐ Specifications additional to those in the pharmacopoeia referred to above if available

☐ Yes ☐ No

- Attach a copy of the FPP manufacturer internal API(s) specifications in Annex L.
- If analytical methods are in-house, different from BP, USP and Ph.Int., attach a copy of the analytical method and analytical validation data in Annex M.

For sterile API:

Please provide the data on validation of the sterile aspects of the product including recent media fill validation data, as applicable, in Annex N.

Describe the method of sterilization used when applicable:

_____

_____

2.1.3 Certificate of analysis

Please provide a copy of the certificate of analysis of the API from the API manufacturer as well as from the finished pharmaceutical product (FPP) manufacturer in Annex O.

2.1.4 Suitability of monograph for API

Are you in a possession of the following information for APIs?

Certificate of suitability to the monograph of the European Pharmacopoeia (CEP): please attach a copy of the CEP and its annexes (Annex P).

Certificate No.: _____

2.1.5. Open part of drug master file (DMF) registered in (country):

_____

_____

Technical file (please attach):

☐ Yes ☐ No

Section 3: Finished pharmaceutical product

3.1 Manufacturing site GMP status

GMP inspections carried out by an NMRA

	NRA of country of origin	Any other inspection of PIC/S member	
GMP certificate no.			
Valid until			
Country			

Please attach the recent/valid GMP certificates/letter (Annex Q)

Other GMP inspections carried out by (include information for all that apply):

Agency	Date of audit	Outcome
WHO Prequalification Programme		
UNICEF Supply Division		
MSF International		
ICRC		
Other (specify)		

3.2 Finished pharmaceutical product specification

Standard	Edition	Year published
BP		
USP		
Ph.Int.		
In-house	Year documented	
Specifications additional to those in the pharmacopoeia referred to above (e.g. dissolution, syringeability) explain:		
Other (specify)		

Please attach copies of release and shelf-life specifications for the FPP in Annex R. If analytical methods are in-house, different from BP, USP and Ph.Int., attach a copy of the analytical method and analytical validation data in the same Annex R.

➢ Please attach a copy of the certificate of analysis for the three last batches released in Annex S.

3.3 Method of manufacture and process validation:

➢ Have the manufacturing methods for each standard batch size been validated?

☐ Yes ☐ No

If no, please clarify:

_____

_____

If yes, please provide details of validation status in the table below:

The batch size of the validated batches	
The batch numbers of the validated batches	
Manufacturing dates of the validated batches	
Reference number for the process validation report	
If processes are yet to be validated, the reference number for the process validation protocol should be indicated	

Provide batch formulae for all proposed batch sizes:

_____

➢ Please provide in Annex T a flow diagram and brief narrative describing the manufacturing and control process of this product with relevant parameters.

3.3.1 Additional information for sterile products

➢ Provide the data on validation of the sterile aspects of the product including recent media fill validation data as applicable in Annex U.

➢ Describe the method of sterilization used if applicable:

_____

3.4 Stability of finished product

3.4.1 Is stability testing data available?

☐ Yes ☐ No

Please provide the protocol and the report for accelerated and long-term stability testing, including: type and material of container; conditions (temperature/relative humidity/duration of stability study); number of batches involved in the study (minimum three); batch sizes for each lot tested; date of beginning of the study; and study conclusions. (These can be provided in Annex V.)

3.4.2 Was the stability testing done on a product of the same formula, same API source, manufactured on the same site and packed in the same packaging material as the product that will be supplied?

☐ Yes ☐ No

If no, describe the differences:

_____

_____

3.4.3 Please specify whether stability studies have been done or are ongoing with all declared API sources:

☐ Yes ☐ No

Submit a declaration in Annex W that stability studies have been done or are being done with all declared API sources.

If no, explain why:

_____

_____

3.4.4 Do you have ongoing stability data for this product?

☐ Yes ☐ No

Attach status report of any ongoing stability studies in Annex X.

3.4.5 Shelf-life as it appears on packaging:

☐ 2 years ☐ 3 years ☐ 4 years ☐ 5 years

Other (please specify): _____

3.4.6 Specific storage conditions for this product as they appear on the packaging and based on stability studies (e.g. "Do not store above 30 °C – Protect from light"):

Temperature	
Light	
Humidity	
Other (specify)	

3.4.7 Product suitable for use in:

- ☐ Zone I
- ☐ Zone II
- ☐ Zone III
- ☐ Zone IVa
- ☐ Zone IVb
- ☐ Other (please specify): _____

3.4.8 For oral powder for suspension and powder for injection, or injection that may be further diluted, or multidose containers provide in-use stability data and storage conditions after reconstitution and/or dilution in Annex Y.

Indicate the period (hours/days) until which the product is stable after reconstitution and/or dilution based on the available in-use stability data:

☐

Section 4: Safety/efficacy and/or therapeutic equivalence

(WHO Technical Report Series (TRS), No. 902, Annex 11/ TRS No. 937, Annex 7 or later)

4.1 For innovator products

Please attach a summary of pharmacology, toxicology and efficacy of the product in Annex Z.

4.2 For generic products: therapeutic equivalence

- ☐ Demonstrated
- ☐ Not demonstrated
- ☐ Not relevant, please explain why: _____

If demonstrated,

4.2.1 **By in vivo bioequivalence studies**

Study period (dd/mm/yyyy): from ☐ to ☐

Reference product

Generic name:	
Dosage form:	
Strength:	
Brand/trade name:	
Manufacturer:	
Manufacture site:	
Batch number:	
Expiry date:	

Study protocol

Contract research organization (CRO) name:	
Country of study:	
Number of volunteers:	
Study design (describe in detail):	

Bio batch size:	
Bio batch number:	
Bio batch API(s) source(s):	
Study conclusion:	

Study results:

Study conclusion:

4.2.2 By comparative in vitro dissolution tests according to conditions described in WHO BCS classification document (WHO Technical Report Series, No. 937, or later)

☐ Yes

☐ No (explain): _____

_____

Reference product

Generic name	
Dosage form	
Strength	
Brand/trade name	
Manufacturer	
Manufacture site	
Batch number	
Expiry date	

Name and contact details of laboratory performing tests:

_____

Study results

F2 (similarity factor) value (standard 50–100%):

_____

F1 (difference factor) value:

_____

Study conclusion:

_____

_____

_____

4.2.3 By another method (please describe study conclusion briefly):

_____

Attach graphic/pictorial representation of summary study results in Annex AA.

4.3 **The product used in the therapeutic equivalence study is essentially the same as the one that will be supplied (same materials from the same suppliers, same formula and same manufacturing method):**

☐ Yes

☐ No (explain what the differences are and justify that the differences do not have any impact on the bioavailability): _____

_____

_____

➢ Provide a copy of the report of the proof of therapeutic equivalence (BE study) comparative dissolution profile, dissolution tests, and others, if any, in Annex AB.

➢ For bioequivalence studies, indicate the stringent regulatory authority (SRA)/ WHO/PIC/S inspection status of the CRO (if the CRO has ever undergone inspections in relation to the current or other studies).

_____

_____

_____

➢ Attach schematic representation of study design (Annex AC)

➢ Attach study protocol summary (Annex AD)

Section 5: Commitment and authorization

5.1 **Commitment**

I, the undersigned, _____ , (*position in the company, e.g. General Manager, Authorized Person, Responsible Pharmacist*), acting as responsible for the company _____ _____ *(name of the company)*, certify that the information provided (above) is correct and true,

(if the product is marketed in the country of origin, select the appropriate box below)

☐ and I certify that the product offered is identical in all aspects of manufacturing and quality to that marketed in _____ (*country of origin*), including formulation, method and site of manufacture, sources of active and excipient starting materials, quality control of the product and starting material, packaging, shelf-life and product information.

☐ and I certify that the product offered is identical to that marketed in _____ *(name of country)*, except:

_____

_____

(e.g. formulation, method and site of manufacture, sources of active and excipient starting materials, quality control of the finished product and starting material, packaging, shelf-life, indications, product information)

If any changes occur to the information after the submission of this product questionnaire, the manufacturer/supplier undertakes to provide the relevant update as soon as possible.

Date: _____ Signature: _____

5.2 Power of attorney

The manufacturer authorizes a distributor to submit the questionnaire

Date: _____ Signature: _____

Distributor (Signed by Distributor for Manufacturer under power of attorney)

Please provide a copy of the power of attorney (Annex AE).

5.3 Authorization for sharing information with other agency

I, the undersigned confirm that the company has no objection to the information contained herein being shared with the agencies listed on page 2 (1.5) except:

_____

_____

I, the undersigned, certify that the information provided above is accurate, correct, complete, up-to-date and true at the time of submission.

Full name:

_____

_____

Full title/position in company:

_____

_____

Company name:

Signature

Date

Company seal/stamp:

Section 6: Attachments/annexes

Attachments or Annexes to the questionnaire should be in PDF format and should be well indexed to facilitate review

Please ensure that all documents necessary to enable objective evaluation of your product are attached. This checklist may not be exhaustive.

- ☐ A. Formulation of the product (complete qualitative and quantitative composition including active ingredient(s) and excipients (1.1.7)
- ☐ B. Description and composition of primary packaging materials (1.2.1)
- ☐ C. Description and composition of secondary packaging materials (1.2.2)
- ☐ D. Copy of product registered and currently marketed – Licence no. (1.6.1)
- ☐ E. Certificate of pharmaceutical product (CPP) according to the WHO Certification Scheme (WHO Technical Report Series, No. 863). An earlier version is not acceptable) (1.6.1)
- ☐ F. Submit recent as well as historical deficiency/acceptance letters issued by PQP/SRA in relation to the specific product dossier (1.6.1)
- ☐ G. Copy of the relevant WHO Prequalification approval letter signed by your company (1.6.3)
- ☐ H. WHO acceptance letter for product dossier review mentioning the WHO reference number assigned by WHO for this specific product (1.6.4)
- ☐ I. Package insert/leaflet (1.7.1)
- ☐ J. Patient information leaflet (1.7.4)
- ☐ K. GMP certificate from the country of origin (2.1.1)

- ☐ L. Attach a copy of the internal API(s) specifications (2.1.2)
- ☐ M. Validated analytical methods if analytical methods for finished product are in-house analytical method, different from BP, USP and Ph.Int. (2.1.2)
- ☐ N. Please provide the data on validation of the sterile aspects of the product including recent media fill validation data, as applicable (2.1.2)
- ☐ O. Copy of the certificate(s) of analysis of the API from the API manufacturer as well as from the FPP manufacturer (2.1.3)
- ☐ P. Copy of the certificate of suitability to the European Pharmacopoeia (CEP) and its annexes (2.1.4)
- ☐ Q. Recent/valid GMP certificates/letter (3.1)
- ☐ R. If specifications are in-house specifications, different from BP, USP and Ph.Int., attach copy of the in-house finished product specifications and also validated analytical methods (3.2)
- ☐ S. Copy of the certificate of analysis for the three last batches released (3.2)
- ☐ T. Flow diagram and brief narrative describing the manufacturing and control process of this product with relevant parameters (3.3)
- ☐ U. Data on validation of the sterile aspects of the product including recent media fill validation data as applicable (3.3.1)
- ☐ V. Protocol and report for accelerated and long-term stability testing (3.4.1)
- ☐ W. Submit a declaration that stability studies have been done or are being done with all declared API sources (3.4.3)
- ☐ X. Attach status report of any ongoing stability studies (3.4.4)
- ☐ Y. For oral powder for suspension and powder for injection, provide in-use stability data and storage conditions after reconstitution (3.4.8)
- ☐ Z. Please attach a summary of pharmacology, toxicology and efficacy of the product (4.1)
- ☐ AA. Attach graphic/pictorial representation of summary study results (4.2.3)
- ☐ AB. Provide a copy of the report of the proof of therapeutic equivalence (BE study) comparative dissolution profile, dissolution tests, and others if any (4.3)
- ☐ AC. Schematic representation of study design (4.3)
- ☐ AD. Study protocol summary (4.3)
- ☐ AE. Copy of the power of attorney (5.2)

Appendix 7

Example of a standard operating procedure for screening and assessing product information

1. Title

Assessing product files

	Signature	Date
Prepared by		9 May 2005
Authorized by		

2. Policy and objective

2.1 Each product file submitted by an interested manufacturer should be assessed as part of the prequalification process.

2.2 Each product file should go through a screening procedure.

2.3 Product files found to comply with the screening requirements will be retained for assessment.

2.4 The objective is to screen product files to determine whether these comply with the requirements. This will prevent loss of valuable assessment time, should the product files be incomplete when received.

2.5 The objective of the assessment process is to verify that the re- quired information regarding safety, efficacy and quality of the product is documented and submitted in the required format. Where possible during inspections, and as a part of the verification process, the data and results should be verified to ensure that correct, accurate and reliable data have been submitted to the procurement agency.

3. Responsibility

Project Manager
Evaluators

4. Action

A. Screening

4.1 Unpack each product file onto the working surface in the presence of at least two other persons. Sign a sheet indicating the names of the persons responsible for opening the containers on that date.

4.2 Complete the relevant details in the "product received register".

4.3 Record details such as the product number, date, product detail (INN), name of supplier, name of manufacturer(s), country of manufacturer(s), screening outcome, date manufacturer informed (Addendum A).

4.4 Allocate the product number in numerical order starting from 001.

4.5 The number should start with the year, e.g. 01 (for 2001).

4.6 Identify the project for which the product was submitted, e.g. HA for HIV/AIDS. The first product for the project would thus be numbered 01HA001.

4.7 Open a WHO file for the product. Write the product name, number and the name of the manufacturer on the outer page.

4.8 Write the product number on the product file and screening form for the product.

4.9 Screen the product file to assess its completeness. Confirm that all the required information, data and forms have been submitted by the manufacturer/supplier.

4.10 Use the attached screening form for this purpose (Addendum B).

4.11 Enter the relevant information in the appropriate column of the screening form as part of the screening process.

4.12 Once the screening is complete, make a copy of the screening form.

4.13 File the copy of the screening form in the screening form file.

4.14 Place the original of the completed screening form in the front of the product file.

4.15 If the product file is complete, place the product file in numerical order in the designated area marked "For evaluation".

4.16 If the product file is incomplete, place the file in the designated area, marked "Incomplete files".

4.17 Enter the outcome in the "product received register".

4.18 For each product file received, send a letter of acknowledgement of receipt to the manufacturer. For an "Incomplete file", inform the manufacturer in writing that the product file submitted was incomplete and cannot be considered for evaluation or assessment (see Addendum C for a model letter).

B. Assessing product files

Note: Each product file must be assessed by at least three evaluators.

Three evaluators should evaluate Part I (quality aspects) and at least two evaluators should evaluate Part II (bioavailability, safety and efficacy aspects).

Step 1 (Evaluator 1)

4.19 Take a product file from the section marked "For evaluation".

4.20 Use the attached product assessment report (Addendum D) for the purpose of evaluating the product information.

4.21 Go through each section and assess compliance with the required standards for the submission of the relevant information.

4.22 Record your findings in the report form.

4.23 On completion of the assessment record your name, signature and the date on the report form.

4.24 Record any specific problem associated with the evaluation of the product on a separate report form, entitled "Product-specific problem report" (Addendum E).

If you are evaluating Part 2, "Bioequivalence (safety and efficacy)", and the efficacy part of the dossier is not included for all oral preparations, except aqueous solutions, at the time of administration, inform the manufacturer in writing that the product file was submitted without bioavailability aspects and cannot be evaluated at present.

4.25 Place the report forms in the front of the product file.

4.26 Replace the file in the section "For evaluation".

Step 2 (Evaluator 2)

Perform steps equivalent to steps 4.19 to 4.26 above.

Step 3 (Evaluator 3)

Perform steps equivalent to steps 4.19 to 4.26 above.

Step 4

4.27 If a file contains the evaluation reports signed by three evaluators (quality aspects) and two evaluators (bioavailability), place the file in the area marked "Evaluation completed".

4.28 Assess whether the relevant number of evaluators (three for quality aspects, and two for bioavailability) have evaluated each product adequately.

4.29 Collate the information in the reports. If additional information is required from the manufacturer or supplier, draft the letter on the basis of the information contained in the reports.

4.30 Request the additional information to be submitted within the specified period. Remind the manufacturer that failure to supply the requested information within the timescale requested may lead to exclusion of the product from further consideration.

4.31 Record the recommendation of evaluators on the list for the inspection of the manufacturing site.

5. Addenda

Addendum A: Product details
Addendum B: Screening form to assess the quality of the submission of EOI
Addendum C: Product information receipt
Addendum D: Product assessment report
Addendum E: Product-specific problem report

6. Distribution and retrieval

The record of distribution and retrieval of the SOP should be entered in a table; see the model below.

	Distribution		Retrieval	
Name	Signature	Date	Signature	Date

7. History

The history of changes to the SOP should be recorded in a table; see the model below.

Date	Reason for change

Addendum A: Product details

Product Number	Date	Product details (INN)	Name of supplier	Name of manufacturer(s)	Country of manufacture	Screening outcome	Date manufacturer informed	Inspection planned (Y/N)

Addendum B: Screening form to assess the quality of the submission of an expression of interest

Access to drugs and diagnostics of acceptable quality
Pilot procurement quality and sourcing project

Complete the following: | Product submission number: |

Product name	
Active pharmaceutical ingredient	
Strength	
Dosage form	
Pack size	
Name of supplier of drug products	
Address of supplier of drug products	
Name and address of manufacturer if different from that of the supplier above	

Table *continued*

Name and address of manufacturer (and if appropriate of supplier) of the active pharmaceutical ingredient			
Date of submission			
Country of origin of the submission	Supplier: _____ Manufacturer: _____		
Is the product licensed in	Japan USA EU*	YES YES YES	NO NO NO
If "Yes", proceed to Appendix 1 If "No", proceed to Appendix 2			

* (EU countries: Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, Netherlands, Portugal, Spain, Sweden, United Kingdom)

Appendix 1

The following is included in the submission:

	YES	NO
A WHO-type certificate of a pharmaceutical product (CPP) issued by one of the regulatory authorities of ICH regions		
The summary of product characteristics (SmPC)		
Assessment report(s) issued by the respective regulatory authority		
WHO-type batch certificate from the manufacturer		
The packaging of the product is the same as that approved by the drug regulatory authorities of the ICH regions		[1]
The product information is the same as on the WHO-type CPP for at least:	_____	_____
Formulation		[2]
Strength		[2]
Specifications		[2]

[1] Stability testing data are submitted

[2] Arguments and/or data to support the applicability of the certificate(s) despite the differences are submitted.

If the answers to 1 and 2 are "no", then the EOI should be rejected.

Appendix 2

	YES	NO
Details of the product (Name of the product; approved generic name(s) (use INN, if any); visual description of the product; visual description of the packaging; strength per unit dosage and dosage form)		
Regulatory situation in other countries (Marketing authorization, withdrawn from the market, application rejected, deferred or withdrawn)		
API		
Properties Chemical structure; solubility in water, other solvents such as ether, ethanol, acetone and buffers of different pH; its isomeric nature including stereochemical configuration; partition coefficient and the existence of polymorphs; copies of infrared, nuclear magnetic resonance (proton and C-13), ultraviolet and mass spectra; information on the chemical and physicochemical stability if relevant (e.g. formation of a hydrate, change of polymorphic form)		
Sites of manufacture Name and street address of each facility of manufacture (synthesis, production), including any alternative manufacturers GMP certificate attached (including for all alternative sites of manufacture being submitted)		
Route(s) of synthesis 1. Including reagents and reaction conditions; specifications for starting materials, reagents, solvents, catalysts and intermediates in the synthesis; synthetic by-products and degradation products 2. If a European certificate of suitability with any appendices is submitted, then an outline of the route of synthesis is sufficient 3. The manufacturer of the finished product should know the full details of the synthesis of the substance so that they are able to conduct a full set of tests on each batch. The results of such testing should be presented for at least two batches. The last option can be used only if the quality of API is described in a pharmacopoeia		
Specifications		
Pharmacopoeial requirements: copy of the monograph and tests, additional specifications, certificates of analysis, two batches, including results for impurities		
Non-pharmacopoeia: tests and limits, methods, results of validation		
Stability testing Results of stability, physical as well as chemical tests, methodology used (WHO guidelines or ICH guidelines), validation		

Table *continued*

	YES	NO
Finished product		
Formulation Formulation and administration unit, excipients not present in final formulation, the qualitative and quantitative composition, overages, function(s) of each excipient, ranges in the content of excipients justified and explained		
Sites of manufacture Name and street address of each facility. Indicate the activity, alternative manufacturers, major production step(s) – certificate issued, product information approved, summary basis of approval		
Manufacturing procedure Outline of manufacturing and packaging Copy of the master formula and a copy of a manufacturing record Details of sterilization Stages of sampling and in-process control tests		
Specifications for excipients Pharmacopoeia: copy of the monograph, test methods referenced Additional specifications Non-pharmacopoeia: list of tests and for each excipient, including solvents, liquids to adjust pH, coatings, capsule shell, and inked imprint (on the dosage form), description of test methods, microbiological limits, colours EU/FDA/Japan		
Specifications for the finished product Two specifications: at release and end of shelf-life List general characteristics, specific standards: tests and limits for results for the finished product must be provided Analytical test procedures described (physicochemical properties, identity of API) Quantitative determination of active, deviations, purity tests, pharmaceutical tests, colouring antimicrobial or chemical preservatives, results of validation studies, comments on the choice of routine tests and standards provided Copy of pharmacopoeia monograph and verification data Results of batch analysis (inc. date of manufacture, place of manufacture, batch size and use of batch tested)		
Container/closure system(s) and other packaging Detailed description (inc. liner or wadding, details of composition); describe other (e.g. outer) packaging; state materials and specifications for part in contact with the product, or if protective. Parenteral: BP, EP, JP or USP		
Stability testing Results for each pack, methodology, validated (accuracy and precision recorded) Related compounds and decomposition: sensitivity, accelerated and real-time data, accelerated 40 °C and 75% RH for six months, real time 30 °C and 70% RH		

Table *continued*

	YES	NO
Container labelling Name, active ingredients, amount of each, batch number, expiry date, storage conditions, directions, warnings or precautions, name and address of the manufacturer, excipients known to be a safety concern		
Product information Copy approved by competent authority		
Patient information and package inserts Copies of package inserts and information for distribution		
Justification for any differences Arguments provided and/or data to support, validation data. Only minor differences are likely to be acceptable		
Interchangeability Multisource (generic): bioequivalence study. Bioequivalence of all oral preparations except aqueous solutions. Orally or parenterally administered aqueous solutions: chemical–pharmaceutical characteristics. Comparative clinical trial using clinical or pharmacodynamic end-points can be presented. End-points justified and validated for the compound and trial should be designed to show equivalence. Trial showing the absence of significant difference cannot be accepted Bioequivalence study report included		
Report Study design, investigators, study site, study dates, preparations used, characterization of study subjects, study procedures, drug determination methods, measured drug concentrations, calculation methodology of pharmacokinetic parameters, statistical methodology and results of statistical calculations		
Summary of pharmacology, toxicology and efficacy of the product New active ingredients and new combinations of active ingredients: full safety and efficacy (EU, FDA, Japan)		

☐ Accept ☐ Reject ☐ Hold

Reasons for rejecting or holding an application: _____

Addendum C: Product information receipt

Dear …

Prequalification of manufacturers and suppliers of drug products

Thank you for submitting a product file after having indicated your company's interest in supplying drug products as part of the prequalification process of drug products to the United Nations organizations and interested procurement agencies.

We herewith acknowledge receipt of your product information sent to this office as part of the prequalification process.

The product information submitted has been screened to assess completeness of the submission in accordance with the guidelines that were sent to you after receiving your Expression of Interest (EOI) in participating in the prequalification programme.

Kindly note that your submission is now pending the full assessment. It is possible that an inspection of the manufacturing site(s) will be performed in due course. Details of this will be advised to you once all the necessary arrangements have been completed.

OR

Kindly note that your submission was found to be incomplete. We therefore regret to inform you that no further evaluation will take place with regards to your product file, and that the manufacturer will be not be included in the prequalification process. Would you kindly contact this office within 30 days to enable us to make the necessary arrangements for the return of the information already submitted.

OR

Kindly note that your submission was found to be incomplete. It is missing the following information.

If you provide the missing data within X days, and it is of satisfactory quality, then your submission will go forward to full assessment.

Your cooperation is appreciated.

Addendum D: Product assessment report

Access to drugs and diagnostics of acceptable quality
Pilot procurement quality and sourcing project

Product number:		
Product name (API):		
Manufacturer:		
Product manufactured and registered/licensed in EU, Japan or USA	YES[1]	NO[2]

This product evaluation report consists of two parts. Both parts should be completed as part of the assessment. The report should be written in clear unambiguous language referring to shortcomings or lack of data submitted, as communication with the manufacturer may result from the assessment.

Part One should be completed by at least three evaluators from different countries, responsible for assessing product quality including pharmaceutical and analytical aspects. (The report should be no longer than six pages.)

Part Two should be completed by an evaluator responsible for the assessment for bioavailability. (The report should be no longer than two pages.)

The report should be signed off by the person responsible for the evaluation and assessment of the product files.

Part I: Quality aspects

[1] Product licensed/registered in the EU, Japan or the USA. Review the data submitted and comment (see also guidelines):

A WHO-type certificate of a pharmaceutical product (CPP) issued by one of the regulatory authority of ICH regions (EU, Japan, USA)
The summary of product characteristics (SmPC)
Assessment report(s) issued by the respective regulatory authority
WHO-type batch certificate from the manufacturer

Table *continued*

The packaging of the product is the same as those approved by the drug regulatory authorities of the ICH regions
The product information is the same as on the WHO-type CPP for at least:
Formulation
Strength
Specifications

[2] Product not licensed/registered in the EU, Japan or the USA. Review the data submitted and comment:

Details of the product
Regulatory situation in other countries
Active pharmaceutical ingredient(s) (API) Properties of the API(s)
Sites of manufacture
Route(s) of synthesis
Specifications API described in a pharmacopoeia (specify the pharmacopoeia, its edition, and any supplement if relevant). The latest edition of the relevant pharmacopoeia should always be used. API not described in a pharmacopoeia
Stability testing

Table *continued*

Finished product
Formulation
Sites of manufacture
Manufacturing procedure
Specifications for excipients
Specifications for the finished product
Container/closure system(s) and other packaging
Stability testing
Container labelling
Product information
Patient information and package inserts
Justification for any differences of the product in the country or countries issuing the submitted WHO-type certificate(s)

Evaluator (name):	Signature:	Date:
1		
2		
3		

Part II: Bioavailability (safety and efficacy)

(See also guidelines)

Bioequivalence study report
Summary of pharmacology, toxicology and efficacy

Evaluator (name):	Signature:	Date:
1		
2		
3		

Addendum E: Product-specific problem report

Access to drugs and diagnostics of acceptable quality
Pilot procurement quality and sourcing project

API:	

This product-specific problem report should highlight any specific problems identified during the evaluation of products. No mention should be made of the specific manufacturer's product. The objective is to identify any problems associated with a specific product containing a specific API, or specific to any dosage form.

Dosage form:	

Problems

General recommendations

Appendix 8

Quality system recommendations for pharmaceutical inspectorates

For a guide to Quality systems requirements for national good manufacturing practice inspectorates, see: *WHO Expert Committee on Specifications for Pharmaceutical Preparations, Thirty-sixth report*. Geneva, World Health Organization, 2002 (WHO Technical Report Series, No. 902), Annex 8.

Available at:
http://who.int/medicines/areas/quality_safety/quality_assurance/inspections/en/

Appendix 9

Technical questionnaire for pharmaceutical manufacturers

1. General information on the manufacturer

Name, address, telephone, telefax, Internet address of the company:

Name	
Postal address	
Physical address	
Telephone	
Fax number	
Web site URL	
Contact email address	

2. Affiliates

If the company is owned by another company, or belongs to a group of companies,
Please describe your position within the structure: _____

_____

3. Regulatory issues

3.1 Good manufacturing practice (GMP)

Indicate the GMP standards (WHO, PIC/EU, FDA or other) with which the company complies: _____

Provide a copy of the latest inspection report or certificate whichever is appropriate.

3.2 Manufacturing licence for medicinal products

Please list the pharmaceutical dosage forms you are licensed to manufacture by the national regulatory authority and attach a copy of the manufacturing licence(s): _____

_____

_____

3.3 Inspection

Date of last inspection by a national or other competent drug regulatory authority:

Drug regulatory authority	Date

Please attach a copy of the last inspection report(s) or certificates for review on a confidential basis.

4. Manufacturing

4.1 Manufacturing site

Please state all the names and addresses at which manufacturing of pharmaceutical products to be prequalified takes place, and indicate in which year the factory was built. Include dates of upgrading and adaptation, as well as a description of the activity:

Name	Physical address	Year built and recent upgrades	Activity (e.g. all, compression, packaging, etc.)

4.2 Personnel

Please indicate the name, qualification and years of experience of the following key staff:

Position	Name	Qualification	Experience
Managing Director			
Technical Director			
Production Manager			
Quality Control Manager			
Quality Assurance Manager			

Number of personnel in total: _____

Number of personnel in production: _____

Number of personnel in quality assurance/control: _____

4.3 Ventilation system

Please indicate whether the manufacturing areas are equipped with controlled ventilation systems ☐ Yes ☐ No

If "Yes", please give a brief description of the ventilation system. *(A diagram complementing the description can be submitted.)*

If "No", explain reasons: _____

_____

_____

4.4 Quality control

Instrumentation?

Chemical laboratory	in-house ☐	contracted out ☐
Biological laboratory	in-house ☐	contracted out ☐
Microbiological laboratory	in-house ☐	contracted out ☐

4.5 Contract manufacture

Do you undertake contract manufacture for other companies? ☐ Yes ☐ No

If "Yes", please indicate the type of products (e.g. pesticides, antibiotics, hormones, cytotoxics, etc.) _____

Do you subcontract to other companies? ☐ Yes ☐ No

If "Yes", please list products and/or services that are subcontracted: _____

_____

_____

4.6 Sterile products

Do you manufacture sterile products? ☐ Yes ☐ No

Give a brief description of the method of sterilization used: _____

_____

_____

4.7 Beta-lactam, highly sensitizing compounds, hormones, cytotoxic products

Do you manufacture penicillins or other beta-lactam, highly sensitizing compounds, hormones or cytotoxic products? ☐ Yes ☐ No

If yes, does this production take place in a separate building provided with its own dedicated air-handling system? ☐ Yes ☐ No

4.8 Complaints and recalls

Do you have a recall procedure, which enables you to recall any product effectively and promptly within 24 hours from the distribution points or market? ☐ Yes ☐ No

Do you have a procedure for handling complaints? ☐ Yes ☐ No

Does it cover analysis of trends? ☐ Yes ☐ No

Please list significant product complaints and any recalls during the last three years:

Product	List complaints		
	Year 1	Year 2	Year 3

4.9 Research and development activities

Please indicate the type of activities and annual investment: _____

_____

_____

4.10 Production capacity

Product	No. of units per year	Last year's production units
Tablets		
Capsules		
Ampoules		

Table *continued*

Vials, liquids		
Vials, dry powder		
Vials, lyophilized		
Ointments		
Liquids		
Powder for oral suspensions		
Suppositories		
Penicillin, tablets/capsules		
Penicillin, powder for oral suspension		
Penicillin, powder for injection		
Other, specify		

Are production capacity figures based on one or more shifts?
(Tick appropriate box)

☐ One ☐ Two ☐ Three

4.11 Stock

Do you maintain a permanent stock? ☐ Yes ☐ No

4.12 Quality systems (including quality management and quality assurance)

Give a brief description of the quality management system, with specific reference to aspects such as procurement agency, documentation infrastructure, validation, training, statistical analysis, and other related aspects: _____

5. Products

5.1 Product licences

Please enclose a list of all products manufactured by your company for which you seek prequalification and which are authorized for sale. For each licensed product, please complete the table below and categorize as shown.

If possible, please attach an indicative price list.

Product	Marketed in the domestic market (Yes or No)	For export only (Yes or No)	Licences are held in the following countries	Name of contract manufacturer and country

5.2 Documentation

The following product documentation must be made available upon request for each product offered. Please indicate if this documentation is NOT available for any of the products on the list shown under point 5.1:

Product composition – master formula _____

Starting materials specification _____

Manufacturing and packaging specification _____

In-process test specifications and methods _____

Finished product specification _____

Packaging and labelling specifications _____

Analytical procedures _____

Upon request, "the common product questionnaire" must be completed and returned.

5.3 Samples

Are you willing to provide product samples and batch documentation (on a confidential basis) when requested? ☐ Yes ☐ No

5.4 Starting materials

List starting materials manufactured by the company or by affiliates, and indicate in the table below whether approved drug master files (DMF) or Certificates of suitability of the Monograph of the European Pharmacopoeia (CEP) are available.

Starting material	DMF (Mark ✓, and state number)	CEP (Mark ✓)

5.5 Stability studies and shelf-life

Do you perform initial and continuous stability studies on your products?

☐ Yes ☐ No

Give a brief description of the stability procedure and programme. If "No", explain reasons: _____

What type(s) of studies do you carry out?

Type *(Mark with ✓)*		Test conditions	
		Temperature *(indicate)*	Relative humidity *(indicate)*
	Accelerated studies		
	Real-time studies		

Explain if necessary: _____

How do you determine the shelf-life of your products? _____

5.6 Bioequivalence

Have you conducted in vivo bioequivalence studies for some of your products?

☐ Yes ☐ No

If "yes", list the products studied and the reference products:

Product	Reference product	Country of study

5.7 Retention samples

Do you keep retention samples? ☐ Yes ☐ No

Samples:	Yes	No	Retention period	Storage conditions
Every finished product				
Active pharmaceutical ingredients				
Excipients				

6. Audit

Can we or any other representative designated by us perform a GMP audit of the manufacturing site? ☐ Yes ☐ No

Can (a) representative(s) from the national regulatory authority participate as observer(s) in the audit? ☐ Yes ☐ No

May we share the inspection report with the other procurement agencies "signatory" to this questionnaire? ☐ Yes ☐ No

Is a site master file (PIC or WHO format) available upon request? ☐ Yes ☐ No

Will any required additional information be provided if we wish to perform an audit of the company? ☐ Yes ☐ No

7. Other information

Contact person (commercial issues):

Name:	
Telephone no.:	
Fax:	
email:	

Contact person (quality issues):

Name:	
Telephone no.:	
Fax:	
email:	

Any additional information: _____

_____

_____

_____

_____

I hereby certify that the information given in this questionnaire and the attachments is correct.

_____ _____

Date **Signature**

_____ _____

Name Position in company

Appendix 10

Example of a standard operating procedure for planning of inspections

1. Title

Inspection, planning of site inspections

	Signature	Date
Prepared by		1 July 2006
Authorized by		

2. Policy and objective

2.1 Manufacturing sites should be inspected as part of the prequalification process. To enable the procurement agency to perform the inspections, they should be properly planned.

2.2 The objective is proper planning of site inspections to ensure that products will be sourced only from manufacturers that comply with international standards.

2.3 Proper planning of inspections should save time and resources (e.g. financial and human) through procurement agency planning.

3. Responsibility

Head of the Section or Department
Project Manager
Evaluator

4. Action

4.1 When assessing product information, make a list of all the products received (see Addendum A). Complete the table.

4.2 On the basis of the outcome of the assessment of the product information, decide which manufacturers should be inspected for prequalification.

4.3 Dossiers lacking information, or of unacceptably low quality, may lead to the manufacturing site failing to qualify for the inspection.

4.4 Group all the manufacturers in one country together to ensure that when a trip is undertaken to one country, more than one manufacturer can be included in the inspection trip where relevant.

4.5 Consult a map to see where the sites are located and plan the trip so as to prevent unnecessary loss of time through travelling.

4.6 Plot the sites on a table (calendar) and allocate at least 3 days for inspection of each manufacturing site, depending on the dosage forms manufactured and the size of the facilities.

4.7 Write a letter to the company informing them of the tentative date allocated for the site inspection. Request the company to indicate whether the dates are suitable to them, and also request them to submit a site master file.

4.8 Appoint inspectors for the inspection team. There should be at least two inspectors on the team, including the representative from WHO.

4.9 Send a letter to the national regulatory authority inviting an inspector from the inspectorate to participate in the inspection.

4.10 Inform the inspectors of the proposed dates for the inspection.

4.11 When the manufacturer confirms the dates for inspection confirm the date with the company and request the information listed in Addendum B.

4.12 Confirm the dates with the inspectors.

4.13 Send the inspectors copies of the SOPs needed to perform the inspections, as well as the terms of reference, confidentiality clause, no conflict of interest declaration and agreement for performance of work.

4.14 Make the relevant bookings (air travel, transport in the country where the inspection will be performed and hotel accommodation).

5. Addenda

Addendum A: Summary list of dossiers received
Addendum B: Manufacturer information

6. Distribution and retrieval

The record of distribution and retrieval of the SOP should be entered in a table; see the model below.

	Distribution		Retrieval	
Name	Signature	Date	Signature	Date

7. History

The history of changes to the SOP should be entered in a table; see the model below.

Date	Reason for change

Addendum A: Summary list of dossiers received

No	API	Strength	Dosage form	Supplier/ Manufac-turer	Manu-facturing site	Country	Sample

Addendum B: Manufacturer information

1. General information

Name	
Physical address of head office	
Postal address	
Telephone number	
Fax number	
Contact person	
Email address	

2. Manufacturing licence

Please attach the manufacturing licence.

3. Product list

Please attach a list of products manufactured at this particular manufacturing site.

4. Inspections by the national regulatory authority

Date of last inspection by the national regulatory authority (NRA)	
List the NRA of other countries that have inspected the site, and dates of inspection	Country Date

5. Manufacturing and testing

Physical address of manufacturing sites for the products indicated in the submission	
Telephone number	
Fax number	
Physical address of quality control laboratories (chemical and microbiological) used for testing the products in the submission	
Telephone number	
Fax number	
Email	

6. Recalls

Please list the products and reasons for implementing a product recall in the last 5 years.

Product and batch number (INN, strength and dosage form)	Reason	Date of recall

7. Complaints

If the company has had any product complaints in the last year, please complete the table below.

Products and batch number (INN, strength and dosage form)	Complaint and source	Corrective action taken

8. Site master file (SMF)

If the SMF for the manufacturing site was submitted previously:

Date submitted	
SMF number	

If the SMF has not yet been submitted to WHO, please attach it now. Please note that the SMF must conform to the requirements specified previously.

9. Audit/inspection

We herewith grant WHO permission to perform the inspection of the manufacturing site to assess compliance with good manufacturing practice, for the purpose of the prequalification of the manufacturing site and product.

I declare that the information given above is true and correct.

Signature: Date:

Name:

Position:

Appendix 11

Example of a standard operating procedure for preparing for an inspection

1. Title

Preparation for an inspection

	Signature	Date
Prepared by		11 May 2006
Authorized by		

2. Policy and objective

2.1 Each manufacturer should be inspected by the procurement agency to assess compliance with good manufacturing practices.

2.2 All inspectors should follow the SOP in preparing for the inspection(s).

2.3 The objective is to ensure that a standardized procedure is followed by all inspectors when preparing for the inspections to prevent inspections being performed by different inspectors in different ways. This should ensure consistency in performance between inspectors.

3. Responsibility

Project Manager
Inspectors

4. Action

All actions described here are taken from the details provided by the WHO publication *Quality assurance of pharmaceuticals*, Volume 2, Chapter 4: Inspection of pharmaceutical manufacturers and inspection of drug distribution channels. These guidelines or other similar systems operated by national drug regulatory agencies should be followed in detail.

4.1 Once the inspection has been allocated to the inspector, he or she should plan for the performance of the inspection according to the steps outlined below.

4.2 Verify the objective of the inspection that is to be carried out.

4.3 Clarify which type of inspection will be performed, e.g. routine GMP or follow-up inspection.

4.4 Decide whether the inspection will cover the entire factory or just part of it.

4.5 Determine what the scope and depth of the inspection will be to enable you to prepare for it properly. (For a company producing sterile products, prepare by reviewing the guidelines for sterile product manufacture in addition to the general GMP guidelines.)

4.6 Scrutinize the product information for the products in the prequalification procedure manufactured at this manufacturing site.

4.7 Decide how long it will take to carry out the inspection and plan the date when the inspection will take place.

4.8 Inform the manufacturer(s) in question of the proposed date for the inspection.

4.9 Ensure that the proposed date for the inspection is suitable for all members of the inspection team.

4.10 Decide on a chief or lead inspector to coordinate and lead the inspection.

4.11 The lead inspector will be the main spokesperson during the closing or exit meeting at the end of an inspection, and has the overall responsibility for the inspection report.

4.12 Inform other interested parties of the proposed or planned inspection, e.g. a regional office of the procurement agency or agency, or the national regulatory authority.

4.13 Review documentation relating to the manufacturer to be inspected such as a completed questionnaire.

4.14 In case of a follow-up inspection, and where the procurement agency or agency has a company file in which general correspondence and previous inspection reports are filed, review the correspondence.

4.15 If a site master file (SMF) exists and is available, study the SMF and make notes to be followed up during the inspection (e.g. available equipment, SOPs and records)

4.16 Study the layout and design of the manufacturing facility, and some of the systems the manufacturer has in place to ensure quality in manufacture of products.

4.17 Look at the information provided on the manufacturing licence and product licence. Make notes of the aspects that need to be inspected to confirm compliance with licence conditions, and to verify data during the inspection.

4.18 Review the reports of previous inspections, reports of adverse drug experiences and complaints, if any exist, as investigations and corrective action taken by the manufacturer should be verified during inspections.

4.19 For a special inspection, review records of the company in relation to complaints and recalls, and regulatory test results (surveillance) where available.

4.20 If an annual report is available, scrutinize the report and note the information in relation to financial aspects of the company, personnel issues and products manufactured.

4.21 If any complaints had been received about the manufacturer or products previously supplied, review the contents of the complaint, investigation, outcome and corrective action.

4.22 If self-inspection/internal audit reports were requested from the manufacturer, review the contents. (Such reports are normally not requested as some manufacturers consider that the inspectors should assess GMP compliance themselves, and not look at the company's own findings of inspections. Requesting such reports would be dependent on the policy of the procurement agency.)

4.23 Study the diagram of the facility to get a better understanding of the flow of material, personnel and processes in the facility.

4.24 If any manuals and/or procedures were submitted by the manufacturer, review these and prepare specific questions relating to the quality policy, validation policy and procedure for performing certain activities.

4.25 Draw up a checklist or aide-memoire of points to be verified during the inspection.

4.26 Draw up a programme for the inspection. Produce an outline of what will be covered each day and clarify what each member of the team will be doing every day or half-day of the visit. Indicate in the programme which sections or departments will be inspected, and when (for an example, see Addendum A).

4.27 Distribute the programme to the team members. In the case of an announced inspection, inform the company of the proposed inspection programme.

5. Addenda

Addendum A: Example of an inspection plan

6. Distribution and retrieval

The record of distribution and retrieval of the SOP should be entered in a table; see the model below.

	Distribution		Retrieval	
Name	Signature	Date	Signature	Date

7. History

The history of changes to the SOP should be entered in a table; see the model below.

Date	Reason for change

Addendum A: Example of an inspection plan

Manufacturer	
Address	
Date	
Inspectors	

Day 1

Time	Activity
08:30	Arrival
08:45	Opening meeting and company presentation
09:15	Receiving area and stores
10:15	Sampling
11:00	Tea
11:15	Weighing
12:00	Packaging components
13:00	Lunch
14:00	Manufacturing (organize time depending on the dosage form(s))
17:00	Summary of the day's observations

Day 2

08:30	Manufacturing, continued
10:00	Tea
10:15	Quality control
12:00	Heating, ventilation and air-conditioning, water and other utilities
13:00	Lunch
14:00	Documentation
17:00	Summary
17:30	Closing meeting

Appendix 12

Example of a standard operating procedure for performing an inspection

1. Title

Performance of inspection

	Signature	Date
Prepared by		1 July 2006
Authorized by		

2. Policy and objective

2.1 Each manufacturer should be inspected by the procurement agency to assess compliance with good manufacturing practices.

2.2 All inspectors should follow the SOP for performing inspections.

2.3 The objective is to ensure that a standardized procedure is followed by all inspectors when performing inspections to prevent inspections being performed by different inspectors in different ways. This should ensure consistency in performance between inspectors.

2.4 One of the objectives is to control and enforce the general standards of production for products that may be sourced as a result of the prequalification procedure.

2.5 Through sequential examination of production and control activities of the manufacturer, the manufacturer of pharmaceutical products may be included on the prequalification list as a manufacturer of pharmaceutical products for possible supply of specified products to procurement agencies and other agencies.

2.6 During inspections, the performance of manufacture of products and data submitted in the relevant product information files should be verified.

3. Responsibility

Project Manager
Inspectors

4. Action

All actions described here are taken from the details provided in the WHO publication *Quality Assurance of Pharmaceuticals*,Volume 2, Chapter 4: Inspection of pharmaceutical manufacturers and inspection of drug distribution channels. These guidelines or other similar systems operated by national drug regulatory authorities should be followed in detail.

4.1 Clarification and definitions

4.1.1 Different types of inspections are identified in the WHO text referred to above. These include:

- routine inspection;
- concise inspection;
- follow-up inspection;
- special inspection;
- quality systems review.

4.2 The performance of the inspection is dependent on the type of inspection; however, in principle, the basic aspects of this procedure can be followed for performance of an inspection.

4.3 A routine inspection is a full review of all aspects and components of GMP within a facility. It is appropriate to perform a routine inspection under the following circumstances:

- when there is a new expression of interest (EOI) from a manufacturer or a newly established manufacturer;
- when the listing on the prequalification list is due for renewal;
- if there have been significant changes such as new products or new product lines; modification to manufacturing methods or processes; or changes in key personnel, premises and/or equipment;
- if an inspection has not been carried out within the past 3–5 years.

4.4 A concise inspection is the evaluation of limited aspects relating to GMP compliance within a facility. (It is known as an abbreviated inspection in some countries.) A limited number of GMP requirements are selected by the inspector to serve as indicators of overall GMP compliance by the manufacturer. The inspector also has to identify and evaluate any significant changes that could have been introduced by the manufacturer since the last inspection.

4.4.1 Collectively, the selected indicators and the changes identified indicate the manufacturer's attitude towards GMP.

4.4.2 A concise inspection is appropriate under the following circumstances:

- where a manufacturer has a consistent record of compliance with GMP through routine inspections in the past;
- where a sample of aspects can be taken as a good indication of the overall level of compliance with GMP.

4.4.3 However, if the concise inspection uncovers evidence that the level of GMP compliance has fallen, a more comprehensive or full GMP inspection should be performed soon after the concise inspection.

4.5 A follow-up inspection is also referred to as a re-inspection or a reassessment of the manufacturer.

4.5.1 A follow-up inspection is performed specifically to monitor the result of corrective actions of the manufacturer following a previous inspection.

4.5.2 Depending on the nature of the defects and the work required, the follow-up inspection could be carried out between 6 weeks and 6 months after the original inspection took place.

4.5.3 The follow-up inspection is limited to specific GMP requirements that have not been observed or that have been inadequately implemented by the manufacturer.

4.6 There are a number of circumstances in which special visits or inspections may be necessary. A special inspection is undertaken to do spot checks. Spot checks could focus on one product, a group of related products, or specific operations e.g. mixing or labelling. If there have been complaints about a specific product that suggest there may be defects, a special inspection could be performed to investigate the quality defects of the product. If there has been a product recall, this can also trigger an inspection, as would adverse drug reactions. In the above cases, the inspection would focus on the specific product or aspect of production that is suspect. A special inspection could also be performed to gather specific information, or to investigate specific operations of the manufacturer.

4.7 The purpose of a quality systems review is to review the manufacturer's quality system and to ascertain whether it has been shown to operate satisfactorily.

4.8 Plan the inspection to ensure that all areas for assessment are covered in the allocated timeframe. The length of time needed for an inspection is determined by a number of factors, including the type of inspection to be performed, the number of inspectors, the size of the company and the purpose of the inspection or visit.

4.9 An inspection can be performed over a period of a few days to several weeks.

4.10 The time taken will also depend on the size of the inspection team. One or more inspectors can perform the inspection as part of an inspection team.

4.11 If necessary, appoint a specialist to accompany the team during the inspection, e.g. for particular dosage forms, chemistry or another aspect, e.g. the manufacture of biologicals.

5. Addenda

Addendum A: Inspection programme
Addendum B: Documentation required for verification during the inspection

6. Distribution and retrieval

The record of distribution and retrieval of the SOP should be entered in a table; see the model below.

	Distribution		Retrieval	
Name	Signature	Date	Signature	Date

7. History

The history of changes to the SOP should be entered in a table; see the model below.

Date	Reason for change

Addendum A: Inspection programme

Manufacturer	
Address	
Date	
Inspectors	

Day 1

08:30	Arrival
08:35	Opening meeting
08:45	Company presentation
09:00	Receiving area and stores
10:30	Tea
10:45	Sampling and weighing areas
11:15	Packaging material stores and control
12:30	Lunch
13:15	Manufacturing areas
15:30	Tea
15:45	Manufacturing (cont.)
16:30	Summary of findings, day 1

Day 2

08:30	Arrival
08:35	Manufacturing area (cont.)
10:30	Tea
10:45	Laboratories
12:30	Lunch
13:15	Laboratories (cont.)
15:30	Tea
15:45	Utilities
16:30	Summary of findings, day 2

Day 3

08:30	Arrival
08:35	Utilities (cont.)
10:30	Tea
10:45	Documentation
12:30	Lunch
13:15	Documentation (cont.)
15:30	Tea
15:45	Preparation for closing meeting
16:00	Closing meeting

Addendum B: Documentation required for verification during the inspection

1. Organigram
2. Job descriptions
3. Quality policy (e.g. quality manual)
4. Validation policy (e.g. validation master plan or programme)
5. Raw material specifications (for specific products)
6. Packaging material specifications
7. Manufacturing formula and method masters
8. Packing instructions master
9. Batch manufacturing records (verification against master documents)
10. SOP index
11. SOP: self inspection
12. SOP: recalls
13. SOP: complaints plus records
14. SOP: batch number allocation
15. SOP: planned preventive maintenance
16. SOP and record: planned preventive maintenance of specific equipment
17. SOP: training (plus record of personnel)
18. SOP: environmental monitoring plus records
19. SOP: water sampling and testing plus records
20. Validation protocol and report for specific products
21.
22.
23.
24.
25.
26.
27.
28.
29.
30.

Appendix 13

Example of a checklist for good manufacturing practices

It is recommended that inspectors prepare an aide-memoire to remind them of points to be checked during an inspection.

Aide-memoires can be prepared to cover one or more aspects, e.g.

- production
- quality control
- utilities
- lyophilization.

The aide-memoire should contain key words to remind the inspector of aspects to be inspected.

An example of an aide-memoire is shown below.

Example: Aide-memoire for inspection of the lyophilization process:

Points to check	Notes
Dissolving Filtration Filling and stoppering Transfer Loading Freezing Vacuum Heating Stoppering Capping	
Validation: Design qualification (DQ) Installation qualification (IQ) Operational qualification (OQ) Commissioning Process qualification (PQ) Media fills Air samples Surface swabs Operator swabs Daily clothing	

Table *continued*

Points to check	Notes
Simulate process with media (not freeze) Smoke test (transport area) Transport Frequent fill volume Pre-cooling of shelves (no ice)	
Freezing Cycle Rate – (slow = crystals, polymorphism) Manner Drying temp. < eutectic point Determine eutectic point, consistent Shelf loading variations *Validate:* shelf temperature product temperature condenser temperature pressure (chamber) pressure (condenser) time, temperature, pressure leakage in contamination (thermal fluid, oil) cleaning	
Cycle Eutectic point determination Scale up Vial size Batch size	
Sterilization of lyophilizer Moist heat used Each cycle Residue if applicable Biological Indicators Design: single door (double door, air class!)	

Appendix 14

Guidance on good manufacturing practices: model inspection report

Model inspection report

Section 1. General information

Name of organization:	
Website (link):	
Physical address:	
Postal address:	
Tel.:	
Fax:	
Contact person:	
Email address:	
Activities:	Prequalification ☐ Purchasing ☐ Receiving and storage ☐ Distribution ☐ Reassessment ☐
Date of assessment/inspection (dd/mm/yyyy):	
Products and/or product category (e.g. pharmaceuticals, diagnostics, medical devices)	
Name of inspector:	

Section 2. Summary

General information about the procurement agent and site
History of inspections
Focus of the inspection and areas inspected
Summary of findings
General activities:
Prequalification:
Purchasing:
Receiving and storage:
Distribution (including the ability to supply the needed products in quantities required):

Table *continued*

Reassessment:

Section 3. Observations and deficiencies/noncompliance

Note: Module I should be used in all cases of assessment of a procurement agency. Modules 2 to 6 may be used depending on the activities performed by the procurement agency.

	Module I: General requirements	Classification (C, M, O)
1.		
2.		
3.		
4.		
5.		
	Module II: Prequalification	
6.		
7.		
8.		
9.		
10.		
	Module III: Purchasing	
11.		
12.		
13.		
14.		

Table *continued*

	Module IV: Receiving and storage	
15.		
16.		
17.		
18.		
	Module V: Distribution	
19.		
20.		
21.		
22.		
	Module VI: Reassessment	
23.		
24.		
25.		
26.		

(C) Critical observation: An observation relating to any activity, action or omission thereof, by the procurement agency, in relation to product(s), that may result in a significant risk to the user.

(M) Major observation: A non-critical observation that:

- may have a negative impact on a product in relation to prequalification, purchasing, storage, distribution or requalification; and/or
- indicates a major deviation from the model quality assurance system (MQAS); and/or
- consists of several other deficiencies, none of which on its own may be major, but which may together represent a major deficiency and should be explained and reported as such.

(O) Other observation: An observation that cannot be classified as either critical or major, but indicates a departure from the recommendations in the MQAS (including good storage practices (GSP) and good distribution practices (GDP)).

Section 4. Outcome of the inspection *(select one of the following options)*

Based on the areas inspected, the personnel met and the documents reviewed, and considering the findings of the inspection, including the observations listed above – the agency was considered to be operating in compliance with the MQAS for the following activities (select the appropriate one(s)) prequalification, purchasing, storage, distribution, requalification).

Or

Based on the areas inspected, the personnel met and the documents reviewed, and considering the findings of the inspection, including the observations listed above – the agency was considered not yet to be operating at an acceptable level of compliance with the MQAS for the following activities (select the appropriate one(s)) prequalification, purchasing, storage, distribution, requalification). The corrective and preventive actions (CAPAs) will be reviewed after which a conclusion will be made as to whether the procurement agency is operating in compliance with the MQAS. (A reinspection may be considered before the conclusion is reached.)

Or

Based on the areas inspected, the personnel met and the documents reviewed, and considering the findings of the inspection, including the observations listed above – the agency was considered to be operating at an unacceptable level of compliance with the MQAS for the following activities (select the appropriate one(s)): prequalification, purchasing, storage, distribution, requalification).

Signature: _____ Date: _____

(Name): _____
(Print)

Appendix 15

Good storage practices

For a guide to good storage practices for pharmaceuticals, see: *WHO Expert Committee on Specifications for Pharmaceutical Preparations, Thirty-seventh report*. Geneva, World Health Organization, 2003 (WHO Technical Report Series No. 908), Annex 9.

Available at:
http//:www.who.int/medicines/areas/quality_safety/quality_assurance/distribution/en/

Appendix 16

Good trade and distribution practices

For a guide to good trade and distribution practices for pharmaceutical starting materials, see: *WHO Expert Committee on Specifications for Pharmaceutical Preparations, Thirty-eighth report*. Geneva, World Health Organization, 2003 (WHO Technical Report Series, No. 917), Annex 2.

Available at:
http://www.who.int/medicines/strategy/quality_safety/tr917ann2.pdf

Annex 4

Assessment tool based on the model quality assurance system for procurement agencies: aide-memoire for inspection

1. Introduction

The Expert Committee on Specifications for Pharmaceutical Preparations of the World Health Organization (WHO) adopted a model quality assurance system for procurement agencies (MQAS) during a meeting in Geneva, Switzerland in 2005. This was subsequently published as Annex 6 in the Technical Report Series, No. 937 in 2006.

The Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM) Secretariat coordinated this project with the aim of preparing a harmonized assessment tool based on the WHO documents: *Model quality assurance system for procurement agencies (MQAS)*; WHO *guidelines on good storage practices (GSP)* and WHO *guidelines on good distribution practices (GDP)* (for current versions, see www.who.int/medicines).

This harmonized tool was developed by a working group consisting of representatives from the following organizations: Committee for Medicinal Products for Human Use (CHMP), Crown Agents, global drug facility (GDF), Global Fund to Fight AIDS, Tuberculosis and Malaria, International Committee of the Red Cross (ICRC), International Development Association (IDA), Médecins Sans Frontières (MSF), Management Sciences for Health (MSH), Partnership for Supply Chain Management (PFSCM), Quality Medicines for All (QUAMED), United Nations Children's Fund (UNICEF), United Nations Office for Project Services (UNOPS) and United States Agency for International Development (USAID).

2. Purpose

This harmonized tool was developed by the working group with the objective that it could result in better use of resources by coordinating procurement agency (PA) assessments; and working towards mutual recognition of the findings of PA assessments.

3. Scope

The assessment tool is based on the six modules in the MQAS:

Module I	General requirements for procurement agencies
Module II	Prequalification
Module III	Purchasing
Module IV	Receiving and storage
Module V	Distribution
Module VI	Reassessment

The tool covers the topics each of the above-listed Modules below. The logical flow considered is the quality system and infrastructure of the PA under assessment, how the PA performed prequalification, then purchasing of the products followed by the receiving and storage thereof. The last two modules then focus on the receiving of orders and dispatch of products followed by the reevaluation concept.

4. Assessment tool

The tool should be used by qualified, experienced persons when assessing a PA (including wholesalers and distributors) for compliance with recommended international standards. It can also be useful for a PA when doing a self-assessment.

The tool is not a checklist, but serves as a document to help and remind inspectors as to what should be assessed during inspections of PAs.

Module I: General requirements for procurement agencies

This Module covers general requirements for PAs including premises, equipment, transport and documentation (such as standard operating procedures (SOPs), confidentiality, code of conduct and complaint handling). Module I should be used in all cases of assessment of a procurement agency. (Modules II to VI may be used depending on the activities performed by the PA.)

Area of operation	Note	Critical aspects
Premises, equipment, furniture, transport	*General* • Licensed to operate • Sufficient space (offices for personnel, products, documents, samples, etc.) • Suitable conditions • Necessary furniture • Working office equipment • Stationery and consumables • Telephone and email access • Appropriate transport available	Compliance with legislation (licence) There must be a sufficient and functional infrastructure to enable the PA to perform its activities

Table *continued*

Area of operation	Note	Critical aspects
Human resources	*Personnel* • Compliance with national legislation (e.g. responsible person) • Sufficient number of people • Key personnel – quality assurance, prequalification, purchasing, storage and distribution • Quality assurance/ prequalification and purchasing independent of one another • Support staff • Contracted personnel and agreements • Training, education and experience	Compliance with legislation Quality assurance/ prequalification and purchasing independent of one another (personnel and reporting structure)
Organization	*Organization chart* • Authorized and current • In line with the job descriptions *Job descriptions* • Written job descriptions • Signed and dated	
Ethical considerations	*Conflict of interest* • Policy on conflict of interest is observed • Signed declaration of interest No vested interests *Code of conduct* • Written, authorized and implemented • Covers conduct of personnel • All personnel to comply with a code of conduct *Confidentiality* • Relevant product information kept confidential • Confidentiality agreements exist	Declaration and management of conflict of interest

Table *continued*

Area of operation	Note	Critical aspects
Computers	*Appropriate hardware and software* • Sufficient capacity and memory • Access control • Data transfer procedures • Reliable and accurate quality and management of data and information • Data storage (e.g. hard copies) • Back-up at defined intervals, storage, access, readable • Virus protection program and firewall • Technical support • Maintenance • Trained personnel	If used, reliable data management (including access control)
Financial systems	• Adequate banking facilities • Signatories of bank accounts appointed • Accounting system in place • National and international financial transactions • Financial transactions performed without delay • Funds available • Regular financial audits are performed	
Documentation	*Comprehensive documented system* • Covers policies, guidelines, norms, standards, manuals, procedures, records and related documents • SOPs for activities *Quality manual (QM)* • Contains a quality policy • Evidence of QM implementation, QM maintained, reviewed and amended as necessary	Activities and responsibilities described in SOPs which are implemented and followed Records reflecting activities

Table *continued*

Area of operation	Note	Critical aspects
	Standard operating procedures • SOP for writing an SOP followed • Written, clear, detailed SOPs for activities • Controlled, distributed and retrieved when required • Available for use • SOPs are reviewed periodically • Quality risk management (QRM) principles applied *Style and layout* • SOPs in defined format • Signed and dated	
Activities to be covered by SOPs	All activities should be covered by SOPs and include: • prequalification • purchasing • receiving and storage • distribution • training • handling of complaints • handling of recalls • document/record control including distribution and retrieval of SOPs • self-inspection • monitoring of environmental conditions (e.g. temperature) • monitoring of supplier performance • identifying and reporting SSFFC medical products • evaluating offers received • ordering product(s) from supplier or manufacturer • change control • variations • corrective and preventive action (CAPA)	Written SOPs followed for prequalification, purchasing, storage, distribution, complaints, recalls, identifying and reporting substandard/ spurious/falsely-labelled/ falsified/counterfeit (SSFFC) medical products Change control

Table *continued*

Area of operation	Note	Critical aspects
List of prequalified products, manufacturers and suppliers	• Current, authorized, access-controlled list • Based on the outcome of evaluation • Contains required information • Product-, manufacturing site- and supplier-specific (where relevant) • A key person responsible	A controlled list is maintained
Maintenance of records	• Records of all operations kept • Sufficient space for archiving • Access controlled • Retention period appropriate	Records are available for review
Contract arrangements	• Written contracts for delegated activities	Written, valid agreements in place

Module II: Prequalification

Prequalification is one of the key elements in ensuring purchase and supply of pharmaceutical products of acceptable quality. The prequalification process can be subdivided into two major parts, i.e. product-related assessment and manufacturer-related inspection.

Area of operation	Note	Critical aspects
Principles	• Documented policy and procedures for prequalification • Include assessment of product and manufacturers/suppliers • If delegated – written agreement in place	

Table *continued*

Area of operation	Note	Critical aspects
Key persons and responsibilities	• Responsible personnel identified • Independent from the purchasing personnel • Job descriptions • Communication between personnel involved in evaluation and inspections *Evaluation of product information (evaluators)* • List of evaluators • Suitable qualifications and experience • Job descriptions • Contracted external evaluators used (confidentiality, conflicts of interest and financial resources, references) *Inspection of manufacturing sites (inspectors)* • List of inspectors • Job descriptions • Qualified, trained, experienced • Contracted inspectors – confidentiality and no conflict of interest	Qualified, trained personnel perform prequalification activities (including assessment and inspections) Quality assurance/ prequalification and purchasing independent of one another (personnel and reporting)
Key steps in prequalification defined	*Step 1: Soliciting information* • Procedures for preparation of detailed, clear specifications; soliciting information; receiving and processing of the information • Policy and procedure for handling late submissions • Recording of data received • Procedure for submitting product information publicly available and accessible • Product information to be submitted defined (as a minimum, see product questionnaire)	Evaluation of product data and information as well as the criteria used to approve or reject a product Ensuring compliance with good manufacturing practices (GMP)

Table *continued*

Area of operation	Note	Critical aspects
	Step 2: Receive product information • Written procedures for receiving, identification, marking files, containers and samples; and sufficient space for unpacking and storage • Procedure to ensure traceability of the product information • Personnel available *Step 3: Screen product information* • SOP: screen for completeness • A screening form used • Record of screening kept • Outcome communicated to manufacturer/supplier *Step 4: Evaluate product information* • Follow SOP for evaluation to check that the product meets requirements • Time frames • Evaluation report for each product exists • Outcome communicated to the manufacturer/supplier • Response invited where needed • Outcome accepted or rejected • Evaluation report kept as record • Samples analysed if needed (see also monitoring below) *Step 5: Plan, prepare and perform inspections* *General points* • Evidence of GMP compliance • Site of manufacture known • Site inspection policy • Contract manufacturing sites known • Control over active pharmaceutical ingredients (APIs) (inspection risk-based)	

Table *continued*

Area of operation	Note	Critical aspects
	Plan • SOP and recording system for inspection planning • Procedure and data reviewed as part of preparation for inspection (e.g. site master file) *Conduct* • SOP: how to perform an inspection • Scope: data and information verified and WHO GMP compliance assessed • If not done – conditions for waiving on-site inspections *Inspection report* • Inspection report for each site inspected • Outcome communicated • CAPA requested, received and reviewed • Conclusion or outcome • Copy of report kept *Step 6: Finalize assessment process* • Written procedure followed • Covers product evaluation plus laboratory results and inspection outcome • Responsible persons (decision-taking) and reasons for decision • Outcome communicated • List of prequalified products, manufacturers and suppliers • Agreement between PA and supplier/manufacturer • List reviewed and updated at regular intervals	
Cost recovery	• If used, transparent procedure • Fee-for-services structure	

Module III: Purchasing

Procurement should be done with the aim of purchasing effective, quality assured products, and not focused on price alone. The term "procurement" in this Module relates specifically to the purchase of health sector goods from manufacturers or suppliers. The module goes on to describe the key activities in purchasing pharmaceutical products, as well as the recommended organizational structure of the procurement agencies which carry out these key activities.

Area of operation	Note	Critical aspects
Procurement strategies	• Policy: suppliers are selected and monitored through a process that takes into account product quality, service reliability and performance, delivery time, ethics, legal status, financial viability and minimum order quantities *Purchase prequalified products (from manufacturers/suppliers)* • Efficient and transparent management • Financial management procedures • Competitive procurement methods • Procedure to calculate lowest possible total cost • Procurement and purchasing procedures are transparent • Independent contract review • Purchasing and tender documents list all pharmaceutical products by their international nonproprietary name (INN) or national generic names • Intellectual property rights are respected in accordance with best practice and national law	Purchasing prequalified products

Table *continued*

Area of operation	Note	Critical aspects
Procurement methods	• If they are responsive to the defined terms and conditions, responses are examined from invited suppliers • Adjudication procedure • Explicit criteria for awarding contracts • Informed of the outcome • Restricted tender • Prequalified products and suppliers • Competitive negotiation • Direct procurement	Adjudication procedure and related records Use a defined, transparent procurement method
Key activities	• Develop a list or catalogue of products (INN) • Develop specifications for the products *Quantification* • Methods of product quantification • Quantities purchased based on reliable estimate *Procurement method* • According to the policy and procedures of the procurement agency	
Organization and responsibilities	• Personnel with appropriate qualifications and training • Job descriptions • Independent from those responsible for prequalification and quality assurance • Procurement planned	

Table *continued*

Area of operation	Note	Critical aspects
Monitoring of the performance of prequalified products, manufacturers and suppliers	• Procedure for continuous monitoring of the performance of products, manufacturers and suppliers *Monitoring may include:* • review of quality control results • verification that the product batches supplied have been manufactured in compliance with standards and specifications accepted in the product information through inspection • adverse events • random samples of batches supplied analysed (risk-based approach) • independent testing – reliable quality control laboratory (see selection criteria for quality control laboratory) • certificates of analysis available where appropriate • status of the laboratory (e.g. authorized, accredited) • handling of out-of-specification results • monitoring of complaints • outcome of inspection of manufacturing sites • outcome of reassessment of product information • monitoring of direct and indirect product costs • monitoring of adherence to delivery schedules • contract terms and conditions • tracking system (values of contracts awarded, total purchases, performance)	Handling out-of-specification results Monitoring performance of products, manufacturers and suppliers and action taken by the PA in case of non-compliance
Donations	• Written procedure	

Module IV: Receiving and storage

The PA should ensure that the pharmaceutical products purchased are received and stored correctly and in compliance with applicable legislation and regulations. Products should be received and stored in such a way that their quality and integrity is preserved, batch traceability is maintained and stock can be rotated.

Area of operation	Note	Critical aspects
General arrangements	• Received and stored correctly • Quality and integrity is maintained • Batch traceability • Stock rotation • Unidirectional flow • Security of materials and products • Subcontracting	Procedures followed for receiving and storage Batch traceability
Pre-shipment quality control	• Batches released by the manufacturer (certificate of analysis (CoA)) • Batches additionally tested (risk-based approach) prior to shipment to PA • Selection criteria for quality control laboratory	Batch release with CoA (meeting specifications)
Receiving of stock	• Receiving and dispatch bays • Incoming containers cleaned, quarantined • Review of CoAs • Released for use or distribution (responsible person involved) *Checks on receipt:* • order, delivery note, labels and transport conditions, integrity of packages and seals and for uniformity of the containers	Goods received and checked according to an appropriate SOP – supported by records Products released by responsible person

Table *continued*

Area of operation	Note	Critical aspects
	Visual inspection for: • contamination, tampering and damage, expiry date, compliance with labelling and packaging instructions • suspect containers and damaged containers – recorded and investigated	
Post-procurement control	• Random sampling for independent laboratory analysis • Selection criteria for quality control laboratory • SOP and national legislation • Representative samples – sampling plans and instructions (risk assessment) • Appropriately trained and qualified personnel	Action taken in case of non-conforming product
Rejected materials	• SOP for rejected products • Separate storage or validated computerized system • Action approved by authorized personnel and recorded	Rejected materials kept separately, access controlled and handled appropriately
Storage of materials/ products	*Personnel* • Trained • Personal hygiene and sanitation • Appropriate garments *Storage areas* • No unauthorized access • Sufficient space • Adequate ventilation, temperature and relative humidity • Conditions checked, monitored and recorded • Segregation of rejected, expired, recalled or returned stock • Toilet and washing facilities separated from storage areas	Access controlled and sufficient space Appropriate conditions for storage

Table *continued*

Area of operation	Note	Critical aspects
	• Narcotics/psychotropic medicines as per national legislation • SOP for fire control • No smoking or eating • SOP and records for cleaning • Waste management • Pest control • SOP for handling spillages *Storage conditions* • As established by the manufacturer • Orderly, batch segregation, stock rotation, first expired-first out (FEFO) • Stored off the floor • Space to permit cleaning and inspection • Pallets in a good state of cleanliness and repair • Stacking of products without damage • Freeze-sensitive products – use monitoring devices • Cold rooms (qualification, temperature mapping, alarm, monitoring, records, back-up system in case of failure) *Monitoring of storage conditions* • Temperature mapping protocol and report • Calibrated sensors/devices • Ongoing monitoring with records • Out-of-limit and out-of-trend results investigated, action taken *Miscellaneous and hazardous materials* • Rodenticides, insecticides, fumigating agents and sanitizing materials • Toxic substances and flammable materials	

Table *continued*

Area of operation	Note	Critical aspects
Re-packaging and re-labelling	• If performed – in compliance with national legislation and WHO GMP	Compliance with national legislation and WHO GMP
Stock control	• Validated stock control system • Batch number control and expiry dating • Periodic stock reconciliation • Significant stock discrepancies investigated • Records maintained • Damaged containers handled *Control of obsolete and outdated materials and products* • SOP • Regular checks *Recalled materials and products* • SOP • Written records of actions with signatures • Products identified, recorded, reconciled and stored separately • Decision by appropriately qualified and experienced member of staff *Returned goods* • SOP • Quarantined and assessed • Resale conditions • Destruction in compliance with national requirements • Records *Waste materials* • SOP • Safe storage while awaiting disposal • Toxic substances and flammable materials • No accumulation • Safe disposal, national regulations	Stock control in place (e.g. reconciliation, obsolete materials, recalled products, returned goods, FEFO and waste)

Table *continued*

Area of operation	Note	Critical aspects
Documentation: written instructions and records:	• SOPs for activities • Handling of expired stock • Ensuring batch traceability • Records for storage conditions, precautions • National regulations concerning labels and containers • Comprehensive records of all activities • Retention of records	Record-keeping ensuring traceability (e.g. receiving, issuing, expired goods)

Module V: Distribution

The PA (or contracted party) should have a well-managed distribution system meeting the objectives of ensuring constant supply of quality medicines. Distribution should be done in accordance with general principles of GMP.

Area of operation	Note	Critical aspects
General	• Constant supply of medicines • Minimize medicines losses (spoilage and expiry) • Accurate inventory records • Prevent theft and fraud	
Transport conditions	• Transport process has no negative impact on product • Required storage conditions maintained • Temperature excursions – risk assessment	Appropriate transport conditions

Table *continued*

Area of operation	Note	Critical aspects
Cold chain	• Validated process • Applied where needed • Appropriate containers • Packaging procedure • Cooling agents used • Calibrated monitoring devices • Monitoring records reviewed, maintained	Cold chain validated, maintained and monitored
Dispatch procedures	• Compliance with legislation • Authorized recipients • Procedures in place • Special packaging requirements observed where needed • Dispatch and transport after receipt of a delivery order	Compliance with legislation Authorized recipients
Dispatch containers	• Provide protection • Appropriately labelled • Prevent theft (e.g. locked/ wrapped)	
Dispatch records	• Detailed records kept (e.g. date, customer name and address; product name and batch number and quantity) • Products and batches traceable • Discrepancies investigated	Records ensure traceability of goods
Port of entry	• Storage conditions met • Temperature-sensitive products handled appropriately • Security measures in place (e.g. prevent theft, fraud and bribery)	

Module VI: Reassessment

Quality of products and services should be continuously monitored. This process includes reassessment.

Area of operation	Note	Critical aspects
Reevaluation of manufacturers	• Reinspection frequency based on risk assessment • Within five-year cycle • Change control • Mechanism for suspension and withdrawal	Reinspection policy and procedure followed
Reevaluation of products	• Reevaluation procedure • Within five-year cycle • Variations procedure	Reevaluation of product policy and procedure followed
Monitoring performance of contractors	• Written procedure • Covers continuous monitoring, periodic review and renewal of contracts • System for documenting service problems	Procedure followed for monitoring performance

Annex 5

Guidelines on submission of documentation for prequalification of finished pharmaceutical products approved by stringent regulatory authorities

Scope

The revision of the WHO *Guidelines on submission of documentation for prequalification of innovator finished pharmaceutical products approved by stringent regulatory authorities*[1] is extended to include not only innovator products, but also multisource products. The title is accordingly changed to *Guidelines on submission of documentation for prequalification of finished pharmaceutical products approved by stringent regulatory authorities*. These guidelines apply to both innovator[2] and multisource (generic) finished pharmaceutical products (FPPs) approved by SRAs.

Introduction

The World Health Organization (WHO) recognizes the scientific evaluation of finished pharmaceutical products (FPPs) by SRAs,[1] which apply similarly stringent standards for quality, safety and efficacy to those recommended by WHO. Where an applicant shares with WHO information on an FPP that has been approved by a stringent SRA (hereinafter called the reference SRA) and that is invited for prequalification, WHO will consider such FPPs for inclusion in the list of WHO-prequalified products, as and when information about such a product becomes available to WHO and when the applicant in question expresses interest in the product being prequalified by WHO.

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[1] Stringent regulatory authority (SRA): a regulatory authority which is: (a) a member of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) (as specified on www.ich.org); or (b) an ICH observer, being the European Free Trade Association (EFTA), as represented by Swissmedic and Health Canada (as may be updated from time to time); or (c) a regulatory authority associated with an ICH member through a legally-binding, mutual recognition agreement including Australia, Iceland, Liechtenstein and Norway (as may be updated from time to time).

[2] Generally the innovator pharmaceutical product is that which was first authorized for marketing, on the basis of documentation of quality, safety and efficacy (WHO Technical Report Series, No. 937, 2006, Annex 7).

Guidelines on submission of documentation

The following should be submitted:

1. A covering letter, which should include:
   - a statement indicating that the information submitted is true and correct;
   - a statement confirming that for WHO prequalification, the FPP – including but not limited to composition/formulation, strength, manufacturing, specifications, packaging, product information – will, at the time of submission and after prequalification, in all respects be the same as the product registered with the reference SRA;
   - a statement indicating that the product is actually on the market of the reference SRA's country or region.
2. A copy of the marketing authorization, or the equivalent thereof, issued by the reference SRA to demonstrate that the product is registered or licensed in accordance with the reference SRA requirements. If applicable, a copy of the latest renewal of the marketing authorization should also be provided.
3. A copy of the current WHO-type certificate of a pharmaceutical product issued and fully completed, including answers to each question, by the reference SRA.
4. The latest SRA-approved product information (summary of product characteristics (SmPC), or an equivalent thereof, the patient information leaflet (PIL), or equivalent thereof, and the labelling). Provide a web link to the SRA-approved product information, preferably on the website of the SRA itself, if available.
5. A list of the SRA-approved manufacturer(s) of the FPP, including manufacturers of intermediates, primary packaging sites and release-testing sites, with the physical address of the manufacturing site(s) (and unit if applicable).
6. A list of the SRA-approved manufacturer(s) of the active pharmaceutical ingredient(s) (API(s)) used in the manufacture of the FPP, with the physical address of the manufacturing site(s) (and unit if applicable).
7. If available, a public assessment report, such as the Scientific Discussion of the European Public Assessment Report (EPAR), issued by the reference SRA. Assessment report(s) issued by the reference SRA that are not publicly available may be requested.

8. A tabular listing of the batches manufactured for the market of the reference SRA's region or country since approval or during the past five years, whichever is shorter. The table should include at least the batch number, batch size (number of units), date of manufacture and pack type/size. Also provide a copy of the most recent product quality review, prepared according to the requirements of the reference SRA.
9. A sample(s) of the product in market packaging(s). This should be provided with the submission to enable visual inspection thereof. Attach the respective certificate of analysis.
10. A copy of the currently approved FPP specifications (release and shelf-life), dated and signed or certified by authorized personnel, with the analytical test procedures.
11. The quality information summary (QIS-SRA). The QIS-SRA template, available on the WHO Prequalification Programme website (http://apps.who.int/prequal/), should be fully completed and submitted with the application. The QIS-SRA provides a condensed summary of key information on the FPP as approved by the reference SRA at the time of application for prequalification of the FPP.

Please note that the submission must be in English, and must include certified English translations of product information and other documents, if applicable. These documents should be made available electronically. The English language version of the product information, in the case of English translations, should also be submitted as Word files.

WHO may request additional data, when considered necessary for the use of the product in populations, settings or regions relevant for prequalified products. If necessary, this additional information, relevant for use of the product within the scope of the Prequalification Programme, will be included in the WHO public assessment report (WHOPAR) as a separate piece of information. Such information could be communicated to the reference SRA where appropriate. The SRA-approved product information will not be changed. WHO would normally not inspect the manufacturing site(s) of an SRA-approved product; however, there may be circumstances necessitating an inspection to be conducted in collaboration with the reference SRA, upon application or after prequalification of the FPP.

Variations to and renewal of the marketing authorization of an FPP that has been prequalified by WHO based on the approval by an SRA, remain the responsibility of the reference SRA.

Once the product has been prequalified, WHO should be provided with a copy of the regulatory approval letter of any changes to the key information on the

FPP (as captured in the QIS-SRA), the product information, the revised QIS-SRA, the FPP specification and test procedures, where appropriate, immediately after the variation has been approved by the reference SRA.

Changes to the QIS-SRA, the product information, the specification and test procedures should be shown in track-change mode in Word files. The clean version (in English language) of the updated product information should also be submitted. Other supporting information may be requested once the variation notification has been submitted.

WHO should be informed immediately in case of discontinuation of the product with the relevant SRA and of any critical safety or quality-related issues reported for batches on the market.

The preferred storage condition for WHO-prequalified products is "do not store above 30 °C", based on demonstrated stability at long-term storage conditions of 30 °C/75% relative humidity (RH) and at accelerated storage conditions (40 °C/75% RH). If this storage condition is not indicated on the SmPC, PIL and labels of the product, applicants are encouraged to apply for a variation in this respect with the relevant SRA. This could also be done after prequalification of the product.

Products that received United States Food and Drug Administration (US-FDA) tentative approval or positive opinions under Article 58 of European Union Regulation (EC) No. 726/2004 or the Canada S.C. 2004, c. 23 (Bill C-9) procedure, are not within the scope of these guidelines. Such products can be co-listed on the WHO list of prequalified products in accordance with mutual agreements between WHO and these regulatory authorities.

Annex 6

Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product: quality part

1. Introduction

1.1 Background

This document is technically and structurally inspired by the generic quality guidelines, WHO *Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part*, published in WHO Technical Report Series, No. 970, Annex 4 (*1*). The resulting guidance document is proposed for wider use by national medicines regulatory authorities (NMRAs) throughout WHO regions.

Through the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) process, considerable harmonization has been achieved on the organization of the *Quality Module* of registration documents with the issuance of the Common Technical Document (CTD) – Quality (ICH M4Q) guideline (*2*). This recommended format in the M4Q guideline for the quality information of registration applications has become widely accepted by regulatory authorities both within and beyond the ICH regions.

This document provides recommendations on the quality information for active pharmaceutical ingredients (APIs) and finished pharmaceutical products (FPPs) that should be submitted to NMRAs to support product dossiers (PDs).

Alternative approaches to the principles and practices described in this document may be acceptable provided they are supported by adequate scientific justification. It is also important to note that the NMRAs may request information or material, or define conditions not specifically described in this guidance, in order to adequately assess the quality of a pharmaceutical product.

1.2 Objectives

These guidelines are intended to:

- assist applicants in the preparation of the *Quality Module* of PDs for multisource products by providing clear general guidance on the format of these dossiers;
- adopt the modular format of the *Common Technical Document – Quality (M4Q)* (*2*) as developed by ICH;
- provide guidance on the technical and other general data requirements.

These measures are intended to promote effective and efficient processes for the development of these PDs by applicants and the subsequent assessment procedures by NMRAs.

1.3 Scope

These guidelines apply to PDs for multisource pharmaceutical products containing existing APIs of synthetic or semi-synthetic origin. For the purposes of these guidelines, an existing API is one that has been previously approved through a finished product by a stringent regulatory authority (SRA)[1] or WHO. Fermentation, biological, biotechnological and herbal APIs are covered by other guidelines.

1.4 General principles

To facilitate the preparation of the PD, these guidelines are organized in accordance with the structure of the *Common Technical Document – Quality (M4Q)* (*2*) guideline, as developed by ICH.

The text of the M4Q (CTD-Q) guideline has been restated in these guidelines in **bold text**, verbatim, with minor modifications to accommodate WHO terminology and include certain text that would be appropriate for multisource pharmaceutical products, notably:

- "drug substance" is replaced with "active pharmaceutical ingredient" or "API";
- "drug product" is replaced with "finished pharmaceutical product" or "FPP";
- "application" is replaced with "product dossier" or "PD";
- "combination product" is replaced with "fixed-dose combination" or "FDC";
- "clinical batches" is replaced with "comparative bioavailability or biowaiver batches".

Following the **bold** text of the M4Q (CTD-Q) guideline, additional guidance is provided in plain text to allow it to be easily distinguished from the ICH text and is included to further clarify the general expectations for the content of PDs. This approach is intended to facilitate the identification of the origin of the text in the guidelines (i.e. from ICH or additional information).

The content of these guidelines should be read in conjunction with relevant information provided in other existing NMRA guidelines, WHO guidelines and/

[1] Stringent regulatory authority (SRA): a regulatory authority which is: a member of the International Conference on Harmonisation (ICH) (as specified at www.ich.org); or an ICH observer, being the European Free Trade Association (EFTA), as represented by Swissmedic, and Health Canada (as may be updated from time to time); or a regulatory authority associated with an ICH member through a legally-binding, mutual recognition agreement including Australia, Iceland, Liechtenstein and Norway (as may be updated from time to time).

or ICH reference documents and guidelines. The quality of existing APIs and corresponding multisource products should not be inferior to that of new APIs and innovator FPPs. Therefore, the principles of the ICH guidelines that are referenced throughout this and other relevant guidelines may also equally apply to existing APIs and multisource products.

Scientific literature may be appropriate to fulfil the requirements for some of the information or parameters outlined in these guidelines (e.g. qualification of specified identified impurities). Furthermore, the requirements outlined in certain sections may not be applicable to the proposed API or FPP. In these situations, a summary and the full reference to the scientific literature should be provided or the non-applicability of the requested information should be clearly indicated as such with an accompanying explanatory note.

1.5 Guidance on format

Recommendations outlined in the WHO general filing guidelines: *Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product (FPP): preparation of product dossiers (PDs) in common technical document (CTD) format* (*3*) may be followed for the format and presentation of the PD, with the understanding that Module 1 contains regionally required information and therefore the required contents will vary depending on the NMRA to which the PD is filed.

There may be a number of instances where repeated sections can be considered appropriate. Whenever a section is repeated, it should be made clear what the section refers to by creating a distinguishing title in parentheses following the M4Q (CTD-Q) guideline heading, e.g. 3.2.S Drug substance (or API) (name, Manufacturer A).

The following are recommendations for the presentation of the information in the *Quality Module* for different scenarios that may be encountered.

- The *Open part* (non-proprietary information) of each APIMF[2] should always be included *in its entirety* in the PD, as an annex to 3.2.S.
- For an FPP containing more than one API: one complete "3.2.S" section should be provided for one API, *followed by* other complete "3.2.S" sections for each of the other APIs.
- For an API from multiple manufacturers: one complete "3.2.S" section should be provided for the API from one manufacturer, *followed by* other complete "3.2.S" sections for each of the other API manufacturers.

[2] API master file. Note that other global terms include DMF (drug master file) and ASMF (active substance master file).

- For an FPP with multiple strengths (e.g. 10, 50, 100 mg): one complete "3.2.P" section should be provided with the information for the different strengths provided *within* the subsections.
- For an FPP with multiple container-closure systems (e.g. bottles and unit dose blisters): one complete "3.2.P" section should be provided with the information for the different presentations provided *within* the subsections.
- For multiple FPPs (e.g. tablets and a parenteral product): a separate dossier is required for each FPP.
- For an FPP supplied with reconstitution diluent(s), one complete "3.2.P" section should be provided for the FPP, *followed by* the information on the diluent(s) in a separate part "3.2.P", as appropriate.
- For a co-blistered FPP, one complete "3.2.P" section should be provided for each product.

2. Glossary

The definitions provided below apply to the words and phrases used in these guidelines. Although an effort has been made to use standard definitions as far as possible, they may have different meanings in other contexts and documents. The following definitions are provided to facilitate interpretation of the guidelines.

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 (*4*).

API starting material. A raw material, intermediate, or an API that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API. An API starting material can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement, or produced in-house (*5*, *6*).

applicant. The person or company who submits an application for marketing authorization of a new pharmaceutical product, an update to an existing marketing authorization or a variation to an existing market authorization (*7*).

BCS highly soluble. An API for which the highest dose recommended by WHO (if the API appears on the WHO Model List of essential medicines (EML)) or highest dose strength available on the market as an oral solid dosage form (if the API does not appear on the EML) is soluble in 250 ml or less of aqueous media over the pH range of 1.2–6.8 at 37 °C (*8*).

commitment batches. Production batches of an API or FPP for which the stability studies are initiated or completed post-approval through a commitment made in a regulatory application (*9*).

comparator product (reference product). A pharmaceutical product with which the generic product is intended to be interchangeable in clinical practice. The comparator or reference product will normally be the innovator product for which efficacy, safety and quality have been established (*8*).

existing API. An API that is not considered a new active substance, that has been previously approved through a finished product by an SRA or WHO, but requires the filing of a dossier. This would include, for example, new PDs and variations to multisource products.

finished pharmaceutical product (FPP). A finished dosage form of a pharmaceutical product, which has undergone all stages of manufacture, including packaging in its final container and labelling (*4*).

innovator pharmaceutical product. Generally the pharmaceutical product that was first authorized for marketing (normally as a patented product) on the basis of documentation of efficacy, safety and quality (*8*).

intermediate. A material produced during steps of the processing of an API that undergoes further molecular change or purification before it becomes an API. Intermediates may or may not be isolated (*5*).

manufacturer. A company that carries out operations such as production, packaging, repackaging, labelling and relabelling of pharmaceuticals (*10*).

multisource (generic) pharmaceutical products. Pharmaceutically equivalent or pharmaceutically alternative products that may or may not be therapeutically equivalent. Multisource pharmaceutical products that are therapeutically equivalent are interchangeable (*8*).

national medicines regulatory authority (NMRA). The national authority responsible for the registration of and other regulatory activities concerning medical products, such as medicines, vaccines, blood products and medical devices.

officially recognized pharmacopoeia (or compendium). Those pharmacopoeias whose standards are officially recognized by an NMRA. These may be national, regional or international pharmacopoeias, at the discretion of the NMRA.

ongoing stability study. The study carried out by the manufacturer on production batches according to a predetermined schedule in order to monitor, confirm and extend the projected retest period (or shelf-life) of the API, or confirm or extend the shelf-life of the FPP (*9*).

pilot-scale batch. A batch of an API or FPP manufactured by a procedure fully representative of and simulating that to be applied to a full production-scale batch. For example, for solid oral dosage forms, a pilot scale is generally, at a

minimum, one-tenth that of a full production scale or 100 000 tablets or capsules, whichever is the larger; unless otherwise adequately justified (*9*).

primary batch. A batch of an API or FPP used in a stability study, from which stability data are submitted in a registration application for the purpose of establishing a retest period or shelf-life (*9*).

production batch. A batch of an API or FPP manufactured at production scale by using production equipment in a production facility as specified in the application (*9*).

3. Quality summaries

3.1 Module 2.3: Quality overall summary – product dossiers (QOS-PD)

The Quality overall summary (QOS) is a summary that follows the scope and the outline of the Body of data in Module 3. The QOS should not include information, data or justification that was not already included in Module 3 or in other parts of the CTD.

The QOS should include sufficient information from each section to provide the Quality assessor with an overview of Module 3. The QOS should also emphasize critical key parameters of the product and provide, for instance, justification in cases where guidelines were not followed. The QOS should include a discussion of key issues that integrates information from sections in the Quality Module and supporting information from other Modules (e.g. qualification of impurities via toxicological studies), including cross-referencing to volume and page number in other Modules.

The WHO *Quality overall summary – product dossiers (QOS-PD)* template or the QOS template associated with the intended NMRA, if available, should be completed for multisource pharmaceutical products containing APIs of synthetic or semi-synthetic origin (see 1.3 Scope for further clarification) and their corresponding FPPs. For the sake of simplicity, these guidelines will refer to the QOS-PD, which can be downloaded from the WHO website.

All sections and fields in the QOS-PD template that would be applicable should be completed. It is understood that certain sections and fields may not apply and should be indicated as such by entering "not applicable" in the appropriate area with an accompanying explanatory note.

The use of tables to summarize the information is encouraged, where possible. The tables included in the template may need to be expanded or duplicated (e.g. for multiple strengths), as necessary. These tables are included as illustrative examples of how to summarize information. Other approaches to summarize the information can be used if they fulfil the same purpose.

4. Module 3: Quality

4.1 Table of contents of Module 3

A table of contents for the filed product dossier should be provided.

4.2 Body of data

3.2.S Drug substance (or active pharmaceutical ingredient (API))

The NMRA, at its discretion, may accept API information in one or more of the following four options:

- Option 1: Confirmation of API prequalification document;
- Option 2: Certificate of suitability of the European Pharmacopoeia (CEP); or
- Option 3: API master file (APIMF) procedure; or
- Option 4: Full details in the PD.

The applicant should clearly indicate at the beginning of the API section (in the PD and in the QOS-PD) how the information on the API for each API manufacturer is being submitted. The API information submitted by the applicant/FPP manufacturer should include the following for each of the options used.

Option 1: Confirmation of API prequalification document

API prequalification is a procedure for manufacturers of APIs that are of interest to WHO. The procedure verifies both the quality of the API and that the API is manufactured in compliance with good manufacturing practices (GMP) (ICH Q7) (5). Complementary information regarding a prequalified API is provided on the Prequalification of Medicines website and in the Confirmation of Prequalification document (CPQ).

A complete copy of the Confirmation of API Prequalification document should be provided in Module 1, together with the duly filled out authorization box in the name of the FPP manufacturer or applicant.

The applicant should supply the following information in the dossier, with data summarized in the QOS-PD.

- *3.2.S.1.3 General properties* – discussions on any additional applicable physicochemical and other relevant API properties that are not controlled by the API manufacturer's specifications, e.g. solubilities and polymorphs according to the guidance in this section.
- *3.2.S.2* If the sterility of the FPP is based upon the sterile manufacture of the API then data on the sterilization process together with full validation data should be provided.

- *3.2.S.3.1 Elucidation of structure and other characteristics* – studies to identify polymorphs and particle size distribution, where applicable, according to the guidance in this section.
- *3.2.S.4.1 Specification* – the specifications of the FPP manufacturer including all tests and limits of the API manufacturer's specifications and any additional tests and acceptance criteria that are not controlled by the API manufacturer's specifications, such as polymorphs and/or particle size distribution.
- *3.2.S.4.2/3.2.S.4.3 Analytical procedures and validation* – for any methods used by the FPP manufacturer in addition to those in the API manufacturer's specifications.
- *3.2.S.4.4 Batch analysis* – results from two batches of at least pilot scale, demonstrating compliance with the FPP manufacturer's API specifications.
- *3.2.S.5 Reference standards or materials* – information on the FPP manufacturer's reference standards.
- *3.2.S.7 Stability* – data to support the retest period if either the proposed retest period is longer or the proposed storage conditions are at a lower temperature or humidity than that of the prequalified API.

Option 2: Certificate of Suitability of the European Pharmacopoeia (CEP)

A complete copy of the CEP (including any annexes) should be provided in Module 1. The declaration of access for the CEP should be duly filled out by the CEP holder on behalf of the FPP manufacturer or applicant to the NMRA who refers to the CEP.

In addition, a written commitment should be included that the applicant will inform the NMRA in the event that the CEP is withdrawn. It should also be acknowledged by the applicant that withdrawal of the CEP would require additional consideration of the API data requirements to support the PD. The written commitment should accompany the copy of the CEP in Module 1.

Together with the CEP, the applicant should supply the following information in the dossier, with data summarized in the QOS-PD.

- *3.2.S.1.3 General properties* – discussions on any additional applicable physicochemical and other relevant API properties that are not controlled by the CEP and *European Pharmacopoeia* (Ph. Eur.) monograph, e.g. solubilities and polymorphs according to the guidance in this section.

- *3.2.S.3.1 Elucidation of structure and other characteristics* – studies to identify polymorphs (exception: where the CEP specifies a polymorphic form) and particle size distribution, where applicable, according to the guidance in this section.
- *3.2.S.4.1 Specification* – the specifications of the FPP manufacturer including all tests and limits of the CEP and Ph.Eur. monograph and any additional tests and acceptance criteria that are not controlled in the CEP and Ph.Eur. monograph, such as polymorphs and/or particle size distribution.
- *3.2.S.4.2/3.2.S.4.3 Analytical procedures and validation* – for any methods used by the FPP manufacturer in addition to those in the CEP and Ph.Eur. monograph.
- *3.2.S.4.4 Batch analysis* – results from two batches of at least pilot scale, demonstrating compliance with the FPP manufacturer's API specifications.
- *3.2.S.5 Reference standards or materials* – information on the FPP manufacturer's reference standards.
- *3.2.S.6 Container-closure system* – specifications including descriptions and identification of primary packaging components. Exception: where the CEP specifies a container-closure system and the applicant declares the intention to use the same container-closure system.
- *3.2.S.7 Stability* – exception: where the CEP specifies a retest period that is the same as or of longer duration, and storage conditions which are at the same or a higher temperature and humidity as proposed by the applicant.

In the case of sterile APIs, data on the process for sterilization of the API, including validation data, should be included in the PD.

Option 3: API master file (APIMF) procedure

Full details of the chemistry, manufacturing process, quality controls during manufacturing and process validation for the API may be submitted to the NMRA as an APIMF by the API manufacturer, for example, as outlined in the WHO *Guidelines on active pharmaceutical ingredient master file procedure* (*11*).

In such cases, the *Open part* (nonproprietary information) needs to be included *in its entirety* in the PD as an annex to 3.2.S. In addition, the applicant/FPP manufacturer should complete the following sections in the PD and QOS-PD *in full* according to the guidance provided unless otherwise indicated in the respective sections:

General information S.1.1–S.1.3
Manufacture S.2
Manufacturer(s) S.2.1
Description of manufacturing process and process controls S.2.2
Controls of critical steps and intermediates S.2.4
Elucidation of structure and other characteristics S.3.1
Impurities S.3.2
Control of the API S.4.1–S.4.5
Reference standards or materials S.5
Container-closure system S.6
Stability S.7.1– S.7.3

It is the responsibility of the applicant to ensure that the complete APIMF (i.e. both the applicant's *Open part* and the API manufacturer's *Restricted part*) is supplied to the NMRA directly by the API manufacturer and that the applicant has access to the relevant information in the APIMF concerning the current manufacture of the API.

A copy of the letter of access should be provided in the PD Module 1.

APIMF holders can use the guidance provided for the option "Full details in the PD" for preparation of the relevant sections of the *Open* and *Restricted* parts of their APIMFs. Reference can also be made to the APIMF guidelines (*11*).

Option 4: Full details in the PD

Information on the *3.2.S Active pharmaceutical ingredient sections*, including full details of chemistry, manufacturing process, quality controls during manufacturing and process validation for the API, should be submitted in the PD as outlined in the subsequent sections of these guidelines. The QOS-PD should be completed according to section 3.1 of these guidelines.

3.2.S.1 General information (name, manufacturer)

3.2.S.1.1 *Nomenclature (name, manufacturer)*

Information on the nomenclature of the API should be provided. For example:

- **(recommended) International Nonproprietary Name (INN);**
- **compendial name, if relevant;**
- **chemical name(s);**
- **company or laboratory code;**
- **other nonproprietary name(s) (e.g. national name, United States Adopted Name (USAN), British Approved Name (BAN)); and**
- **Chemical Abstracts Service (CAS) registry number.**

The listed chemical names should be consistent with those appearing in scientific literature and those appearing on the product labelling information (e.g. summary of product characteristics, package leaflet (also known as patient information leaflet (PIL)), and labelling). Where several names exist, the preferred name should be indicated.

3.2.S.1.2 *Structure (name, manufacturer)*

The structural formula, including relative and absolute stereochemistry, the molecular formula and the relative molecular mass should be provided.

This information should be consistent with that provided in Section 3.2.S.1.1. For APIs existing as salts, the molecular mass of the free base or acid should also be provided.

3.2.S.1.3 *General properties (name, manufacturer)*

A list should be provided of physicochemical and other relevant properties of the API.

This information can be used in developing the specifications, in formulating FPPs and in the testing for release and stability purposes.

The physical and chemical properties of the API should be discussed, including the physical description, solubilities in common solvents (e.g. water, alcohols, dichloromethane, acetone), quantitative aqueous pH solubility profile (e.g. pH 1.2 to 6.8, dose/solubility volume), polymorphism, pH and pKa values, UV absorption maxima and molar absorptivity, melting point, refractive index (for a liquid), hygroscopicity, partition coefficient (see table in the QOS-PD). This list is not intended to be exhaustive, but provides an indication as to the type of information that could be included.

Some of the more relevant properties to be considered for APIs are discussed below in greater detail.

Physical description

The description should include appearance, colour and physical state. Solid forms should be identified as being crystalline or amorphous (see 3.2.S.3.1 for further information on API solid forms).

Solubilities/quantitative aqueous pH solubility profile

The following should be provided whichever option is adopted for the submission of API data.

- The solubilities in a number of common solvents (e.g. water, alcohols, dichloromethane, and acetone).

- The solubilities over the physiological pH range (pH 1.2 to 6.8) in several buffered media in mg/ml. If this information is not readily available (e.g. in literature references), it should be generated in-house.
- For solid oral dosage forms, the dose/solubility volume as determined by:

$$\text{dose/solubility volume} = \frac{\text{largest dosage strength (mg)}}{\text{the minimum concentration of the API (mg/ml)*}}$$

* corresponding to the lowest solubility determined over the physiological pH range (pH 1.2 to 6.8) and temperature (37 ± 0.5 °C).

In line with the Biopharmaceutics Classification System (BCS), *highly soluble (or highly water soluble)* APIs are those with a dose/solubility volume of less than or equal to 250 ml.

For example, compound A has as its lowest solubility at 37 ± 0.5 °C, 1.0 mg/ml at pH 6.8 and is available in 100 mg, 200 mg and 400 mg strengths. This API would not be considered a *BCS highly soluble* API as its dose/solubility volume is greater than 250 ml (400 mg/1.0 mg/ml = 400 ml).

Polymorphism

As recommended in ICH's *CTD-Q Questions and answers/location issues* document (*12*), the following refers to where specific data should be located in the PD:

- the polymorphic form(s) present in the proposed API should be listed in section 3.2.S.1.3;
- the description of manufacturing process and process controls (3.2.S.2.2) should indicate which polymorphic form is manufactured, where relevant;
- the literature references or studies performed to identify the potential polymorphic forms of the API, including the study results, should be provided in section 3.2.S.3.1;
- if a polymorphic form is to be defined or limited (e.g. for APIs that are not *BCS highly soluble* and/or where polymorphism has been identified as an issue), details should be included in 3.2.S.4.1–3.2.S.4.5.

Additional information is included in the sections mentioned in the above bullet points of these guidelines. In addition, 3.2.P.2.2.3 discusses considerations for control of the polymorphic form of the API in the FPP.

Particle size distribution

As recommended in ICH's *CTD-Q Questions and answers/location issues* document (*12*), the studies performed to identify the particle size distribution of the API should be provided in section 3.2.S.3.1 (refer to this section of these guidelines for additional information).

Information from literature

Supportive data and results from specific studies or published literature can be included within or attached to this section.

Reference documents: ICH Q6A (*13*).

3.2.S.2 Manufacture (name, manufacturer)

3.2.S.2.1 *Manufacturer(s) (name, manufacturer)*

The name, address and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in manufacturing and testing should be provided.

The facilities involved in the manufacturing, packaging, labelling, testing and storage of the API should be listed. If certain companies are responsible only for specific steps (e.g. milling of the API), this should be clearly indicated. This includes any manufacturing sites responsible for the preparation and supply of intermediates to the API manufacturer.

The list of manufacturers/companies should specify the actual addresses of production or manufacturing site(s) involved (including block(s) and units(s)), rather than the administrative offices. Telephone number(s), fax number(s) and email address(es) should be provided.

A valid manufacturing authorization for the production of APIs should be provided. If available, a certificate of GMP compliance should be provided in the PD in Module 1. For manufacturers of API intermediates, the basis for establishing that these sites are operating under GMP should be provided.

3.2.S.2.2 *Description of manufacturing process and process controls (name, manufacturer)*

The description of the API manufacturing process represents the applicant's commitment for the manufacture of the API. Information should be provided to adequately describe the manufacturing process and process controls. For example: a flow diagram of the synthetic process(es) should be provided that includes molecular formulae, weights, yield ranges, chemical structures of starting materials, intermediates, reagents and API reflecting stereochemistry, and identifies operating conditions and solvents.

A sequential procedural narrative of the manufacturing process should be submitted. The narrative should include, for example, quantities of raw

materials, solvents, catalysts and reagents reflecting the representative batch scale for commercial manufacture, identification of critical steps, process controls, equipment and operating conditions (e.g. temperature, pressure, pH, time).

Alternate processes should be explained and described with the same level of detail as the primary process. Reprocessing steps should be identified and justified. Any data to support this justification should be either referenced or filed in 3.2.S.2.5.

Where the APIMF procedure is used, a cross-reference to the *Restricted part* of the APIMF may be indicated for confidential information. In this case, if detailed information is presented in the *Restricted part*, the information to be provided for this section of the PD includes a flow chart (including molecular structures and all reagents and solvents) and a brief outline of the manufacturing process, with special emphasis on the final steps including purification procedures. However, for sterile APIs full validation data on the sterilization process should be provided in the *Open part* (in cases where there is no further sterilization of the final product).

The following requirements apply in cases where the fourth option for submission of API information has been chosen, where full details are provided in the dossier.

As discussed in ICH Q7 (*5*) and WHO Technical Report Series, No. 957, Annex 2 (*6*), the point at which the *API starting material* is introduced into the manufacturing process is the starting point of the application of GMP requirements. The *API starting material* itself needs to be proposed and its choice justified by the manufacturer and accepted as such by assessors. The *API starting material* should be proposed, taking into account the complexity of the molecule, the proximity of the *API starting material* to the final API, the availability of the *API starting material* as a commercial chemical and the quality controls placed upon the *API starting material*. This justification should be documented in the dossier and be available for review by WHO GMP inspectors.

In the case where the precursor to the API is obtained by fermentation, or is of plant or animal origin, such a molecule can be considered the API starting material regardless of complexity.

A one-step synthesis may be accepted in exceptional cases, for example, where the API starting material is covered by a CEP, or where the API starting material is an API accepted through the APIMF procedure, or when the structure of the API is so simple that a one-step synthesis can be justified, e.g. ethambutol.

In addition to the detailed description of the manufacturing process according to ICH M4Q, the recovery of materials, if any, should be described in detail with the step in which they are introduced into the process. Recovery operations should be adequately controlled such that impurity levels do not

increase over time. For recovery of solvents, any processing to improve the quality of the recovered solvent should be described. Regarding recycling of filtrates (mother liquors) to obtain second crops, information should be available on maximum holding times of mother liquors and maximum number of times the material can be recycled. Data on impurity levels should be provided to justify recycling of filtrates.

Where there are multiple manufacturing sites for one API manufacturer, a comprehensive list in tabular form should be provided comparing the processes at each site and highlighting any differences; this includes preparation of the API intermediates from external suppliers. The manufacturing details described in this section should either be declared to be identical for all intermediate manufacturers involved in the preparation of the API, or each alternative manufacturing process employed should be described in this section, for each intermediate manufacturer, using the same level of detail as that supplied for the primary manufacturing process.

All solvents used in the manufacture (including purification and/or crystallization step(s)) should be clearly identified. Solvents used in the final steps should be of high purity. Use of recovered solvent in the final step or purification is not recommended unless the specification of the recovered solvent is essentially the same as the fresh solvent. It is essential that the quality standard applied to recovered solvents and the use of such solvents is validated thoroughly.

Where polymorphic/amorphous forms have been identified the form resulting from the synthesis should be stated.

Where particle size is considered a critical attribute (see 3.2.S.3.1 for details), the particle size reduction method(s) (milling, micronization) should be described.

Justification should be provided for alternative manufacturing processes. Alternative processes should be explained using the same level of detail as is used to describe the primary process. It should be demonstrated that batches obtained by the alternative processes have the same impurity profile as the principal process. If the impurity profile obtained is different it should be demonstrated to be acceptable according to the requirements described under S.3.2.

It is acceptable to provide information on pilot-scale manufacture, provided it is representative of production scale and scale-up is reported immediately to the NMRA according to the requirements of the associated variation guidelines (e.g. WHO Technical Report Series, No. 981, 2013, Annex 3 (*14*)).

Reference documents: ICH Q7 (*5*), Q11 (*15*)

3.2.S.2.3 *Control of materials (name, manufacturer)*

Materials used in the manufacture of the API (e.g. raw materials, starting materials, solvents, reagents, catalysts) should be listed identifying where

each material is used in the process. Information on the quality and control of these materials should be provided. Information demonstrating that materials meet standards appropriate for their intended use should be provided, as appropriate (details in 3.2.A.2).

Where the APIMF procedure is used, a cross-reference to the *Restricted part* of the APIMF is considered sufficient for this section.

The following requirements apply to the fourth option for submission of API information, where full details are provided in the dossier.

The *API starting material* should be fully characterized and suitable specifications proposed and justified, including, at a minimum, control for identity, assay, impurity content and any other critical attribute of the material. For each *API starting material*, the name and manufacturing site address of the manufacturer(s) should be indicated, including of those manufacturers supplying API starting material to an external intermediate manufacturer. A brief description of the preparation of the *API starting material* should be provided for each manufacturer, including the solvents, catalysts and reagents used. A single set of specifications should be proposed for the starting material that applies to material from all sources. Any future changes to the API starting material manufacturers, mode of preparation or specifications should be notified.

In general, the starting material described in the PD should:

- be a synthetic precursor of one or more synthesis steps prior to the final API intermediate. Acids, bases, salts, esters and similar derivatives of the API, as well as the racemate of a single enantiomer API, are not considered final intermediates;
- be a well-characterized, isolated and purified substance with its structure fully elucidated including its stereochemistry (when applicable);
- have well-defined specifications that include, among others, one or more specific identity tests and tests and limits for assay and specified, unspecified and total impurities;
- be incorporated as a significant structural fragment into the structure of the API.

Copies of the specifications for the materials used in the synthesis, extraction, isolation and purification steps should be provided in the PD, including starting materials, reagents, solvents, catalysts and recovered materials. Confirmation should be provided that the specifications apply to materials used at each manufacturing site. A certificate of analysis of the starting material should be provided. A summary of the information on starting materials should be provided in the QOS-PD.

The carry-over of impurities of the starting materials into the final API should be considered and discussed.

A letter of attestation should be provided confirming that the API and the starting materials and reagents used to manufacture the API are *without* risk of transmitting agents of animal spongiform encephalopathies.

When available, a CEP demonstrating TSE compliance should be provided. A complete copy of the CEP (including any annexes) should be provided in Module 1.

Reference documents: ICH Q6A (*13*)

3.2.S.2.4 *Controls of critical steps and intermediates (name, manufacturer)*

Critical steps: Tests and acceptance criteria (with justification including experimental data) performed at critical steps identified in 3.2.S.2.2 of the manufacturing process to ensure that the process is controlled should be provided.

Intermediates: Information on the quality and control of intermediates isolated during the process should be provided.

Where the APIMF procedure is used, a cross-reference to the *Restricted part* of the APIMF is considered sufficient for this section of the PD, with the exception of information that is also relevant for the applicant (see APIMF guidelines in WHO Technical Report Series, No. 948, Annex 4) (*11*).

The following requirements apply to the fourth option for submission of API information, where full details are provided in the dossier.

The critical steps should be identified. These can be among others: steps where significant impurities are removed or introduced, steps introducing an essential molecular structural element such as a chiral centre or resulting in a major chemical transformation, steps having an impact on solid-state properties and homogeneity of the API that may be relevant for use in solid dosage forms.

Specifications for isolated intermediates should be provided and should include tests and acceptance criteria for identity, purity and assay, where applicable.

Where API intermediates are sourced externally, these materials should be controlled to a single specification maintained by the API manufacturer. Evidence of the quality of the supplied materials should be provided in the form of certificates of analysis for batches of intermediate, issued by the intermediate supplier and by the API manufacturer upon retesting.

Reference documents: ICH Q6A

3.2.S.2.5 *Process validation and/or evaluation (name, manufacturer)*

Process validation and/or evaluation studies for aseptic processing and sterilization should be included.

Where the APIMF procedure is used, a cross-reference to the *Restricted part* of the APIMF is considered sufficient for this section of the PD.

The following requirements apply to the fourth option for submission of API information, where full details are provided in the dossier.

The manufacturing processes for all APIs are expected to be properly controlled. If the API is prepared as sterile, a complete description should be provided of the aseptic processing and/or sterilization methods. The controls used to maintain the sterility of the API during storage and transportation should also be provided. Alternative processes should be justified and described (see guidance in 3.2.S.2.2 for the level of detail expected).

3.2.S.2.6 *Manufacturing process development (name, manufacturer)*

A description and discussion should be provided of the significant changes made to the manufacturing process and/or manufacturing site of the API used in producing comparative bioavailability or biowaiver, scale-up, pilot and, if available, production-scale batches.

Reference should be made to the API data provided in Section 3.2.S.4.4.

Where the APIMF procedure is used, a cross-reference to the *Restricted part* of the APIMF is considered sufficient for this section of the PD.

3.2.S.3 Characterization (name, manufacturer)

3.2.S.3.1 *Elucidation of structure and other characteristics (name, manufacturer)*

Confirmation of structure based on e.g. synthetic route and spectral analyses should be provided. Information such as the potential for isomerism, the identification of stereochemistry, or the potential for forming polymorphs should also be included.

Elucidation of structure

The PD should include quality assurance-certified copies of the spectra, peak assignments and a detailed interpretation of the data on the studies performed to elucidate and/or confirm the structure of the API. The QOS-PD should include a list of the studies performed and a conclusion from the studies (e.g. if the results support the proposed structure).

For APIs that are not described in an officially-recognized pharmacopoeia, the studies carried out to elucidate and/or confirm the chemical structure normally include elemental analysis, infrared (IR), ultraviolet (UV), nuclear magnetic resonance (NMR) and mass spectra (MS) studies. Other tests could include X-ray powder diffraction (XRPD) and differential scanning calorimetry (DSC), for example, where polymorphism is identified as an issue.

For APIs that are described in an officially-recognized pharmacopoeia, it is generally sufficient to provide copies of the IR spectrum of the API from each of the proposed manufacturer(s) run concomitantly with an officially-recognized pharmacopoeial reference standard. See Section 3.2.S.5 for details on acceptable reference standards or materials.

Isomerism/stereochemistry

When an API is chiral, it should be specified whether specific stereoisomers or a mixture of stereoisomers have been used in the comparative biostudies, and information should be given as to the stereoisomer of the API that is to be used in the FPP.

Where the potential for stereoisomerism exists, a discussion should be included of the possible isomers that can result from the manufacturing process and the steps where chirality was introduced. The identicality of the isomeric composition of the API to that of the API in the comparator product should be established. Information on the physical and chemical properties of the isomeric mixture or single enantiomer should be provided, as appropriate. The API specification should include a test to ensure isomeric identity and purity.

The potential for interconversion of the isomers in the isomeric mixture, or racemization of the single enantiomer should be discussed.

When a single enantiomer of the API is claimed for non-pharmacopoeial APIs, unequivocal proof of absolute configuration of asymmetric centres should be provided such as determined by X-ray of a single crystal.

If, based on the structure of the API, there is not a potential for stereoisomerism, it is sufficient to include a statement to this effect.

Polymorphism

Many APIs can exist in different physical forms in the solid state. Polymorphism is characterized as the ability of an API to exist as two or more crystalline phases that have different arrangements and/or conformations of the molecules in the crystal lattice. Amorphous solids consist of disordered arrangements of molecules and do not possess a distinguishable crystal lattice. Solvates are crystal forms containing either stoichiometric or nonstoichiometric amounts of a solvent. If the incorporated solvent is water, the solvates are also commonly known as hydrates.

Polymorphic forms of the same chemical compound differ in internal solid-state structure and, therefore, may possess different chemical and physical properties, including packing, thermodynamic, spectroscopic, kinetic, interfacial and mechanical properties. These properties can have a direct impact on API process ability, pharmaceutical product manufacturability and product quality/

performance, including stability, dissolution and bioavailability. Unexpected appearance or disappearance of a polymorphic form may lead to serious pharmaceutical consequences.

Applicants and API manufacturers are expected to have adequate knowledge about the polymorphism of the APIs used and/or produced. Information on polymorphism can come from the scientific literature, patents, compendia or other references to determine if polymorphism is a concern, e.g. for APIs that are not *BCS highly soluble*. In the absence of published data for APIs that are not *BSC highly soluble*, polymorphic screening will be necessary to determine if the API can exist in more than one crystalline form. Polymorphic screening is generally accomplished via crystallization studies using different solvents and conditions.

There are a number of methods that can be used to characterize the polymorphic forms of an API. Demonstration of a non-equivalent structure by single crystal X-ray diffraction is currently regarded as the definitive evidence of polymorphism. XRPD can also be used to provide unequivocal proof of polymorphism. Other complementary methods, including microscopy, thermal analysis (e.g. DSC, thermal gravimetric analysis and hot-stage microscopy) and spectroscopy (e.g. IR, Raman, solid-state nuclear magnetic resonance (ssNMR)) are helpful to further characterize polymorphic forms. Where polymorphism is a concern, the applicants/manufacturers of APIs should demonstrate that a suitable method, capable of distinguishing different polymorphs, is available to them.

Decision tree 4(1) of ICH Q6A (*13*) can be used where screening is necessary and 4(2) can be used to investigate if different polymorphic forms have different properties that may affect performance, bioavailability and stability of the FPP and to decide whether a preferred polymorph should be monitored at release and on storage of the API. Where there is a preferred polymorph, acceptance criteria should be incorporated into the API specification to ensure polymorphic equivalence of the commercial material and that of the API batches used in the comparative bioavailability or biowaiver studies. The polymorphic characterization of the API batches used in comparative bioavailability or biowaiver studies by the above-mentioned methods should be provided. The method used to control polymorphic form should be demonstrated to be specific for the preferred form.

Polymorphism can also include solvation or hydration products (also known as pseudopolymorphs). If the API is used in a solvated form, the following information should be provided:

- specifications for the solvent-free API in 3.2.S.2.4, if that compound is a synthetic precursor;

- specifications for the solvated API including appropriate limits on the weight ratio of API to solvent (with data to support the proposed limits);
- a description of the method used to prepare the solvate in 3.2.S.2.2.

Particle size distribution

For APIs that are not *BCS highly soluble* contained in solid FPPs, or liquid FPPs containing undissolved API, the particle size distribution of the material can have an effect on the in vitro and/or in vivo behaviour of the FPP. Particle size distribution can also be important in dosage form performance (e.g. delivery of inhalation products), achieving uniformity of content in low-dose tablets (e.g. 2 mg or less), desired smoothness in ophthalmic preparations and stability of suspensions.

If particle size distribution is an important parameter (e.g. as in the above cases), results from an investigation of several batches of the API should be provided, including characterization of the batch(es) used in the comparative bioavailability or biowaiver studies. API specifications should include controls on the particle size distribution to ensure consistency with the material in the batch(es) used in the comparative bioavailability and biowaiver studies (e.g. limits for d10, d50 and d90). The criteria should be established statistically based on the standard deviation of the test results from the previously mentioned studies. The following are provided for illustrative purposes as possible acceptance criteria for particle size distribution limits:

- d10 not more than (NMT) 10% of total volume less than X μm
- d50 XX μm – XXX μm
- d90 not less than (NLT) 90% of total volume less than XXXX μm.

Other controls on particle size distribution can be considered acceptable, if scientifically justified.

Reference documents: ICH Q6A (*13*)

3.2.S.3.2 ***Impurities (name, manufacturer)***

Information on impurities should be provided.

Details on the principles for the control of impurities (e.g. reporting, identification and qualification) are outlined in the ICH Q3A, Q3B and Q3C impurity guidelines (*16–18*). Additional information to provide further guidance on some of the elements discussed in the ICH guidelines is outlined below.

Regardless of whether a pharmacopoeial standard is claimed, a discussion should be provided of the potential and actual impurities arising from the

synthesis, manufacture, or degradation of the API. This should cover starting materials, by-products, intermediates, chiral impurities and degradation products and should include the chemical names, structures and origins. The discussion of pharmacopoeial APIs should not be limited to the impurities specified in the API monograph.

The tables in the QOS-PD template should be used to summarize the information on the API-related and process-related impurities. In the QOS-PD, the term *origin* refers to how and where the impurity was introduced (e.g. "Synthetic intermediate from Step 4 of the synthesis", "Potential by-product due to rearrangement from Step 6 of the synthesis"). If the impurity is a metabolite of the API, this should also be indicated.

The ICH thresholds for reporting, identification (used to set the limit for individual unknown impurities) and qualification are determined on the basis of potential exposure to the impurity, e.g. by the maximum daily dose (MDD) of the API. For APIs available in multiple dosage forms and strengths having different MDD values, it is imperative that the thresholds and corresponding controls for each of the presentations be considered to ensure that the risks posed by impurities have been addressed. This is normally achieved by using the *highest potential daily MDD*, rather than the *maintenance dose*. For parenteral products the maximum hourly dose of the API should also be included.

It is acknowledged that APIs of semi-synthetic origin do not fall within the scope of the ICH impurity guidelines. However, depending on the nature of the API and the extent of the chemical modification steps, the *principles* for the control of impurities (e.g. reporting, identification and qualification) could also be extended to APIs of semi-synthetic origin. As an illustrative example, an API whose precursor molecule was derived from a fermentation process, or a natural product of plant or animal origin that has subsequently undergone *several* chemical modification reactions would generally fall within this scope, whereas an API whose sole chemical step was the formation of a salt from a fermentation product generally would not. It is understood that there is some latitude for these types of APIs.

Identification of impurities

It is recognized by the pharmacopoeias that APIs can be obtained from various sources and thus can contain impurities not considered during the development of the monograph. Furthermore, a change in the production or source may give rise to additional impurities that are not adequately controlled by the official compendial monograph. As a result each PD is assessed independently to consider the potential impurities that may arise from the proposed route(s) of synthesis. For these reasons, the ICH limits for unspecified impurities (e.g. NMT 0.10% or 1.0 mg per day intake (whichever is lower) for APIs having a maximum

daily dose ≤ 2 g/day) are generally recommended, rather than the general limits for unspecified impurities that may appear in the official compendial monograph that could potentially be higher than the applicable ICH limit.

Qualification of impurities

The ICH impurity guidelines should be consulted for options on the qualification of impurities. The limit specified for an identified impurity in an *officially recognized pharmacopoeia* is generally considered to be qualified. The following is an additional option for qualification of impurities in existing APIs:

> The limit for an impurity present in an existing API can be accepted by comparing the impurity results found in the existing API with those observed in an innovator product using the same validated, stability-indicating analytical procedure (e.g. comparative high-performance liquid chromatography (HPLC) studies). If samples of the innovator product are not available, the impurity profile may also be compared to a different approved FPP with the same route of administration and similar characteristics (e.g. tablet versus capsule). It is recommended that the studies be conducted on comparable samples (e.g. samples of the same age) to obtain a meaningful comparison of the impurity profiles.

Levels of impurities generated from studies under accelerated or stressed storage conditions of the innovator or approved FPP are not considered acceptable/qualified.

A specified impurity present in the existing API is considered qualified if the amount of the impurity in the existing API reflects the levels observed in the innovator or approved FPP.

Basis for setting the acceptance criteria

The basis for setting the acceptance criteria for the impurities should be provided. This is established by considering the identification and qualification thresholds for API-related impurities (e.g. starting materials, by-products, intermediates, chiral impurities or degradation products) and the concentration limits for process-related impurities (e.g. residual solvents) according to the applicable ICH guidelines (e.g. Q3A (*16*), Q3C (*18*)).

The qualified level should be considered as the maximum allowable limit. However, limits which are considerably wider than the actual manufacturing process capability are generally discouraged. For this reason, the acceptance criteria are also set taking into consideration the actual levels of impurities found in several batches of the API from each manufacturer, including the levels found in the batches used for the comparative bioavailability or biowaiver studies. When reporting the results of quantitative tests, the actual numerical

results should be provided rather than vague statements such as "within limits" or "conforms". In cases where a large number of batches have been tested it is acceptable to summarize the results of the total number of batches tested with a range of analytical results.

If there are identified impurities specified in an official compendial monograph that are not controlled by the proposed routine in-house analytical procedure, a justification for their exclusion from routine analyses should be provided (e.g. "Impurities D, E and F listed in *The International Pharmacopoeia* (Ph.Int.) monograph are not potential impurities from the proposed route of synthesis used by manufacturer X"). If acceptable justification cannot be provided it should be demonstrated that the routine in-house method is capable of separating and detecting the impurities specified in the official compendial monograph at an acceptable level (e.g. 0.10%). If such a demonstration cannot be performed, a one-time study should be conducted applying the pharmacopoeial method to several recent batches to demonstrate the absence of impurities listed in the pharmacopoeial monograph.

ICH class II solvent(s) used prior to the last step of the manufacturing process may be exempted from routine control in API specifications if suitable justification is provided. Submission of results demonstrating less than 10% of the ICH Q3C limit (option I) of the solvent(s) in three consecutive production-scale batches or six consecutive pilot-scale batches of the API or a suitable intermediate would be considered acceptable justification (*18*). The last-step solvents used in the process should always be routinely controlled in the final API.

For guidance on acceptable residual solvent limits, refer to ICH Q3C (*18*). The limit for residues of triethylamine (TEA) is either 320 ppm on the basis of ICH Q3C option I or 3.2 mg/day on the basis of permitted daily exposure (PDE).

The absence of known established highly toxic (genotoxic) impurities used in the process or formed as a by-product should be discussed and suitable limits should be proposed where absence cannot be assured. The limits should be justified by appropriate reference to available guidance (e.g. EMEA/CHMP/QWP/ 251344/2006 (*19*) or USFDA guidance (*20*) or by providing experimental safety data or published data in peer-reviewed journals.

Residues of metal catalysts used in the manufacturing process and determined to be present in batches of API are to be controlled in specifications. This requirement does not apply to metals that are deliberate components of the pharmaceutical substance (such as a counter ion of a salt) or metals that are used as a pharmaceutical excipient in the FPP (e.g. an iron oxide pigment). The guideline on the specification limits for residues of metal catalysts or metal reagents EMEA/CHMP/SWP/4446/2000 (*21*) or any equivalent approach can be used to address this issue. The requirement normally does not apply to extraneous metal contaminants that are more appropriately addressed by GMP, GDP or any

other relevant quality provision, such as the heavy metal test in monographs of recognized pharmacopoeias that cover metal contamination originating from manufacturing equipment and the environment.

Reference documents: ICH Q3A (*16*), Q3C (*18*), Q6A (*13*)

3.2.S.4 Control of the API (name, manufacturer)

3.2.S.4.1 *Specification (name, manufacturer)*

The specification for the API should be provided.

As defined in ICH's Q6A guideline, a specification is:

> a list of tests, references to analytical procedures and appropriate acceptance criteria, which are numerical limits, ranges, or other criteria for the tests described. It establishes the set of criteria to which an API or FPP should conform to be considered acceptable for its intended use. "Conformance to specifications" means that the API and/or FPP, when tested according to the listed analytical procedures, will meet the listed acceptance criteria. Specifications are critical quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities.

Copies of the API specifications, dated and signed by authorized personnel (e.g. the person in charge of the quality control (QC) or quality assurance (QA) department) should be provided in the PD, including specifications from each API manufacturer as well as those of the FPP manufacturer.

The FPP manufacturer's API specification should be summarized according to the table in the QOS-PD template under the headings: tests, acceptance criteria and analytical procedures (including types, sources and versions for the methods).

- The *standard* declared by the applicant could be an officially recognized compendial standard (e.g. British Pharmacopoeia (BP), Ph.Eur., Ph.Int., Japanese Pharmacopoeia (JP), United States Pharmacopeia (USP)), or an in-house (manufacturer's) standard.
- The *specification reference number and version (e.g. revision number and/or date)* should be provided for version control purposes.
- For the analytical procedures, the *type* should indicate the kind of analytical procedure used (e.g. visual, IR, UV, HPLC, or laser diffraction), the *source* refers to the origin of the analytical procedure (e.g. BP, Ph.Eur., Ph.Int., JP, USP, or in-house) and the *version (e.g. code number/version/date)* should be provided for version control purposes.

In cases where there is more than one API manufacturer, the FPP manufacturer's API specifications should be one single compiled set of specifications that apply to the API from all manufacturers. It is acceptable to lay down in the specification more than one acceptance criterion and/or analytical method for a single parameter with the statement "for API from manufacturer A" (e.g. in the case of residual solvents).

Any non-routine testing should be clearly identified as such and justified along with the proposal on the frequency of non-routine testing.

The ICH Q6A guideline outlines recommendations for a number of *universal* and *specific tests* and criteria for APIs.

Reference documents: ICH Q3A (*16*), Q3C (*18*), Q6A (*13*), officially-recognized pharmacopoeia

3.2.S.4.2 *Analytical procedures (name, manufacturer)*

The analytical procedures used for testing the API should be provided.

Copies of the in-house analytical procedures used to generate testing results provided in the PD, as well as those proposed for routine testing of the API by the FPP manufacturer, should be provided. Unless modified it is not necessary to provide copies of officially-recognized compendial analytical procedures.

Tables for summarizing a number of the different analytical procedures and the validation information (e.g. HPLC assay/impurity methods, gas chromatography (GC) methods) can be found in section 2.3.R Regional information, of the QOS-PD (i.e. *2.3.R.2*). These tables may be used to summarize the in-house analytical procedures *of the FPP manufacturer* for determination of the residual solvents, assay and purity of the API, in section 2.3.S.4.2 of the QOS-PD. Other methods used to generate assay and purity data in the PD can be summarized in 2.3.S.4.4 (c) or 2.3.S.7.3 (b) of the QOS-PD. Officially recognized compendial methods need not be summarized unless modifications have been made.

Although HPLC is normally considered the method of choice for determining API-related impurities, other chromatographic methods such as GC and thin-layer chromatography (TLC) can also be used, if appropriately validated. For determination of related substances, reference standards should normally be available for each of the identified impurities, particularly those known to be toxic and the concentration of the impurities should be quantitated against their own reference standards. Impurity standards may be obtained from pharmacopoeias (individual impurities or resolution mixtures), from commercial sources or prepared in-house. It is considered acceptable to use the API as an external standard to estimate the levels of impurities, provided the response factors of those impurities are sufficiently close to that of the API, i.e.

between 80 and 120%. In cases where the response factor is outside this range, it may still be acceptable to use the API, provided a correction factor is applied. Data to support calculation of the correction factor should be provided for an in-house method. Unspecified impurities may be quantitated using a solution of the API as the reference standard at a concentration corresponding to the limit established for individual unspecified impurities (e.g. 0.10%). The test for related substances in the Ph.Int. monograph for lamivudine serves as a typical example.

The system suitability tests (SSTs) represent an integral part of the method and are used to ensure adequate performance of the chosen chromatographic system. As a minimum, HPLC and GC purity methods should include SSTs for resolution and repeatability. For HPLC methods to control API-related impurities, this is typically done using a solution of the API with a concentration corresponding to the limit for unspecified impurities. Resolution of the two closest eluting peaks is generally recommended. However, the choice of alternative peaks can be used if justified (e.g. choice of a toxic impurity). In accordance with the Ph.Int. section on Methods of analysis, the repeatability test should include an acceptable number of replicate injections. HPLC assay methods should include SSTs for repeatability and, in addition, either peak asymmetry, theoretical plates or resolution. For TLC methods, the SSTs should verify the ability of the system to separate and detect the analyte(s) (e.g. by applying a spot corresponding to the API at a concentration corresponding to the limit of unspecified impurities).

Reference documents: ICH Q2 (*22*); WHO Technical Report Series, No. 943, 2007, Annex 3 (*23*)

3.2.S.4.3 *Validation of analytical procedures (name, manufacturer)*

Analytical validation information, including experimental data for the analytical procedures used for testing the API, should be provided.

Copies of the validation reports for the analytical procedures used to generate test results provided in the PD, as well as those proposed for routine testing of the API by the FPP manufacturer, should be provided.

Tables for summarizing a number of the different analytical procedures and validation information (e.g. HPLC assay/impurity methods, GC methods) can be found in section 2.3.R Regional information, of the QOS-PD (i.e. *2.3.R.2*). These tables may be used to summarize the validation information on the analytical procedures *of the FPP manufacturer* for determination of residual solvents, assay and purity of the API, in section 2.3.S.4.3 of the QOS-PD. The validation data for other methods used to generate assay and purity data in the PD can be summarized in 2.3.S.4.4 (c) or 2.3.S.7.3 (b) of the QOS-PD.

As recognized by regulatory authorities and pharmacopoeias themselves, verification of compendial methods can be necessary. The compendial methods as published are typically validated based on an API or an FPP originating from a specific manufacturer. Different sources of the same API or FPP can contain impurities and/or degradation products that were not considered during the development of the monograph. Therefore the monograph and compendial method should be demonstrated as being suitable to control the impurity profile of the API from the intended source(s).

In general, verification is not necessary for compendial API *assay* methods. However, specificity of a specific compendial assay method should be demonstrated if there are any potential impurities that are not specified in the compendial monograph. If an officially-recognized compendial method is used to control API-related impurities that are not specified in the monograph, full validation of the method is expected with respect to those impurities.

If an officially-recognized compendial standard is claimed and an in-house method is used in lieu of the compendial method (e.g. for assay or for specified impurities), equivalency of the in-house and compendial methods should be demonstrated. This could be accomplished by performing duplicate analyses of one sample by both methods and providing the results from the study. For impurity methods, the sample analysed should be the API spiked with impurities at concentrations equivalent to their specification limits.

Reference documents: ICH Q2

3.2.S.4.4 *Batch analyses (name, manufacturer)*

Description of batches and results of batch analyses should be provided.

The information provided should include batch number, batch size, date, and production site of relevant API batches used in comparative bioavailability or biowaiver studies, preclinical and clinical data (if relevant), stability, pilot, scale-up and, if available, production-scale batches. These data are used to establish the specifications and evaluate consistency in API quality.

Analytical results should be provided from at least two batches of at least pilot-scale from each proposed manufacturing site of the API and should include the batch(es) used in the comparative bioavailability or biowaiver studies. A pilot-scale batch should be manufactured by a procedure fully representative of and simulating that to be applied to a full production-scale batch.

Copies of the certificates of analysis, both from the API manufacturer(s) and the FPP manufacturer, should be provided for the profiled batches and any company responsible for generating the test results should be identified. The FPP manufacturer's test results should be summarized in the QOS-PD.

The discussion of results should focus on observations noted for the various tests, rather than reporting comments such as "all tests meet specifications". For quantitative tests (e.g. individual and total impurity tests and assay tests), it should be ensured that actual *numerical results* are provided rather than vague statements such as "within limits" or "conforms".

A discussion and justification should be provided for any incomplete analyses (e.g. results not tested according to the proposed specification).

Reference documents: ICH Q3A (*16*), Q3C (*18*), Q6A (*13*)

3.2.S.4.5 *Justification of specification (name, manufacturer)*

Justification for the API specification should be provided.

A discussion should be provided on the inclusion of particular tests, evolution of tests, analytical procedures and acceptance criteria, and differences from the officially-recognized compendial standard(s). If the officially-recognized compendial methods have been modified or replaced, a discussion should be included.

The justification for certain tests, analytical procedures and acceptance criteria may have been discussed in other sections of the PD (e.g. impurities, particle size distribution) and does not need to be repeated here, although a cross-reference to the location should be provided.

Reference documents: ICH Q3A (*16*), Q3C (*18*), Q6A (*13*), officially-recognized pharmacopoeia

3.2.S.5 Reference standards or materials (name, manufacturer)

Information on the reference standards or reference materials used for testing of the API should be provided.

Information should be provided on the reference standard(s) used to generate data in the PD, as well as those to be used by the FPP manufacturer in routine API and FPP testing.

The source(s) of the reference standards or materials used in the testing of the API should be provided (e.g. those used for the identification, purity, and assay tests). These could be classified as *primary* or *secondary* reference standards.

A suitable primary reference standard should be obtained from an officially recognized pharmacopoeial source (e.g. BP, Ph.Eur., Ph.Int., JP, USP) where one exists and the lot number should be provided. Where a pharmacopoeial standard is claimed for the API and/or the FPP, the primary reference standard should be obtained from that pharmacopoeia when available. Primary reference standards from officially-recognized pharmacopoeial sources do not need further structural elucidation.

Otherwise, a primary standard may be a batch of the API that has been fully characterized (e.g. by IR, UV, nuclear magnetic resonance (NMR), and MS analyses). Further purification techniques may be needed to render the material acceptable for use as a chemical reference standard. The purity requirements for a chemical reference substance depend upon its intended use. A chemical reference substance proposed for an identification test does not require meticulous purification, since the presence of a small percentage of impurities in the substance often has no noticeable effect on the test. On the other hand, chemical reference substances that are to be used in assays should possess a high degree of purity (such as 99.5% on the dried or water-/solvent-free basis). Absolute content of the primary reference standard must be declared and should follow the scheme: 100% minus organic impurities (quantitated by an assay procedure, e.g. HPLC or DSC) minus inorganic impurities minus volatile impurities by loss on drying (or water content minus residual solvents).

A secondary (or in-house) reference standard can be used by establishing it against a suitable primary reference standard, e.g. by providing legible copies of the IR of the primary and secondary reference standards run concomitantly and by providing its certificate of analysis, including assay determined against the primary reference standard. A secondary reference standard is often characterized and evaluated for its intended purpose with additional procedures other than those used in routine testing (e.g. if additional solvents are used during the additional purification process that are not used for routine purposes).

Reference standards should normally be established for specified impurities. Refer to section 3.2.S.4.2 for additional guidance.

Reference documents: ICH Q6A (*13*), WHO Technical Report Series, No. 943, Annex 3, 2007 (*23*)

3.2.S.6 Container-closure system (name, manufacturer)

A description of the container-closure system(s) should be provided, including the identity of materials of construction of each primary packaging component and their specifications. The specifications should include description and identification (and critical dimensions with drawings, where appropriate). Non-compendial methods (with validation) should be included, where appropriate.

For non-functional secondary packaging components (e.g. those that do not provide additional protection), only a brief description should be provided. For functional secondary packaging components, additional information should be provided.

The suitability should be discussed with respect to, for example, choice of materials, protection from moisture and light, compatibility of the materials of construction with the API, including sorption to container and leaching, and/or safety of materials of construction.

The WHO *Guidelines on packaging for pharmaceutical products* (*24*) and the officially-recognized pharmacopoeias should be consulted for recommendations on the packaging information for APIs.

Primary packaging components are those that are in direct contact with the API or FPP. The specifications for the primary packaging components should be provided and should include a specific test for identification (e.g. IR).

The name and address of the manufacturer of the API should be stated on the container, regardless of whether relabelling is conducted at any stage during the API distribution process.

3.2.S.7 Stability (name, manufacturer)

3.2.S.7.1 *Stability summary and conclusions (name, manufacturer)*

The types of studies conducted, protocols used and the results of the studies should be summarized. The summary should include results, for example, from forced degradation studies and stress conditions, as well as conclusions with respect to storage conditions and retest date or shelf-life, as appropriate.

The WHO *Guidelines on Stability testing of active pharmaceutical ingredients and finished pharmaceutical products* (*9*) should be consulted for recommendations on the core stability data package.

As outlined in the WHO *stability guidelines*, the purpose of stability testing is to:

> "provide evidence of how the quality of an API or FPP varies with time under the influence of a variety of environmental factors such as temperature, humidity and light."

The tables in the QOS-PD template should be used to summarize the results from the stability studies and related information (e.g. conditions, testing parameters, conclusions, commitments).

Stress testing

As outlined in the ICH Q1A guidance document, stress testing of the API can help identify the likely degradation products, which in turn can help establish the degradation pathways and the intrinsic stability of the molecule and validate the stability-indicating power of the analytical procedures used. The nature of the stress testing will depend on the individual API and the type of FPP involved.

Stress testing may be carried out on a single batch of the API. For examples of typical stress conditions refer to WHO Technical Report Series, No. 953, Annex 2, section 2.1.2 *(9)*, as well as, "A typical set of studies of the degradation paths of an active pharmaceutical ingredient" in WHO Technical Report Series, No. 929, Annex 5, 2005, Table A.1 (*7*).

The objective of stress testing is not to completely degrade the API, but to cause degradation to occur to a small extent, typically 10–30% loss of active by assay when compared with non-degraded API. This target is chosen so that some degradation occurs, but not enough to generate secondary products. For this reason, the conditions and duration may need to be varied when the API is especially susceptible to a particular stress factor. If there is total absence of degradation products after 10 days, the API is considered stable under the stress condition under investigation.

The tables in the QOS-PD template should be used to summarize the results of the stress testing and should include the treatment conditions (e.g. temperatures, relative humidities, concentrations of solutions, and durations) and the observations for the various test parameters (e.g. assay, degradation products). The discussion of results should highlight whether mass balance was observed.

Photostability testing should be an integral part of stress testing. The standard conditions are described in ICH Q1B (*25*). If "protect from light" is stated in one of the officially-recognized pharmacopoeias for the API, it is sufficient to state "protect from light" on labelling, in lieu of photostability studies, when the container-closure system is shown to be light protective.

When available, it is acceptable to provide the relevant data published in the scientific literature (inter alia WHOPARs, EPARs) to support the identified degradation products and pathways.

Accelerated and long-term testing

Available information on the stability of the API under accelerated and long-term conditions should be provided, including information in the public domain or obtained from the scientific literature. The source of the information should be identified.

The storage conditions and the lengths of studies chosen should be sufficient to cover storage and shipment. Refer to the WHO *stability guidelines* in WHO Technical Report Series, No. 953, Annex 2, 2009 (*9*).

To establish the retest period, data should normally be provided on not less than three batches of at least pilot scale. The batches should be manufactured by the same synthesis route as production batches and using a method of manufacture and a procedure that simulates the final process to be used for production batches. The stability testing programme should be summarized and the results of stability testing should be summarized in the dossier and in the tables in the QOS-PD.

The information on the stability studies should include details such as storage conditions, batch number, batch size, container-closure system and completed (and proposed) test intervals. The discussion of results should focus

on observations noted for the various tests, rather than reporting comments such as "all tests meet specifications". Ranges of analytical results where relevant and any trends that were observed should be included. For quantitative tests (e.g. individual and total degradation product tests and assay tests), it should be ensured that actual numerical results are provided rather than vague statements such as "within limits" or "conforms". Where different from the methods described in S.4.2, descriptions and validation of the methodology used in stability studies should be provided.

Refer to WHO Technical Report Series, No. 953, Annex 2, 2009 (*9*), for further information regarding the minimum data required at the time of submitting the dossier, storage conditions, container-closure system, test specifications and testing frequency.

Proposed storage statement and retest period

A storage statement should be established for display on the label based on the stability evaluation of the API. The WHO *stability guidelines* include a number of recommended storage statements that should be used, when supported by the stability studies.

A retest period should be derived from the stability information and the retest date should be displayed on the container label.

After this retest period, a batch of API destined for use in the manufacture of an FPP could be retested and then, if in compliance with the specification, could be used immediately (e.g. within 30 days). If retested and found compliant, the batch does *not* receive an additional period corresponding to the time established for the retest period. However, an API batch can be retested multiple times and a different portion of the batch used after each retest, as long as it continues to comply with the specification. For APIs known to be labile (e.g. certain antibiotics), it is more appropriate to establish a shelf-life rather than a retest period (ICH Q1A (*26*)).

Limited extrapolation of the real-time data from the long-term storage condition beyond the observed range to extend the retest period can be undertaken at the time of assessment of the PD, if justified. Applicants should consult the ICH Q1E guideline for further details on the evaluation and extrapolation of results from stability data (e.g. if significant change was not observed within 6 months in accelerated stability studies and the data show little or no variability, the proposed retest period could be up to two times the period covered by the long-term data, but should not exceed the long-term data by more than 12 months).

Reference documents: ICH Q1A (*26*), Q1B (*25*), Q1D (*27*), Q1E (*28*), WHO Technical Report Series, No. 953, 2009, Annex 2 (*9*).

3.2.S.7.2 Post-approval stability protocol and stability commitment (name, manufacturer)

The post-approval stability protocol and stability commitment should be provided.

Primary stability study commitment

When the available long-term data on the stability of primary batches do not cover the proposed retest period granted at the time of assessment of the PD, a commitment should be made to continue the stability studies in order to firmly establish the retest period. A written commitment (signed and dated) to continue long-term testing over the retest period should be included in the dossier when relevant.

Commitment stability studies

The long-term stability studies for the *commitment batches* should be conducted through the proposed retest period on at least three production batches. Where stability data were not provided for three production batches, a written commitment (signed and dated) should be included in the dossier.

The stability protocol for the *commitment batches* should be provided and should include, but not be limited to, the following parameters:

- number of batch(es) and different batch sizes, if applicable;
- relevant physical, chemical, microbiological and biological test methods;
- acceptance criteria;
- reference to test methods;
- description of the container-closure system(s);
- testing frequency;
- description of the conditions of storage (standardized conditions for long-term testing as described in these guidelines and consistent with the API labelling should be used);
- other applicable parameters specific to the API.

Ongoing stability studies

The stability of the API should be monitored according to a continuous and appropriate programme that will permit the detection of any stability issue (e.g. changes in levels of degradation products). The purpose of the ongoing stability programme is to monitor the API and to determine that the API remains within specifications and can be expected to remain within the retest period in all future batches.

At least one production batch per year of API (unless none is produced during that year) should be added to the stability monitoring programme and tested at least annually to confirm the stability. In certain situations, additional batches should be included. A written commitment (signed and dated) for ongoing stability studies should be included in the dossier.

Refer to WHO Technical Report Series, No. 953, 2009, Annex 2, Section 2.1.11 for further information on ongoing stability studies (*9*).

Any differences between the stability protocols used for the primary batches and those proposed for the *commitment batches* or *ongoing batches* should be scientifically justified.

Reference documents: ICH Q1A (*26*), Q1B (*25*), Q1D (*27*), Q1E (*28*), WHO Technical Report Series, No. 953, 2009, Annex 2 (*9*)

3.2.S.7.3 *Stability data (name, manufacturer)*

Results of the stability studies (e.g. forced degradation studies and stress conditions) should be presented in an appropriate format such as tabular, graphical or narrative. Information on the analytical procedures used to generate the data and validation of these procedures should be included.

The actual stability results used to support the proposed retest period should be included in the dossier. For quantitative tests (e.g. individual and total degradation product tests and assay tests), actual numerical results should be provided rather than vague statements such as "within limits" or "conforms".

Reference documents: ICH Q1A (*26*), Q1B (*25*), Q1D (*27*), Q1E (*28*), Q2 (*22*), WHO Technical Report Series, No. 953, 2009, Annex 2 (*9*)

3.2.P Drug product (or finished pharmaceutical product (FPP)) (name, dosage form)

3.2.P.1 Description and composition of the FPP (name, dosage form)

A description of the FPP and its composition should be provided. The information provided should include, for example:

- **Description of the dosage form**

  The description of the FPP should include the physical description, available strengths, release mechanism if not conventional immediate release (e.g. dispersible, modified (delayed or extended)), as well as any other distinguishing characteristics, e.g.

  "The proposed XYZ 50 mg dispersible tablets are available as white, oval, film-coated tablets, debossed with '50' on one side and a break-line on the other side.

The proposed ABC 100 mg tablets are available as yellow, round, film-coated tablets, debossed with '100' on one side and plain on the other side."

- **Composition, i.e. list of all components of the dosage form and their amount on a per unit basis (including overages, if any), the function of the components and a reference to their quality standards (e.g. compendial monographs or manufacturer's specifications)**

  The tables in the QOS-PD template should be used to summarize the composition of the FPP and express the quantity of each component on a per unit basis (e.g. mg per tablet, mg per ml, mg per vial) and a percentage basis, including a statement of the total weight or measure of the dosage unit. The individual components for mixtures prepared in-house (e.g. coatings) should be included in the tables, where applicable.

  All components used in the manufacturing process should be included, including those that may not be added to every batch (e.g. acid and alkali), those that may be removed during processing (e.g. solvents) and any others (e.g. nitrogen, silicon for stoppers). If the FPP is formulated using an active moiety, then the composition for the active ingredient should be clearly indicated (e.g. "1 mg of active ingredient base = 1.075 mg active ingredient hydrochloride"). All overages should be clearly indicated (e.g. "contains 2% overage of the API to compensate for manufacturing losses").

  The components should be declared by their proper or common names, quality standards (e.g. BP, Ph.Eur., Ph.Int., JP, USP, in-house) and, if applicable, their grades (e.g. "microcrystalline cellulose NF (PH 102)") and special technical characteristics (e.g. lyophilized, micronized, solubilized, or emulsified).

  The function of each component (e.g. diluent/filler, binder, disintegrant, lubricant, glidant, granulating solvent, coating agent, or antimicrobial preservative) should be stated. If an excipient performs multiple functions, the predominant function should be indicated.

  The qualitative composition, including solvents, should be provided for all proprietary components or blends (e.g. capsule shells, colouring blends, or imprinting inks). This information (excluding the solvents) is to be listed in the product information (e.g. summary of product characteristics, labelling, and package leaflet).

- **Description of accompanying reconstitution diluent(s)**

  For FPPs supplied with reconstitution diluent(s) that are commercially available or have been assessed and considered acceptable in connection with another approved PD, a brief description of the reconstitution diluents(s) should be provided.

  For FPPs supplied with reconstitution diluent(s) that are not commercially available or have not been assessed and considered acceptable in connection with another approved PD, information on the diluent(s) should be provided in a separate FPP portion ("3.2.P"), as appropriate.

- **Type of container and closure used for the dosage form and accompanying reconstitution diluent, if applicable**

  The container-closure used for the FPP (and accompanying reconstitution diluent, if applicable) should be briefly described, with further details provided under 3.2.P.7 Container-closure system, e.g.

  > "The product is available in high-density polyethylene (HDPE) bottles with polypropylene caps (in sizes of 100s, 500s and 1000s) and in PVC/aluminium foil unit dose blisters (in packages of 100s (cards of 5 × 2, 10 cards per package)."

Reference documents: ICH Q6A (*13*)

3.2.P.2 Pharmaceutical Development (name, dosage form)

The Pharmaceutical Development section should contain information on the development studies conducted to establish that the dosage form, the formulation, manufacturing process, container-closure system, microbiological attributes and usage instructions are appropriate for the purpose specified in the product dossier. The studies described here are distinguished from routine control tests conducted according to specifications. Additionally, this section should identify and describe the formulation and process attributes (critical parameters) that can influence batch reproducibility, product performance and FPP quality. Supportive data and results from specific studies or published literature can be included within or attached to the Pharmaceutical Development section. Additional supportive data can be referenced to the relevant nonclinical or clinical sections of the product dossier.

Pharmaceutical development information should include, at a minimum:

- the definition of the quality target product profile (QTPP) as it relates to quality, safety and efficacy, considering for example the

route of administration, dosage form, bioavailability, strength and stability;

- identification of the potential critical quality attributes (CQAs) of the FPP so as to adequately control the product characteristics that could have an impact on quality;
- discussion of the potential CQAs of the API(s), excipients and container-closure system(s) including the selection of the type, grade and amount to deliver pharmaceutical product of the desired quality;
- discussion of the selection criteria for the manufacturing process and the control strategy required to manufacture commercial lots meeting the QTPP in a consistent manner.

These features should be discussed as part of the product development using the principles of risk management over the entire lifecycle of the product (ICH Q8) (*29*).

For a discussion of additional pharmaceutical development issues specific to the development of FDCs, reference should be made to WHO Technical Report Series, No. 929, 2005, Annex 5, section 6.3.2 (*7*).

Reference documents: ICH Q6A (*13*), Q8 (*29*), Q9 (*30*), Q10 (*31*)

3.2.P.2.1 *Components of the FPP (name, dosage form)*

3.2.P.2.1.1 Active pharmaceutical ingredient (name, dosage form)

The compatibility of the API with excipients listed in 3.2.P.1 should be discussed. Additionally, key physicochemical characteristics (e.g. water content, solubility, particle size distribution, polymorphic or solid state form) of the API that can influence the performance of the FPP should be discussed. For fixed-dose combinations, the compatibility of APIs with each other should be discussed.

Physicochemical characteristics of the API may influence both the manufacturing capability and the performance of the FPP.

Guidance on compatibility studies is provided in appendix 3 of the WHO *Guidelines for registration of fixed-dose combination medicinal products* (WHO Technical Report Series, No. 929, 2005, Annex 5) (*7*). In addition to visual examination, chromatographic results (assay, purity) are required to demonstrate API–API and API–excipient compatibility. In general, API–excipient compatibility is not required to be established for specific excipients when evidence is provided (e.g. in the SmPC or product leaflet) that the excipients are present in the comparator product.

3.2.P.2.1.2 **Excipients (name, dosage form)**

The choice of excipients listed in 3.2.P.1, their concentration, their characteristics that can influence the FPP performance should be discussed relative to their respective functions.

When choosing excipients, those with a compendial monograph are generally preferred and may be required in certain jurisdictions. Other resources are available for information on acceptable excipients and their concentrations, such as the US-FDA IIG list and the *Handbook of pharmaceutical excipients* (*32*). Use of excipients in concentrations outside established ranges is discouraged and generally requires justification. In addition, available guidelines should be referred to, which address particular excipients to be avoided, for example azo colorants as listed in the EMA Guideline CPMP/463/00 (*33*). Other guidance such as the WHO *Guidelines on development of paediatric medicines* (WHO Technical Report Series, No. 970, 2012, Annex 5) (*34*) may provide useful general guidance in this regard.

Ranges or alternatives for excipients are normally not accepted, unless supported by appropriate process validation data. Where relevant, compatibility study results (e.g. compatibility of a primary or secondary amine API with lactose) should be included to justify the choice of excipients. Specific details should be provided where necessary (e.g. on use of potato or corn starch).

Where antioxidants are included in the formulation, the effectiveness of the proposed concentration of the antioxidant should be justified and verified by appropriate studies.

Antimicrobial preservatives are discussed in 3.2.P.2.5.

3.2.P.2.2 ***Finished pharmaceutical product (name, dosage form)***

3.2.P.2.2.1 **Formulation development (name, dosage form)**

A brief summary describing the development of the FPP should be provided, taking into consideration the proposed route of administration and usage. The differences between the comparative bioavailability or biowaiver formulations and the formulation (i.e. composition) described in 3.2.P.1 should be discussed. Results from comparative in vitro studies (e.g. dissolution) or comparative in vivo studies (e.g. bioequivalence) should be discussed, when appropriate.

The requirements for bioequivalence studies should be taken into consideration for example when formulating multiple strengths and/or when the product(s) may be eligible for a biowaiver. WHO reference documents (e.g. WHO Technical Report Series, No. 937, 2006, Annex 7) (*8*) may be consulted.

Product scoring may be recommended or required, for example, when division into fractional doses may be necessary according to approved posology.

If the proposed FPP is a functionally scored tablet, a study should be undertaken to ensure the uniformity of dose in the tablet fragments. The data provided in the PD should include a description of the test method, individual values, mean and relative standard deviation (RSD) of the results. Uniformity testing (i.e. content uniformity for split portions containing less than 5 mg or less than 5% of the weight of the dosage unit portion, or mass uniformity for other situations) should be performed on each split portion from a minimum of 10 randomly selected whole tablets. As an illustrative example, the number of units (i.e. the splits) would be 10 halves for bisected tablets (one half of each tablet is retained for the test) or 10 quarters for quadrisected tablets (one quarter of each tablet is retained for the test). At least one batch of each strength should be tested. Ideally, the study should cover a range of the hardness values. The splitting of the tablets should be performed in a manner that would be representative of that used by the consumer (e.g. manually split by hand). The uniformity test on split portions can be demonstrated on a one-time basis and does not need to be added to the FPP specification(s). The tablet description in the FPP specification and in the product information (e.g. summary of product characteristics, labelling, package leaflet) should reflect the presence of a score.

If splitting of a tablet is intended for a paediatric dose, a demonstration of content uniformity of tablet fragments may be required.

Where relevant, labelling should state that the score line is only to facilitate breaking for ease of swallowing and not to divide tablets into equal doses.

Additional quality data may be required to support special dosing instructions (for example, crushing) stated in product information.

In vitro dissolution or drug release

A discussion should be included as to how the development of the formulation relates to development of the dissolution method(s) and the generation of the dissolution profile.

The results of studies justifying the choice of in vitro dissolution or drug release conditions (e.g. apparatus, rotation speed, and medium) should be provided. Data should also be submitted to demonstrate whether the method is sensitive to changes in manufacturing processes and/or changes in grades and/or amounts of critical excipients and particle size where relevant. The dissolution method should be sensitive to any changes in the product that would result in a change in one or more of the pharmacokinetic parameters. Use of a single point test or a dissolution range should be justified based on the solubility and/or biopharmaceutical classification of the API.

For slower dissolving, immediate-release products (e.g. Q = 80% in 90 minutes), a second time point may be warranted (e.g. Q = 60% in 45 minutes).

Delayed release (enteric coated) products are intended to resist gastric fluid but disintegrate in intestinal fluid; therefore dissolution should include acid and buffer phases with separate criteria for each. Refer to compendial monographs for examples.

Modified-release FPPs should have a meaningful in vitro release rate (dissolution) test that is used for routine quality control. Preferably, this test should possess in vitro–in vivo correlation. Results demonstrating the effect of pH on the dissolution profile should be submitted if appropriate for the type of dosage form.

For extended-release FPPs, the testing conditions should be set to cover the entire time period of expected release (e.g. at least three test intervals chosen for a 12-hour release and additional test intervals for longer duration of release). One of the test points should be at the early stage of drug release (e.g. within the first hour) to demonstrate absence of dose dumping. At each test period, upper and lower limits should be set for individual units. Generally, the acceptance range at each intermediate test point should not exceed 20% or ± 10% of the targeted value. Dissolution results should be submitted for several lots, including those lots used for pharmacokinetic and bioavailability or biowaiver studies.

Recommendations for conducting and assessing comparative dissolution profiles can be found in Appendix 1.

3.2.P.2.2.2 Overages (name, dosage form)

Any overages in the formulation(s) described in 3.2.P.1 should be justified.

Justification of an overage to compensate for loss during manufacture should be provided, including the step(s) where the loss occurs, the reasons for the loss and batch analysis release data (assay results).

Overages for the sole purpose of extending the shelf-life of the FPP are generally not acceptable.

3.2.P.2.2.3 Physicochemical and biological properties (name, dosage form)

Parameters relevant to the performance of the FPP, such as pH, ionic strength, dissolution, redispersion, reconstitution, particle size distribution, aggregation, polymorphism, rheological properties, biological activity or potency, and/or immunological activity, should be addressed.

When polymorphism is an issue for the API as discussed in 3.2.S.3.1, it may be necessary to provide information on the form present in the FPP, for example, when the manufacturing process may affect the form. Such studies may not be necessary when sufficient information has been provided on the polymorphism observed during API stability studies.

3.2.P.2.3 *Manufacturing process development (name, dosage form)*

The selection and optimisation of the manufacturing process described in 3.2.P.3.3, in particular its critical aspects, should be explained. Where relevant, the method of sterilization should be explained and justified.

Where relevant, justification for the selection of aseptic processing or other sterilization methods over terminal sterilization should be provided.

Differences between the manufacturing process(es) used to produce comparative bioavailability or biowaiver batches and the process described in 3.2.P.3.3 that can influence the performance of the product should be discussed.

The rationale for choosing the particular pharmaceutical product (e.g. dosage form, delivery system) should be provided. The scientific rationale for the choice of the manufacturing, filling and packaging processes that can influence FPP quality and performance should be explained (e.g. wet granulation using high shear granulator). API stress study results may be included in the rationale. Any developmental work undertaken to protect the FPP from deterioration should also be included (e.g. protection from light or moisture).

The scientific rationale for the selection, optimization and scale-up of the manufacturing process described in 3.2.P.3.3 should be explained, in particular the critical aspects (e.g. rate of addition of granulating fluid, massing time, and granulation end-point). A discussion of the critical process parameters (CPP), controls and robustness with respect to the QTPP and CQA of the product should be included (ICH Q8 (*29*)).

3.2.P.2.4 *Container-closure system (name, dosage form)*

The suitability of the container closure system (described in 3.2.P.7) used for the storage, transportation (shipping) and use of the FPP should be discussed. This discussion should consider, e.g. choice of materials, protection from moisture and light, compatibility of the materials of construction with the dosage form (including sorption to container and leaching) safety of materials of construction and performance (such as reproducibility of the dose delivery from the device when presented as part of the FPP).

Testing requirements to verify the suitability of the container-closure system contact material(s) depend on the dosage form and route of administration. The pharmacopoeias provide standards that are required for packaging materials, including, for example, the following :

Glass containers:	USP <660>
	Ph.Eur. 3.2.1

Plastic containers:	Ph.Eur. 3.2.2, 3.2.2.1 USP <661>, <671>
Rubber/elastomeric closures:	USP <381> Ph.Eur. 3.2.9

Table A6.1 outlines the general recommendations for the various dosage forms for one-time studies to establish the suitability of the container-closure system contact materials.

Table A6.1
General recommendations for the various dosage forms for one-time studies to establish the suitability of the container-closure system contact materials

	Solid oral products	Oral liquid and topical products	Sterile products (including ophthalmics)
Description of any additional treatments[a]	X	X	X (sterilization and depyrogenation of the components)
Extraction studies	–	X	X
Interaction studies (migration/sorption)	–	X	X
Moisture permeability	X (uptake)	X (usually loss)	X (usually loss)
Light transmission	X[b]	X	X

X, information should be submitted; –, information does not need to be submitted.

[a] e.g. coating of tubes, siliconization of rubber stoppers, sulfur treatment of ampoules/vials;

[b] not required if product has been shown to be photostable.

For solid oral dosage forms and solid APIs, compliance with regulations on plastic materials that come into contact with food (for example (EU) No. 10/2011) (*35*) can be considered acceptable in lieu of extraction studies.

The suitability of the container-closure system used for the storage, transportation (shipping) and use of any intermediate/in-process products (e.g. premixes or bulk FPP) should also be discussed.

A dosage device should be included with the container-closure system for oral liquids or solids (e.g. solutions, emulsions, suspensions and powders/granules for such), any time the package provides for multiple doses.

In accordance with the Ph.Int. general chapter Liquid preparations for oral use:

> "Each dose from a multidose container is administered by means of a device suitable for measuring the prescribed volume. The device is usually a spoon or a cup for volumes of 5 ml or multiples thereof, or an oral syringe for other volumes or, for oral drops, a suitable dropper."

For a device accompanying a multidose container, the results of a study should be provided demonstrating the reproducibility of the device (e.g. consistent delivery of the intended volume), generally at the lowest intended dose.

A sample of the device should be provided with Module 1.

3.2.P.2.5 *Microbiological attributes (name, dosage form)*

Where appropriate, the microbiological attributes of the dosage form should be discussed, including, for example, the rationale for not performing microbial limits testing for non-sterile products and the selection and effectiveness of preservative systems in products containing antimicrobial preservatives. For sterile products, the integrity of the container-closure system to prevent microbial contamination should be addressed.

Where an antimicrobial preservative is included in the formulation, the amount used should be justified by submission of results of the product formulated with different concentrations of the preservative(s) to demonstrate the lowest necessary but still effective concentration. The effectiveness of the agent should be justified and verified by appropriate studies (e.g. according to Ph.Eur. or USP general chapters on antimicrobial preservatives) using a batch of the FPP. If the lower limit for the proposed acceptance criterion for the assay of the preservative is less than 90.0%, the effectiveness of the agent should be established with a batch of the FPP containing a concentration of the antimicrobial preservative corresponding to the lower proposed acceptance criterion.

As outlined in the WHO *stability guidelines* (WHO Technical Report Series, No. 953, 2009, Annex 2) (*9*), a single primary stability batch of the FPP should be tested for effectiveness of the antimicrobial preservative (in addition to preservative content) at the proposed shelf-life for verification purposes, regardless of whether there is a difference between the release and shelf-life acceptance criteria for preservative content.

3.2.P.2.6 *Compatibility (name, dosage form)*

The compatibility of the FPP with reconstitution diluent(s) or dosage devices (e.g. precipitation of API in solution, sorption on injection vessels, stability) should be addressed to provide appropriate and supportive information for the labelling.

Where a dosage device is required for oral liquids or solids (e.g. solutions, emulsions, suspensions and powders or granules for reconstitution) that are

intended to be administered immediately after being added to the device, the compatibility studies mentioned in the following paragraphs are not required.

Where sterile, reconstituted products are to be further diluted, compatibility should be demonstrated with all diluents over the range of dilution proposed in the labelling. These studies should preferably be conducted on aged samples. Where the labelling does not specify the type of containers, compatibility (with respect to parameters such as appearance, pH, assay, levels of individual and total degradation products, subvisible particulate matter and extractables from the packaging components) should be demonstrated in glass, PVC and polyolefin containers. However, if one or more containers are identified in the labelling, compatibility of admixtures needs to be demonstrated only in the specified containers.

Studies should cover the duration of storage reported in the labelling (e.g. 24 hours under controlled room temperature and 72 hours under refrigeration). Where the labelling specifies co-administration with other FPPs, compatibility should be demonstrated with respect to the principal FPP as well as the co-administered FPP (i.e. in addition to the other aforementioned parameters for the mixture, the assay and degradation levels of each co-administered FPP should be reported).

3.2.P.3 Manufacture (name, dosage form)

3.2.P.3.1 *Manufacturer(s) (name, dosage form)*

The name, address and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in manufacturing and testing should be provided.

The facilities involved in the manufacturing, packaging, labelling and testing should be listed. If certain companies are responsible only for specific steps (e.g. manufacturing of an intermediate), this should be clearly indicated (refer to WHO Good distribution practices for pharmaceutical products (*36*)).

The list of manufacturers or companies should specify the *actual addresses* of production or manufacturing site(s) involved (including block(s) and unit(s)) if applicable, rather than the administrative offices.

For a mixture of an API with an excipient, the blending of the API with the excipient is considered to be the first step in the manufacture of the final product and therefore the mixture does not fall under the definition of an API. The only exceptions occur in the cases where the API cannot exist on its own. Similarly, for a mixture of APIs, the blending of the APIs is considered to be the first step in the manufacture of the final product. Sites for such manufacturing steps should be included in this section.

A valid manufacturing authorization for pharmaceutical production is generally required and a marketing authorization may be required to demonstrate

that the product is registered or licensed in accordance with national requirements (Module 1, 1.2.2).

For each site where the major production step(s) are carried out, when applicable, a WHO-type certificate of GMP may be required, issued by the competent authority in terms of the WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce (Module 1, 1.2.2).

Justification for any differences to the product in the country or countries issuing the WHO-type certificate(s)

When there are differences between the product for which this application is submitted and that marketed in the country or countries which provided the WHO-type certificate(s), data to support the applicability of the certificate(s) despite the differences should be provided. Depending on the case, it may be necessary to provide validation data for differences, for example, in site of manufacture, specifications, or formulation. Note that only minor differences are likely to be acceptable. Differences in container labelling need not normally be justified.

Regulatory situation in other countries

A list should be made of countries in which this product has been granted a marketing authorization, this product has been withdrawn from the market and/or this application for marketing has been rejected, deferred or withdrawn (Module 1, 1.2.2).

Reference documents: WHO Technical Report Series, No. 961, 2011, Annex 3 (*10*) and WHO Technical Report Series, No. 957, 2010, Annex 5 (*36*)

3.2.P.3.2 *Batch formula (name, dosage form)*

A batch formula should be provided that includes a list of all components of the dosage form to be used in the manufacturing process, their amounts on a per batch basis, including overages, and a reference to their quality standards.

The tables in the QOS-PD template should be used to summarize the batch formula of the FPP *for each proposed commercial batch size* and express the quantity of each component on a per batch basis, including a statement of the total weight or measure (e.g. volume) of the batch.

All components used in the manufacturing process should be included, including those that may not be added to every batch (e.g. acid and alkali), those that may be removed during processing (e.g. solvents) and any others (e.g. nitrogen, or silicon for stoppers). If the FPP is formulated using an active moiety, then the composition for the active ingredient should be clearly indicated (e.g. "1 kg of active ingredient base = 1.075 kg active ingredient hydrochloride").

All overages should be clearly indicated (e.g. "Contains 5 kg (corresponding to 2%) overage of the API to compensate for manufacturing losses").

The components should be declared by their proper or common names, quality standards (e.g. Ph.Int., Ph.Eur., BP, USP, JP, in-house) and, if applicable, their grades (e.g. "microcrystalline cellulose NF (PH 102)") and special technical characteristics (e.g. lyophilized, micronized, solubilized, emulsified).

3.2.P.3.3 *Description of manufacturing process and process controls (name, dosage form)*

A flow diagram should be presented giving the steps of the process and showing where materials enter the process. The critical steps and points at which process controls, intermediate tests or final product controls are conducted should be identified.

A narrative description of the manufacturing process, including packaging, that represents the sequence of steps undertaken and the scale of production should also be provided. Novel processes or technologies and packaging operations that directly affect product quality should be described with a greater level of detail. Equipment should, at least, be identified by type (e.g. tumble blender, in-line homogeniser) and working capacity, where relevant.

Steps in the process should have the appropriate process parameters identified, such as time, temperature or pH. Associated numeric values can be presented as an expected range. Numeric ranges for critical steps should be justified in Section 3.2.P.3.4. In certain cases, environmental conditions (e.g. low humidity for an effervescent product) should be stated.

The maximum holding time for bulk FPP (product prior to final packaging, e.g. tablets in HDPE drums) should be stated. The holding time should be supported by the submission of stability data, if longer than 30 days. For an aseptically processed FPP, sterile filtration of the bulk and filling into final containers should preferably be continuous; any holding time should be justified.

Proposals for the reprocessing of materials should be justified. Any data to support this justification should be either referenced or filed in this section (3.2.P.3.3).

The information above should be summarized in the QOS-PD template and should reflect the production of the proposed commercial batches.

For the manufacture of sterile products, the class (e.g. A, B, C, etc.) of the areas should be stated for each activity (e.g. compounding, filling, sealing, etc.), as well as the sterilization parameters for equipment, container/closure, terminal sterilization, etc.

Reference documents: ICH Q8 (*29*), Q9 (*30*), Q10 (*31*)

3.2.P.3.4 *Controls of critical steps and intermediates (name, dosage form)*

Critical steps: Tests and acceptance criteria should be provided (with justification, including experimental data) performed at the critical steps identified in 3.2.P.3.3 of the manufacturing process, to ensure that the process is controlled.

Intermediates: Information on the quality and control of intermediates isolated during the process should be provided.

Examples of applicable in-process controls include:

- granulations: moisture (limits expressed as a range), blend uniformity (e.g. low dose tablets), bulk and tapped densities, particle size distribution;
- solid oral products: average weight, weight variation, hardness, thickness, friability, and disintegration checked periodically throughout compression, weight gain during coating;
- semi-solids: viscosity, homogeneity, pH;
- transdermal dosage forms: assay of API–adhesive mixture, weight per area of coated patch without backing;
- metered dose inhalers: fill weight/volume, leak testing, valve delivery;
- dry powder inhalers: assay of API–excipient blend, moisture, weight variation of individually contained doses such as capsules or blisters;
- liquids: pH, specific gravity, clarity of solutions;
- parenterals: appearance, clarity, fill volume/weight, pH, filter integrity tests, particulate matter, leak testing of ampoules, pre-filtration and/or presterilization bioburden testing.

Reference documents: ICH Q2 (*22*), Q6A (*13*), Q8 (*29*), Q9 (*30*), Q10 (*31*); WHO Technical Report Series, No. 970, 2012, Annex 5 (*34*)

3.2.P.3.5 *Process validation and/or evaluation (name, dosage form)*

Description, documentation, and results of the validation and/or evaluation studies should be provided for critical steps or critical assays used in the manufacturing process (e.g. validation of the sterilisation process or aseptic processing or filling). Viral safety evaluation should be provided in 3.2A.2, if necessary.

The following information should be provided for all products:

a) a copy of the *process validation protocol*, specific to this FPP, described below;

b) a *commitment* that three consecutive, production-scale batches of this FPP will be subjected to *prospective validation* in accordance with the above protocol; the applicant should submit a written commitment that information from these studies will be available for verification after approval by the NMRA inspection team;

c) if the process validation studies have already been conducted (e.g. for sterile products), a copy of the *process validation report* should be provided in the PD in lieu of (a) and (b) above.

One of the most practical forms of process validation, mainly for non-sterile products, is the final testing of the product to an extent greater than that required in routine quality control. It may involve extensive sampling, far beyond that called for in routine quality control and testing to normal quality control specifications and often for certain parameters only. Thus, for instance, several hundred tablets per batch may be weighed to determine unit dose uniformity. The results are then treated statistically to verify the "normality" of the distribution and to determine the standard deviation from the average weight. Confidence limits for individual results and for batch homogeneity are also estimated. Strong assurance is provided that samples taken at random will meet regulatory requirements if the confidence limits are well within compendial specifications.

Similarly, extensive sampling and testing may be performed with regard to any quality requirements. In addition, intermediate stages may be validated in the same way, e.g. dozens of samples may be assayed individually to validate mixing or granulation stages of low-dose tablet production by using the content uniformity test. Certain product characteristics may occasionally be skip tested. Thus, subvisual particulate matter in parenteral preparations may be determined by means of electronic devices, or tablets or capsules tested for dissolution profile if such tests are not performed on every batch.

Where ranges of batch sizes are proposed, it should be shown that variations in batch size would not adversely alter the characteristics of the finished product. It is envisaged that those parameters listed in the following validation scheme will need to be revalidated once further scale-up is proposed after approval.

The process validation protocol should include, but is not limited to, the following:

- a reference to the current master production document;
- a discussion of the critical equipment;
- the process parameters that can affect the quality of the FPP (critical process parameters (CPPs)) including challenge experiments and failure mode operation;

- details of the sampling: sampling points, stages of sampling, methods of sampling and the sampling plans (including schematics of blender/storage bins for uniformity testing of the final blend);
- the testing parameters/acceptance criteria including in-process and release specifications and including comparative dissolution profiles of validation batches against the batch(es) used in the bioavailability or biowaiver studies;
- the analytical procedures or a reference to appropriate section(s) of the dossier;
- the methods for recording and evaluating results;
- the proposed timeframe for completion of the protocol.

The manufacture of sterile FPPs needs a well-controlled manufacturing area (e.g. a strictly controlled environment, highly reliable procedures and appropriate in-process controls). A detailed description of these conditions, procedures and controls should be provided, together with actual copies of the following standard operating procedures (SOPs):

- washing, treatment, sterilization and depyrogenation of containers, closures and equipment;
- filtration of solutions;
- lyophilization process;
- leaker test of filled and sealed ampoules;
- final inspection of the product;
- sterilization cycle.

The sterilization process used to destroy or remove microorganisms is probably the single most important process in the manufacture of parenteral FPPs. The process can make use of moist heat (e.g. steam), dry heat, filtration, gaseous sterilization (e.g. ethylene oxide) or radiation. It should be noted that terminal steam sterilization, when practical, is considered to be the method of choice to ensure sterility of the final FPP. Therefore, scientific justification for selecting any other method of sterilization should be provided.

The sterilization process should be described in detail and evidence should be provided to confirm that it will produce a sterile product with a high degree of reliability and that the physical and chemical properties as well as the safety of the FPP will not be affected. Details such as Fo range, temperature range and peak dwell time for an FPP and the container closure should be provided. Although standard autoclaving cycles of 121 °C for 15 minutes or more would not need a detailed rationale, such justifications should be provided for reduced

temperature cycles or elevated temperature cycles with shortened exposure times. If ethylene oxide is used, studies and acceptance criteria should control the levels of residual ethylene oxide and related compounds.

Filters used should be validated with respect to pore size, compatibility with the product, absence of extractables and lack of adsorption of the API or any of the components.

For the validation of aseptic processing of parenteral products that cannot be terminally sterilized, simulation process trials should be conducted. This involves filling containers with culture media under normal conditions, followed by incubation. Refer to current WHO GMP guidelines for details.

Reference documents: ICH Q8 (*29*), Q9 (*30*), Q10 (*31*), WHO Technical Report Series, No. 961, 2011, Annex 3 (*10*)

3.2.P.4 Control of excipients (name, dosage form)

3.2.P.4.1 *Specifications (name, dosage form)*

The specifications for excipients should be provided.

The specifications from the applicant or the FPP manufacturer should be provided for all excipients, including those that may not be added to every batch (e.g. acid and alkali), those that do not appear in the final FPP (e.g. solvents) and any others used in the manufacturing process (e.g. nitrogen, silicon for stoppers).

If the standard claimed for an excipient is an officially-recognized compendial standard, it is sufficient to state that the excipient is tested according to the requirements of that standard, rather than reproducing the specifications found in the officially-recognized compendial monograph.

If the standard claimed for an excipient is a non-compendial standard (e.g. in-house standard) or includes tests that are supplementary to those appearing in the officially-recognized compendial monograph, a copy of the specification for the excipient should be provided.

In general, excipients with an officially-recognized pharmacopoeial monograph should be used. Exceptions should be justified.

For excipients of natural origin, microbial limit testing should be included in the specifications. Skip testing is acceptable if justified (submission of acceptable results of five production batches).

For oils of plant origin (e.g. soy bean oil, peanut oil) the absence of aflatoxins and biocides should be demonstrated.

The colours permitted for use should be limited to those listed in suitable guidelines such as the *Japanese pharmaceutical excipients directory* (*37*), the EU "List of permitted food colours", and the FDA "Inactive ingredient guide". For

proprietary mixtures, the supplier's product sheet with the qualitative formulation should be submitted in addition to the FPP manufacturer's specifications for the product, including identification testing.

For flavours the qualitative composition should be submitted, as well as a declaration that the excipients comply with foodstuff regulations (e.g. EU or USA).

Information that is considered confidential may be submitted directly to the NMRA by the supplier with reference to the specific related product.

Other certifications of at-risk components may be required on a case-by-case basis.

If additional purification is undertaken on commercially available excipients, details of the process of purification and modified specifications should be submitted.

Reference documents: ICH Q6A (*13*)

3.2.P.4.2 *Analytical procedures (name, dosage form)*

The analytical procedures used for testing the excipients should be provided, where appropriate.

Copies of analytical procedures from officially-recognized compendial monographs do not need to be submitted.

Reference documents: ICH Q2 (*22*)

3.2.P.4.3 *Validation of analytical procedures (name, dosage form)*

Analytical validation information, including experimental data, for the analytical procedures used for testing the excipients should be provided, where appropriate.

Copies of analytical validation information are generally not submitted for the testing of excipients, with the exception of the validation of in-house methods where appropriate.

Reference documents: ICH Q2 (*22*)

3.2.P.4.4 *Justification of specifications (name, dosage form)*

Justification for the proposed excipient specifications should be provided, where appropriate.

A discussion of the tests that are supplementary to those appearing in the officially-recognized compendial monograph should be provided.

3.2.P.4.5 *Excipients of human or animal origin (name, dosage form)*

For excipients of human or animal origin, information should be provided regarding adventitious agents (e.g. sources, specifications, description of the testing performed, viral safety data) (details in 3.2.A.2.)

The excipients to be addressed in this section may include gelatin, phosphates, stearic acid, magnesium stearate and other stearates. If an excipient is of plant origin a declaration to this effect will suffice.

For excipients of animal origin, a letter of attestation should be provided confirming that the excipients used to manufacture the FPP are without risk of transmitting agents of animal spongiform encephalopathies. Materials of animal origin should be avoided whenever possible.

When available, a CEP demonstrating TSE compliance should be provided. A complete copy of the CEP (including any annexes) should be provided in Module 1.

Reference documents: ICH Q5A (*38*), Q5D (*39*), Q6B (*40*), WHO Technical Report Series, No. 908, 2003, Annex 1 (*41*)

3.2.P.4.6 *Novel excipients (name, dosage form)*

For excipient(s) used for the first time in an FPP or by a new route of administration, full details of manufacture, characterisation, and controls, with cross-references to supporting safety data (nonclinical and/or clinical) should be provided according to the API and/or FPP format (details in 3.2.A.3).

At its discretion an NMRA may choose not to accept the use of novel excipients in submitted PDs. For the purpose of these guidelines, a novel excipient is one that has not been used (at a similar level and by the same route of administration) in a product approved by an SRA or WHO. If novel excipients are accepted, full information should be provided in 3.2.A.3.

3.2.P.5 Control of FPP (name, dosage form)

3.2.P.5.1 *Specification(s) (name, dosage form)*

The specification(s) for the FPP should be provided.

As defined in ICH's Q6A guideline, a specification is:

> "a list of tests, references to analytical procedures and appropriate acceptance criteria, which are numerical limits, ranges, or other criteria for the tests described. It establishes the set of criteria to which an API or FPP should conform to be considered acceptable for its intended use.

> 'Conformance to specifications' means that the API and /or FPP, when tested according to the listed analytical procedures, will meet the listed acceptance criteria. Specifications are critical quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities."

A copy of the FPP specification(s) from the applicant (as well as the company responsible for the batch release of the FPP, if different from the applicant), dated and signed by authorized personnel (i.e. the person in charge of the quality control or quality assurance department) should be provided in the PD. Two separate sets of specifications may be set out: after packaging of the FPP (release) and at the end of shelf-life.

The specifications should be summarized according to the tables in the QOS-PD template including the tests, acceptance criteria and analytical procedures (including types, sources and versions for the methods):

- the *standard* declared by the applicant could be an officially recognized compendial standard (e.g. BP, Ph.Eur., Ph.Int., JP, USP) or an in-house (manufacturer's) standard;
- the *specification reference number and version (e.g. revision number and/or date)* should be provided for version control purposes;
- for the analytical procedures, the *type* should indicate the kind of analytical procedure used (e.g. visual, IR, UV, HPLC), the *source* refers to the origin of the analytical procedure (e.g. BP, Ph.Eur., Ph.Int., JP, USP, in-house) and the *version (e.g. code number, version and date)* should be provided for version control purposes.

ICH's Q6A guideline outlines recommendations for a number of universal and specific tests and criteria for FPPs. Specifications should include, at the minimum, tests for appearance, identification, assay, purity, performance tests (e.g. dissolution), physical tests (e.g. loss on drying, hardness, friability, particle size), uniformity of dosage units, and, as applicable, identification and assay of antimicrobial or chemical preservatives (e.g. antioxidants) and microbial limit tests.

The following information provides guidance for specific tests that are not addressed by ICH's Q6A guideline (*13*):

- fixed-dose combination FPPs (FDC-FPPs):
  - analytical methods that can distinguish each API in the presence of the other API(s) should be developed and validated,

  - acceptance criteria for degradation products should be established with reference to the API they are derived from. If an impurity results from a chemical reaction between two or more APIs, its acceptance limits should in general be calculated with reference to the worst case (the API with the smaller area under the curve). Alternatively the content of such impurities could be calculated in relation to their reference standards,
  - a test and limit for content uniformity is required for each API present in the FPP at less than 5 mg or less than 5% of the weight of the dosage unit,
  - for the API(s) present at greater than or equal to 5 mg and greater than or equal to 5% of the weight of the dosage unit, a test and limit for weight variation may be established in lieu of content uniformity testing;

- modified-release products: a meaningful API release method;
- inhalation and nasal products: mean delivered dose, consistency of delivered dose (throughout the use of the product), particle or droplet size distribution profiles (comparable to the product used in in vivo studies, where applicable) and if applicable for the dosage form, moisture content, leak rate, microbial limits, preservative assay, sterility and weight loss;
- suppositories: uniformity of dosage units, melting point;
- transdermal dosage forms: peel or shear force, mean weight per unit area, dissolution.

Unless there is appropriate justification, the generally accepted limit for the API content of the FPP in the release specifications is ± 5% of the label claim (i.e. 95.0–105.0%).

For products such as tablets, capsules and suppositories where a test for uniformity of single dose preparations is required, a test and limit for content uniformity is required when the API is present in the FPP at less than 5 mg or less than 5% of the weight of the dosage unit. Otherwise, the test for mass uniformity may be applied.

Skip testing is generally acceptable for parameters such as identification of colouring materials and microbial limits, when justified by the submission of acceptable supportive results for five production batches. When skip testing justification has been accepted, the specifications should include a footnote, stating at a minimum the following skip testing requirements: at a minimum every tenth batch and at least one batch annually is tested. In addition, for stability-indicating parameters such as microbial limits, testing will be performed at release and at the end of the shelf-life during stability studies.

Any differences between release and shelf-life tests and acceptance criteria should be clearly indicated and justified. Note that such differences for parameters such as dissolution are normally not accepted.

Reference documents: ICH Q3B (*17*), Q3C (*18*), Q6A (*13*)

3.2.P.5.2 *Analytical procedures (name, dosage form)*

The analytical procedures used for testing the FPP should be provided.

Copies of the in-house analytical procedures used during pharmaceutical development (if used to generate testing results provided in the PD) as well as those proposed for routine testing should be provided. Unless modified, it is not necessary to provide copies of officially-recognized compendial analytical procedures.

Tables for summarizing a number of the different analytical procedures and validation information (e.g. HPLC assay/impurity methods) can be found in section 2.3.R Regional information, of the QOS-PD (i.e. *2.3.R.2*). These tables may be used to summarize the analytical procedures used for determination of the assay, related substances and dissolution of the FPP.

Refer to section 3.2.S.4.2 of these guidelines for additional guidance on analytical procedures.

Reference document: ICH Q2 (*22*)

3.2.P.5.3 *Validation of analytical procedures (name, dosage form)*

Analytical validation information, including experimental data, for the analytical procedures used for testing the FPP, should be provided.

Copies of the validation reports for the in-house analytical procedures used during pharmaceutical development (if used to support testing results provided in the PD) as well as those proposed for routine testing should be provided.

Tables for summarizing a number of the different analytical procedures and validation information (e.g. HPLC assay/impurity methods, GC methods) can be found in section 2.3.R Regional information, of the QOS-PD (i.e. *2.3.R.2*). These tables may be used to summarize the validation information of the analytical procedures used for determination of the assay, related substances and dissolution of the FPP.

As recognized by regulatory authorities and pharmacopoeias themselves, verification of compendial methods may be necessary. The compendial methods, as published, are typically validated based on an API or an FPP originating from a specific manufacturer. Different sources of the same API or FPP can contain impurities and/or degradation products or excipients that were not considered during the development of the monograph. Therefore the monograph and

compendial method(s) should be demonstrated to be suitable for the control of the proposed FPP.

For officially-recognized compendial FPP *assay* methods, verification should include a demonstration of specificity, accuracy and repeatability (method precision). If an officially-recognized compendial method is used to control related substances that are not specified in the monograph, full validation of the method is expected with respect to those related substances.

If an officially-recognized compendial standard is claimed and an in-house method is used in lieu of the compendial method (e.g. for assay or for related compounds), equivalency of the in-house and compendial methods should be demonstrated. This could be accomplished by performing duplicate analyses of one sample by both methods and providing the results from the study. For related compound methods, the sample analysed should be the placebo spiked with related compounds at concentrations equivalent to their specification limits.

Reference document: ICH Q2 (*22*)

3.2.P.5.4 *Batch analyses (name, dosage form)*

A description of batches and results of batch analyses should be provided.

Information should include strength and batch number, batch size, date and site of production and use (e.g. used in comparative bioavailability or biowaiver studies, preclinical and clinical studies (if relevant), stability, pilot, scale-up and, if available, production-scale batches) on relevant FPP batches used to establish the specification(s) and evaluate consistency in manufacturing.

Analytical results tested by the company responsible for the batch release of the FPP (generally, the applicant or the FPP manufacturer, if different from the applicant) should be provided for not less than two batches of at least pilot scale, or in the case of an uncomplicated[3] FPP (e.g. immediate-release solid FPPs (with noted exceptions), non-sterile solutions), not less than one batch of at least pilot scale and a second batch which may be smaller (e.g. for solid oral dosage forms, 25 000 or 50 000 tablets or capsules) of each proposed strength of the FPP. These batches should be manufactured by a procedure fully representative of and simulating that to be applied to a full production-scale batch.

The testing results should include the batch(es) used in the comparative bioavailability or biowaiver studies. Copies of the certificates of analysis for these

[3] Examples of products that could be included under the term "complicated FPP" include sterile products, metered dose inhaler products, dry powder inhaler products and transdermal delivery systems, as well as FDC and monocomponent products containing APIs known to be of low solubility, or known to have poor stability or polymorphism issues.

batches should be provided in the PD and the company responsible for generating the testing results should be identified.

The discussion of results should focus on observations noted for the various tests, rather than reporting comments such as "all tests meet specifications". This should include ranges of analytical results, where relevant. For quantitative tests (e.g. individual and total impurity tests and assay tests), it should be ensured that actual *numerical results* are provided rather than vague statements such as "within limits" or "conforms" (e.g. "levels of degradation product A ranged from 0.2 to 0.4%"). Dissolution results should be expressed at a minimum as both the average and the range of individual results. Recommendations for conducting and assessing comparative dissolution profiles can be found in Appendix 1.

A discussion and justification should be provided for any incomplete analyses (e.g. results not tested according to the proposed specification).

Reference documents: ICH Q3B (*17*), Q3C (*18*), Q6A (*13*)

3.2.P.5.5 *Characterization of impurities (name, dosage form)*

Information on the characterization of impurities should be provided, if not previously provided in "3.2.S.3.2 Impurities".

A discussion should be provided of all impurities that are potential degradation products (including any of the impurities identified in 3.2.S.3.2 as well as potential degradation products resulting from interaction of the API with other APIs (FDCs), excipients or the container-closure system) and FPP process-related impurities (e.g. residual solvents in the manufacturing process for the FPP).

Reference documents: ICH Q3B (*17*), Q3C (*18*), Q6A (*13*)

3.2.P.5.6 *Justification of specification(s) (name, dosage form)*

Justification for the proposed FPP specification(s) should be provided.

A discussion should be provided on the omission or inclusion of particular tests, evolution of tests, analytical procedures and acceptance criteria, differences from the officially-recognized compendial standard(s). If the officially-recognized compendial methods have been modified or replaced, a discussion should be included.

The justification for certain tests, analytical procedures and acceptance criteria (e.g. degradation products or dissolution method development) may have been discussed in other sections of the PD and does not need to be repeated here, although a cross-reference to their location should be provided.

ICH Q6A (*13*) should be consulted for the development of specifications for FPPs.

3.2.P.6 Reference standards or materials (name, dosage form)

Information on the reference standards or reference materials used for testing of the FPP should be provided, if not previously provided in "3.2.S.5 Reference standards or materials".

See Section 3.2.S.5 for information that should be provided on reference standards or materials. Information should be provided on reference materials of FPP degradation products, where not included in 3.2.S.5.

Reference documents: ICH Q6A (*13*), WHO Technical Report Series, No. 943, 2007 Annex 3 (*23*)

3.2.P.7 Container-closure system (name, dosage form)

A description of the container-closure systems should be provided, including the identity of materials of construction of each primary packaging component and its specification. The specifications should include description and identification (and critical dimensions, with drawings where appropriate). Non-compendial methods (with validation) should be included, where appropriate.

For non-functional secondary packaging components (e.g. those that neither provide additional protection nor serve to deliver the product), only a brief description should be provided. For functional secondary packaging components, additional information should be provided.

Suitability information should be located in 3.2.P.2.

The WHO *Guidelines on packaging for pharmaceutical products* (WHO Technical Report Series, No. 902, Annex 9, 2002) and the officially-recognized pharmacopoeias should be consulted for recommendations on the packaging information for FPPs (*24*).

Descriptions, materials of construction and specifications (of the company responsible for packaging the FPP, generally the FPP manufacturer) should be provided for the packaging components that are:

- in direct contact with the dosage form (e.g. container, closure, liner, desiccant, filler);
- used for drug delivery (including the device(s) for multidose solutions, emulsions, suspensions and powders/granules for such);
- used as a protective barrier to help ensure stability or sterility;
- necessary to ensure FPP quality during storage and shipping.

Primary packaging components are those that are in direct contact with the API or FPP. The specifications for the primary packaging components should include a specific test for identification (e.g. IR). Specifications for film and foil materials should include limits for thickness or area weight.

Information to establish the suitability (e.g. qualification) of the container-closure system should be discussed in Section 3.2.P.2.4. Comparative studies may be warranted for certain changes in packaging components (e.g. comparative delivery study (droplet size) for a change in manufacturer of dropper tips).

3.2.P.8 Stability (name, dosage form)

3.2.P.8.1 *Stability summary and conclusions (name, dosage form)*

The types of studies conducted, protocols used, and the results of the studies should be summarised. The summary should include, for example, conclusions with respect to storage conditions and shelf-life, and, if applicable, in-use storage conditions and shelf-life.

The WHO *Guidelines on Stability testing of active pharmaceutical ingredients and finished pharmaceutical products* (WHO Technical Report Series, No. 953, 2009, Annex 2) should be consulted for recommendations on the core stability data package (*9*).

As outlined in the WHO *stability guidelines*, the purpose of stability testing is to provide evidence of how the quality of an API or FPP varies with time under the influence of a variety of environmental factors such as temperature, humidity and light. The stability programme also includes the study of product-related factors that influence its quality, for example, interaction of API with excipients, container-closure systems and packaging materials.

Stress testing

As outlined in the WHO *stability guidelines*, photostability testing should be conducted on at least one primary batch of the FPP if appropriate. If "protect from light" is stated in one of the officially recognized pharmacopoeias for the API or FPP, it is sufficient to state "protect from light" on labelling, in lieu of photostability studies, when the container-closure system is shown to be light protective. Additional stress testing of specific types of dosage forms may be appropriate (e.g. cyclic studies for semi-solid products, freeze-thaw studies for liquid products).

Accelerated, intermediate (if necessary) and long-term testing

Stability data must demonstrate stability of the medicinal product throughout its intended shelf-life under the climatic conditions prevalent in the target countries. Merely applying the same requirements applicable to other markets could potentially lead to substandard products, e.g. stability studies conducted for countries in Climatic Zone I/II when the products are supplied to countries in Climatic Zones III and IV. Refer to WHO Technical Report Series, No. 953, 2009, Annex 2, Appendix 1, for information on climatic zones (*9*).

Refer to WHO Technical Report Series, No. 953, 2009, Annex 2 for further information regarding the storage conditions, including the minimum data required at the time of submitting the dossier (*9*).

To establish the shelf-life, data should be provided on not less than two batches of at least pilot scale, or in the case of an uncomplicated FPP (e.g. immediate-release solid FPPs (with noted exceptions), non-sterile solutions), not less than one batch of at least pilot scale and a second batch which may be smaller (e.g. for solid oral dosage forms, 25 000 or 50 000 tablets or capsules) of each proposed strength of the FPP. These batches should be manufactured by a procedure fully representative of and simulating that to be applied to a full production-scale batch. Where possible, batches of the FPP should be manufactured using different batches of the API(s). Stability studies should be performed on each individual strength, dosage form and container type and size of the FPP unless bracketing or matrixing is applied.

The stability testing programme should be summarized and the results of stability testing should be reported in the dossier and summarized in the tables in the QOS-PD. Bracketing and matrixing of proportional strengths can be applied, if scientifically justified.

For sterile products, sterility should be reported at the beginning and end of shelf-life. For parenteral products, subvisible particulate matter should be reported frequently, but not necessarily at every test interval. Bacterial endotoxins need only be reported at the initial test interval. Weight loss from plastic containers should be reported over the shelf-life.

Any in-use period and associated storage conditions should be justified with experimental data, for example after opening, reconstitution and/or dilution of any sterile and/or multidose products or after first opening of FPPs packed in bulk multidose containers (e.g. bottles of 1000s). If applicable, the in-use period and storage conditions should be stated in the product information.

The information on the stability studies should include details such as:

- storage conditions;
- strength;
- batch number, including the API batch number(s) and manufacturer(s);
- batch size;
- container-closure system including orientation (e.g. erect, inverted, on-side) where applicable (e.g. semi-solids and liquids in plastic containers);
- completed (and proposed) test intervals.

The discussion of results should focus on observations noted for the various tests, rather than reporting comments such as "all tests meet specifications". This should include ranges of analytical results and any trends that were observed. For quantitative tests (e.g. individual and total degradation product tests and assay tests), it should be ensured that actual numerical results are provided rather than vague statements such as "within limits" or "conforms". Dissolution results should be expressed at a minimum as both the average and range of individual results.

Applicants should consult ICH's Q1E guideline (*28*) for details on the evaluation and extrapolation of results from stability data (e.g. if significant change was not observed within 6 months at accelerated condition and the data show little or no variability, the proposed shelf-life could be up to two times the period covered by the long-term data, but should not exceed the long-term data by more than 12 months).

Proposed storage statement and shelf-life

The proposed storage statement and shelf-life (and in-use storage conditions and in-use period, if applicable) for the FPP should be provided.

The recommended labelling statements for use, based on the stability studies, are provided in the WHO *stability guidelines* (*9*).

Reference documents: WHO Technical Report Series, No. 953, 2009, Annex 2 (*9*), ICH Q1A (*26*), Q1B (*25*), Q1C (*42*), Q1D (*27*), Q1E (*28*), Q3B (*17*), Q6A (*43*)

3.2.P.8.2 ***Post-approval stability protocol and stability commitment (name, dosage form)***

The post-approval stability protocol and stability commitment should be provided.

Primary stability study commitment

When the available data on long-term stability of primary batches do not cover the proposed shelf-life granted at the time of assessment of the PD, a commitment should be made to continue the stability studies in order to firmly establish the shelf-life. A written commitment (signed and dated) to continue long-term testing over the shelf-life period should be included in the dossier.

Commitment stability studies

The long-term stability studies for the *Commitment batches* should be conducted throughout the proposed shelf-life on at least three production batches of each strength in each container-closure system. Where stability data were not provided for three production batches of each strength, a written commitment (signed and dated) should be included in the dossier.

Ongoing stability studies

As described in the WHO *stability guidelines*, an *ongoing stability programme* is established to monitor the product over its shelf-life and to determine that the product remains and can be expected to remain within specifications when kept under the storage conditions on the label. Unless otherwise justified, at least one batch per year of product manufactured, in every strength, and every container-closure system, if relevant, should be included in the stability programme (unless none is produced during that year). Bracketing and matrixing may be applicable. A written commitment (signed and dated) to this effect should be included in the dossier.

Any differences in the stability protocols used for the primary batches and those proposed for the *commitment batches* or *ongoing batches* should be scientifically justified.

Reference documents: ICH Q1A (*26*)

3.2.P.8.3 *Stability data (name, dosage form)*

Results of the stability studies should be presented in an appropriate format (e.g. tabular, graphical, narrative). Information on the analytical procedures used to generate the data and validation of these procedures should be included.

Information on characterization of impurities is located in 3.2.P.5.5.

The actual stability results/reports used to support the proposed shelf-life should be provided in the PD. For quantitative tests (e.g. individual and total degradation product tests and assay tests), it should be ensured that actual numerical results are provided rather than vague statements such as "within limits" or "conforms". Dissolution results should be expressed at a minimum as both the average and range of individual results.

Reference documents: ICH Q1A (*26*), Q1B (*25*), Q1C (*42*), Q1D (*27*), Q1E (*28*), Q2 (*22*)

3.2.A Appendices

3.2.A.1 Facilities and equipment

Not applicable (i.e. not a biotech product).

3.2.A.2 Adventitious agents safety evaluation

3.2.A.3 Novel excipients

At its discretion an NMRA may choose not to accept the use of novel excipients in submitted PDs. If novel excipients are accepted, full information should be provided in the format of the sections in 3.2.P.

3.2.R Regional information

Refer to 1.5 for additional guidance on regional information.

3.2.R.1 Production documentation

3.2.R.1.1 *Executed production documents*

A minimum of two batches of at least pilot scale, or in the case of an uncomplicated FPP (e.g. immediate-release solid FPPs (with noted exceptions), non-sterile solutions), not less than one batch of at least pilot scale (the batch used in comparative bioavailability or biowaiver studies) and a second batch which may be smaller (e.g. for solid oral dosage forms, 25 000 or 50 000 tablets or capsules), should be manufactured for each strength. These batches should be manufactured by a procedure fully representative of and simulating that to be applied to a full production-scale batch.

For solid oral dosage forms, pilot scale is generally, at a minimum, one-tenth that of full production scale or 100 000 tablets or capsules, whichever is the larger.

Copies of the executed production documents should be provided for the batches used in the comparative bioavailability or biowaiver studies. Any notations made by operators on the executed production documents should be clearly legible.

If not included in the executed batch records through sufficient in-process testing, data should be provided for the batch used in comparative bioavailability or biowaiver studies that demonstrates the uniformity of this batch. The data to establish the uniformity of the biobatch should involve testing to an extent greater than that required in routine quality control.

English translations of executed records should be provided, where relevant.

3.2.R.1.2 *Master production documents*

Copies of the FPP master production documents should be provided for each proposed strength, commercial batch size and manufacturing site.

The details in the master production documents should include, but not be limited to, the following:

a) master formula;
b) dispensing, processing and packaging sections with relevant material and operational details;
c) relevant calculations (e.g. if the amount of API is adjusted based on the assay results or on the anhydrous basis);
d) identification of all equipment by, at a minimum, its type and working capacity (including make, model and equipment number, where possible);

e) process parameters (e.g. mixing time, mixing speed, milling screen size, processing temperature range, granulation end-point, tablet machine speed (expressed as target and range));

f) list of in-process tests (e.g. appearance, pH, assay, blend uniformity, viscosity, particle size distribution, loss on drying, weight variation, hardness, disintegration time, weight gain during coating, leaker test, minimum fill, clarity, filter integrity checks) and specifications;

g) sampling plan with regard to the:

- steps where sampling should be done (e.g. drying, lubrication, compression),
- number of samples that should be tested (e.g. for blend uniformity testing of low dose FPPs, blend drawn using a sampling thief from x positions in the blender),
- frequency of testing (e.g. weight variation every x minutes during compression or capsule filling);

h) precautions necessary to ensure product quality (e.g. temperature and humidity control, maximum holding times);

i) for sterile products, reference to SOPs in appropriate sections and a list of all relevant SOPs at the end of the document;

j) theoretical and actual yield;

k) compliance with the GMP requirements.

Reference documents: WHO Technical Report Series, No. 961, 2011, Annex 3 (*10*) and Annex 6 (*44*)

3.2.R.2 Analytical procedures and validation information

The tables presented in section 2.3.R.2 in the QOS-PD template may be used to summarize the analytical procedures and validation information from sections 3.2.S.4.2, 3.2.S.4.3, 2.3.S.4.4 (c), 2.3.S.7.3 (b), 3.2.P.5.2 and 3.2.P.5.3, where relevant.

4.3 Literature references

References to the scientific literature relating to both the API and FPP should be included in this section of the PD when appropriate.

References

1. Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-sixth report*. Geneva, World Health Organization, 2012 (WHO Technical Report Series, No. 970), Annex 4.
2. International Conference on Harmonisation, *ICH Harmonised Tripartitite Guideline: The Common Technical Document for the registration of pharmaceuticals for human use: quality – M4Q*, September 2002.
3. Guidelines on submission of documentation for a multisource (generic) finished product: general format: preparation of product dossiers in common technical document format. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth report*. Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 15.
4. Procedure for prequalification of pharmaceutical products. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-third report*. Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 10.
5. International Conference on Harmonisation, *ICH Harmonised Tripartitite Guideline: Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients – Q7*, November 2000.
6. WHO good manufacturing practices for active pharmaceutical ingredients. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth report.* Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex 2.
7. Guidelines for registration of fixed-dose combination medicinal products. Appendix 3: Pharmaceutical development (or preformulation) studies. Table A1: Typical stress conditions in preformulation stability studies. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-ninth report*. Geneva, World Health Organization, 2005 (WHO Technical Report Series, No. 929), Annex 5.
8. Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fortieth report*. Geneva, World Health Organization, 2006 (WHO Technical Report Series, No. 937), Annex 7.
9. Stability testing of active pharmaceutical ingredients and finished pharmaceutical products. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-third report*. Geneva, World Health Organization, 2009 (WHO Technical Report Series, No. 953), Annex 2.
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Appendix 1

Recommendations for conducting and assessing comparative dissolution profiles[1]

The dissolution measurements of the two FPPs (e.g. test and reference (comparator), or two different strengths) should be made under the same test conditions. A minimum of three time points (zero excluded) should be included, the time points for both reference and test product being the same. The sampling intervals should be short for a scientifically sound comparison of the profiles (e.g. 5, 10, 15, 20, 30, 45 (60, 90, 120) minutes). Inclusion of the 15-minute time point in the schedule is of strategic importance for profile similarity determinations (very rapidly dissolving scenario). For extended-release FPPs, the time points should be set to cover the entire time period of expected release, e.g. 1, 2, 3, 5 and 8 hours for a 12-hour release and additional test intervals for longer duration of release.

Studies should be performed in at least three media covering the physiological range, including pH 1.2 hydrochloric acid, pH 4.5 buffer and pH 6.8 buffer. International Pharmacopoeia buffers are recommended; alternative compendia buffers with the same pH and buffer capacity are also accepted. Water may be considered as an additional medium, especially when the API is unstable in the buffered media to the extent that the data are unusable.

If both the test and reference products show more than 85% dissolution in 15 minutes, the profiles are considered similar (no calculations required). Otherwise:

- *similarity* of the resulting comparative dissolution profiles should be calculated using the following equation that defines a similarity factor (f_2):

$$f_2 = 50 \text{ LOG } \{[1+1/n \sum^{n}_{t=1} (R_t - T_t)^2]^{-0.5} \times 100\}$$

where R_t and T_t are the mean percentage of API dissolved in reference and test product, respectively, at each time point. An f_2 value between 50 and 100 suggests that the two dissolution profiles are similar:

[1] The information provided is with reference to the quality aspects of the dossier. Refer to relevant bioequivalence documents for guidance specific to the requirements for dissolution studies related to bioequivalence studies.

- a maximum of one time-point should be considered after 85% dissolution of the reference product has been reached. In the case where 85% dissolution cannot be reached due to poor solubility of the API, the dissolution should be conducted until an asymptote (plateau) has been reached;
- at least 12 units should be used for each profile determination. Mean dissolution values can be used to estimate the similarity factor, f_2. To use mean data, the percentage coefficient of variation at the first time point should be not more than 20% and at other time points should be not more than 10%;
- when delayed-release products (e.g. enteric coated) are being compared, the recommended conditions are acid medium (pH 1.2) for 2 hours and buffer pH 6.8 medium;
- when comparing extended-release beaded capsules, where different strengths have been achieved solely by means of adjusting the number of beads containing the API, one condition (normally the release condition) will suffice;
- surfactants should be avoided in comparative dissolution testing. A statement that the API is not soluble in any of the media is not sufficient and profiles in the absence of surfactant should be provided. The rationale for the choice and concentration of surfactant should be provided. The concentration of the surfactant should be such that the discriminatory power of the test will not be compromised.