WHO Technical Report Series
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WHO EXPERT COMMITTEE ON SPECIFICATIONS FOR PHARMACEUTICAL PREPARATIONS

Forty-third report

World Health Organization

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 standards and guidelines were adopted and recommended for use: the current list of available International Chemical Reference Substances and International Infrared Reference Spectra; guidelines on stability testing of active pharmaceutical ingredients and finished pharmaceutical products; procedure for prequalification of pharmaceutical products; and the procedure for assessing the acceptability, in principle, of active pharmaceutical ingredients for use in pharmaceutical products.

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SPECIFICATIONS FOR PHARMACEUTICAL PREPARATIONS

WHO Technical Report Series — 953

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Geneva, 13–17 October 2008

Members

Professor Saleh A. Bawazir, Head of Drug Sector and Vice-President, Saudi Food and Drug Authority (SFDA), Riyadh, Saudi Arabia

Professor Theo G. Dekker, Research Institute for Industrial Pharmacy, North-West University, Potchefstroom, South Africa

Ms Nilka M. Guerrero Rivas, Instituto Especializado de Análisis (IEA), Ciudad Universitaria Octavio Méndez Pereira, University of Panama, Panama (*Co-Rapporteur*)

Professor Jos Hoogmartens, Labo voor Farmaceutische Analyse, Leuven, Belgium (*Chairperson*)

Professor Jin Shaohong, Executive Deputy Director, National Institute for the Control of Pharmaceutical and Biological Products, Ministry of Public Health, Beijing, People's Republic of China

Dr Sulaikah V.K. Moideen, Head, Centre for Quality Control and Deputy Director, National Pharmaceutical Control Bureau, Ministry of Health, Jalan University, Petaling Jaya, Selangor, Malaysia

Dr Justina A. Molzon, Associate Director for International Programs, Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, MD, USA (*Co-Chairperson*)

Professor Tamás L. Paál, Director-General, National Institute of Pharmacy, Budapest, Hungary

Mr Eshetu Wondemagegnehu, Addis Ababa, Ethiopia (*Co-Rapporteur*)

Temporary advisers

Dr E. Ehrin, Director, Centrallaboratoriet, ACL, Apoteket AB, Kungens Kurva, Sweden

Professor H.G. Kristensen, Vedbaek, Denmark

Dr J.-L. Robert, Service du Contrôle des Médicaments, Laboratoire National de Santé, Luxembourg

Dr S. Singh, Professor and Head, Department of Pharmaceutical Analysis, National Institute of Pharmaceutical Education and Research, Nagar, India

Dr Lucky S. Slamet, Deputy, Therapeutic Product and Narcotic, Psychotropic and Addictive Substance Control, National Agency for Drugs and Food Control, Jakarta, Indonesia[1]

[1] Unable to attend.

Special advisers (prequalification)

Mr P. Hargreaves, Inspection, Enforcement and Standards Division, Medicines and Healthcare Products Regulatory Agency, London, England

Dr J. Pogány, Budapest, Hungary

Mr D. Smith, Guateng, South Africa

Representation from United Nations offices[1]

United Nations Children's Fund (UNICEF)

Dr Peter Svarrer Jakobsen, Quality Assurance Officer, UNICEF Supply Division, Copenhagen, Denmark

Representation from specialized agencies and related organizations[2]

Global Fund to Fight AIDS, Tuberculosis and Malaria

Ms Joelle Daviaud, Senior Pharmaceutical QA Officer, Pharmaceutical Procurement Unit, Geneva, Switzerland

International Atomic Energy Agency (IAEA)

Mr K.K. Solanki, Technical Officer, Nuclear Medicine Section, Division of Human Health, Vienna, Austria

World Intellectual Property Organization (WIPO)

Ms Marie Paule Rizo, Senior Legal Officer, Law and International Classifications Division, Sector of Trademarks, Industrial Designs, and Geographical Indications, Geneva, Switzerland

World Bank

Mr Andreas Seiter, Senior Health Specialist and Pharmaceutical Policy Expert, Human Development Network, Washington, DC, USA

Representation from intergovernmental organizations[3]

Council of Europe

Dr Susanne Keitel, Director, European Directorate for the Quality of Medicines & HealthCare (EDQM) and Dr John H.McB. Miller, Head, Laboratory Division, EDQM, Strasbourg, France

European Medicines Agency (EMEA)

Dr Katrin Nodop, Inspections Sector and Dr Piotr Kozarewicz, Scientific Administrator, Quality of Medicines Sector, London, England

---

[1] Unable to attend: United Nations Development Programme (UNDP), New York, NY, USA.

[2] Unable to attend: United Nations Industrial Development Organization (UNIDO), Vienna, Austria; World Customs Organization (WCO), Brussels, Belgium; World Trade Organization (WTO), Geneva, Switzerland.

[3] Unable to attend: European Commission (EC), Brussels, Belgium.

Representation from nongovernmental organizations[1]

International Federation of Pharmaceutical Manufacturers and Associations (IFPMA)

Dr Michael G. Beatrice, Vice President, Corporate Regulatory & Quality Science, Abbott, Geneva, Switzerland

International Pharmaceutical Federation (FIP)

Mr A.J.M. Hoek, General Secretary and CEO and Mr Xuan Hao Chan, Project Manager, the Hague, the Netherlands

World Self-Medication Industry (WSMI)

Dr Martin Cranmer, Head, Global Laboratory Compliance and Processes, Product Development Operations, OTC R&D, Novartis Consumer Health SA Nyon, Switzerland

Observer[2]

Pharmacopoeias[3]

Farmacopéia Brasileira

Professor Gerson A. Pianetti, President, Comissão Permanente de Revisão de Farmacopéia Brasileira, Santa Maria RS, Brazil

British Pharmacopoeia Commission Secretariat

Mrs Maria Barrett, Senior Pharmacopoeial Scientist, Deputy Head of Science, London, England

Pharmacopoeia of the People's Republic of China

Dr Li Huiyi, Chief, Modern Drug Division, State Pharmacopoeia Commission, Beijing, People's Republic of China

European Pharmacopoeia[4]

Council of Europe, Strasbourg, France

Pharmacopoeia of the Republic of Korea

Dr Bokyung Choi, Director/Pharmacist, Antibiotic & Oncology Division, Drug Evaluation Department, Korea Food and Drug Administration Seoul, Republic of Korea

United States Pharmacopeia

Dr Roger L. Williams, Executive Vice President and CEO and Dr William Koch, Chief Metrology Officer, Reference Materials Division, Rockville, MD, USA

---

[1] Unable to attend: Commonwealth Pharmaceutical Association (CPA), London, England; European Chemical Industry Council (CEFIC)/APIC, Brussels, Belgium; International Society for Pharmaceutical Engineering (ISPE), Tampa, FL, USA; International Generic Pharmaceutical Alliance (IGPA), Brussels, Belgium; International Pharmaceutical Excipients Council (IPEC), Strasbourg, France.

[2] Unable to attend: Pharmaceutical Inspection Co-operation Scheme (PIC/S), Geneva, Switzerland.

[3] Unable to attend: Farmacopea Argentina, Buenos Aires, Argentina; Indian Pharmacopoeia, Indian Pharmacopoeia Committee, New Delhi, India; Japanese Pharmacopoeia, Committee of the Japanese Pharmacopoeia, Tokyo, Japan; State Pharmacopoeia of the Russian Federation, Pharmacopoeia Committee, Moscow, Russian Federation.

[4] See Council of Europe.

Representation from WHO regional offices[1]

WHO Secretariat

Dr C.F. Etienne, Assistant Director-General, Health Systems and Services, WHO, Geneva, Switzerland

Dr H.V. Hogerzeil, Director, Essential Medicines and Pharmaceutical Policies, WHO, Geneva, Switzerland

Dr L. Rägo, Coordinator, Quality Assurance and Safety: Medicines, WHO, Geneva, Switzerland

Dr S. Kopp, Manager, Medicines Quality Assurance Programme, Quality Assurance and Safety: Medicines, WHO, Geneva, Switzerland (*Secretary*)

Ms C. Mendy, Medicines Quality Assurance Programme, Quality Assurance and Safety: Medicines, WHO, Geneva, Switzerland

Ms M.-L. Rabouhans, Medicines Quality Assurance Programme, Quality Assurance and Safety: Medicines, WHO, Geneva, Switzerland

Dr R. Balocco, Manager, International Nonproprietary Names (INN) Programme, Quality Assurance and Safety: Medicines, WHO, Geneva, Switzerland

Dr R. Kiivet, Manager, Prequalification Programme, Quality Assurance and Safety: Medicines, WHO, Geneva, Switzerland

Dr M. Mehmandoust, Prequalification Programme, Quality Assurance and Safety: Medicines, WHO, Geneva, Switzerland

Mr D. Mubangizi, Prequalification Programme, Quality Assurance and Safety: Medicines, WHO, Geneva, Switzerland

Ms J. Sabartova, Prequalification Programme, Quality Assurance and Safety: Medicines, WHO, Geneva, Switzerland

Dr H. Yin, Prequalification Programme, Quality Assurance and Safety: Medicines, WHO, Geneva, Switzerland

Dr A. van Zyl, Prequalification Programme, Quality Assurance and Safety: Medicines, WHO, Geneva, Switzerland

Dr S. Azatyan, Medicines Regulatory Support, WHO, Geneva, Switzerland

Dr A. Bosman, Global Malaria Programme, WHO, Geneva, Switzerland

Mr J. Hetzke, Health Systems and Services , WHO, Geneva, Switzerland

Dr S. Hill, Medicine Access and Rational Use, WHO, Geneva, Switzerland

Dr H. Möller, Medicine Access and Rational Use, WHO, Geneva, Switzerland

Dr C. Ondari, Coordinator, Medicine Access and Rational Use, WHO, Geneva, Switzerland[2]

Dr A. Prat, Medicines Regulatory Support, WHO, Geneva, Switzerland

Dr V. Reggi, Executive Secretary, International Medical Products Anti-Counterfeiting Taskforce (IMPACT), WHO, Geneva, Switzerland

Ms Y. Maruyama, Traditional Medicine, WHO, Geneva, Switzerland

---

[1] Unable to attend: Regional Office for Africa; Regional Office for the Americas; Regional Office for the Eastern Mediterranean; Regional Office for Europe; Regional Office for South-East Asia; Regional Office for the Western Pacific.

[2] Unable to attend.

Declarations of interest

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

Ms Nilka M. Guerrero Rivas reported that she works in a quality control laboratory, with no connection to a particular manufacturer, the laboratory's sole interest being quality of pharmaceutical products.

Dr Justina A. Molzon reported that she works for the US Food and Drug Administration/Center for Drug Evaluation and Research (USFDA/CDER) and has no financial conflicts.

Professor Saleh A. Bawazir, Professor Theo G. Dekker, Professor Jos Hoogmartens, Professor Jin Shaohong, Dr Sulaikah V.K. Moideen, Professor Tamás L. Paál and Mr Eshetu Wondemagegnehu reported no conflict of interest.

Temporary and special advisers as follows reported no conflict of interest:

Dr Erling Ehrin, Mr Paul Hargreaves, Professor Henning G. Kristensen, Dr János Pogány, Dr Jean-Louis Robert, Dr Saranjit Singh and Mr Deryck Smith.

1. Introduction

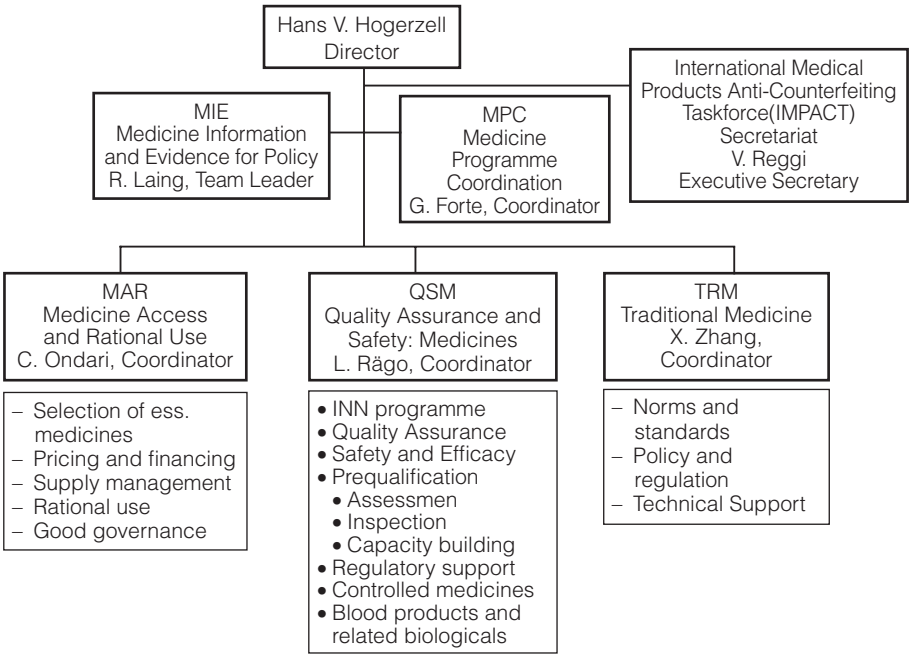
The WHO Expert Committee on Specifications for Pharmaceutical Preparations met in Geneva from 13 to 17 October 2008. Dr Hans V. Hogerzeil, Director, Department of Essential Medicines and Pharmaceutical Policies, opened the meeting, and on behalf of the Director-General of the World Health Organization, welcomed all the participants to the forty-third meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations. He expressed his appreciation of the Expert Committee for its knowledge of and expertise in the work of WHO in the area of quality assurance of medicines. Dr Hogerzeil welcomed the members of the Committee, temporary advisers and special advisers for prequalification; representatives of the United Nations Children's Fund, the Global Fund to Fight AIDS, Tuberculosis and Malaria, the International Atomic Energy Agency, World Intellectual Property Organization, the World Bank, Council of Europe/European Directorate for the Quality of Medicines and HealthCare, European Medicines Agency, International Federation of Pharmaceutical Manufacturers and Associations, International Pharmaceutical Federation and the World Self-Medication Industry; representatives of the Secretariats of the Pharmacopoeias of Brazil, People's Republic of China, Europe, Great Britain, Republic of Korea and the United States of America; as well as representatives from WHO Collaborating Centres in China, Hungary, South Africa and Sweden.

Dr Hogerzeil stressed the importance of the discussion by the Expert Committee on Specifications for Pharmaceutical Preparations of a large number of monographs for antiretrovirals, antituberculosis medicines, antimalarials, radiopharmaceuticals and other medicines.

Dr Lembit Rägo, Coordinator of Quality Assurance and Safety: Medicines (QSM), welcomed everyone to the meeting. He focused his presentation on three aspects: organizational changes, areas of collaboration and some highlights. With respect to the first he informed the Committee that the Regulatory Support Programme, which had previously been under another department, was now part of QSM. Under the new structure (see Figure 1) he said that there were seven areas of work which were interlinked, the first being the Medicines Quality Assurance Programme responsible for developing standards and norms. This programme also served as the Secretariat to the Expert Committee. The second was the International Nonproprietary Names (INN) Programme which was linked to the Quality Assurance and Prequalification Programmes and was mainly responsible for developing INN. The third was the Prequalification Programme whose main functions were assessment, inspection and capacity building. In the past donor countries had traditionally provided developing countries with medicines without consideration of building capacities for quality testing.

This meant that recipient countries had to send samples of medicines of questionable quality and with serious health consequences elsewhere for testing, which was not sustainable owing to lack of resources. However, under the Prequalification Programme, QSM had developed a strategy to build national capacity to test the quality of medicines by supporting national quality control laboratories. Currently the quality control laboratories in four countries (Algeria, Kenya, Morocco and South Africa) had been strengthened. Dr Rägo said that the Regulatory Support Programme under QSM gave regulatory technical and administrative support to strengthen the regulatory system. The Blood Products and Related Biologicals Programme, now within QSM, was linked to the Expert Committee on Biological Standardization. The remaining programme in QSM was Safety and Efficacy under which were 89 pharmacovigilance centres that were full members, and 29 associate members. There was also a WHO Collaborating Centre at Uppsala, Sweden which was governed by an international board. The Centre provided information on safety which was sometimes related to quality.

Figure 1
Essential Medicines and Pharmaceutical Policies (EMP)



Dr Rägo mentioned that another role of WHO was to assess psychoactive substances for dependence-producing liability. The Expert Committee on Drug Dependence, whose function was to undertake scientific assessment in practice, could decide to recommend scheduling of substances to the Commission on Narcotic Drugs under the international drug conventions.

He said that another activity related to QSM was the International Medical Products Anti-Counterfeiting Taskforce (IMPACT), the Secretariat for which fell under the direction of the Department of Essential Medicines and Pharmaceutical Policies.

Dr Rägo stressed that QSM collaborated well with different organizations, associations and national medicines regulatory authorities, for example, the International Conference of Drug Regulatory Authorities (ICDRA) which was organized by WHO with a different host country chosen every two years to discuss important current issues and to make recommendations. QSM also worked with national and regional pharmacopoeias (for example, the pharmacopoeias of Brazil, People's Republic of China, Europe, Great Britain, Japan, Republic of Korea and the United States of America); United Nations agencies (for example, United Nations Children's Fund (UNICEF), Joint United Nations Programme on HIV/AIDS (UNAIDS), World Intellectual Property Organization (WIPO)); professional associations such as the International Pharmaceutical Federation (FIP); and the pharmaceutical industry (for example, the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA), International Generic Pharmaceutical Association (IGPA) and the World Self-Medication Industry (WSMI)).

He emphasized that quality was still a problem. In the past donors considered price to be the main factor in pharmaceutical procurement; however, nowadays there was an awareness about the circulation of poor quality medicines and, therefore, quality was now being considered as the main factor in the procurement of medicines. Similarly, there had been denial by certain countries that they had problems with quality of medicines, but they were now taking steps to address this problem. Some donor countries focused on the fact that quality was achieved by testing quality into a product. However, quality had to be built into a product at the time of manufacture. Testing the final product alone could not assure its quality.

Dr Rägo also outlined some of the achievements of the Medicines Quality Assurance Programme since October 2007:

- the report of the forty-second meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations (WHO Technical Report Series, No. 948) was available in printed and electronic form;
- the First Supplement to the Fourth Edition of *The International Pharmacopoeia* was available in print, on CD-ROM and online.

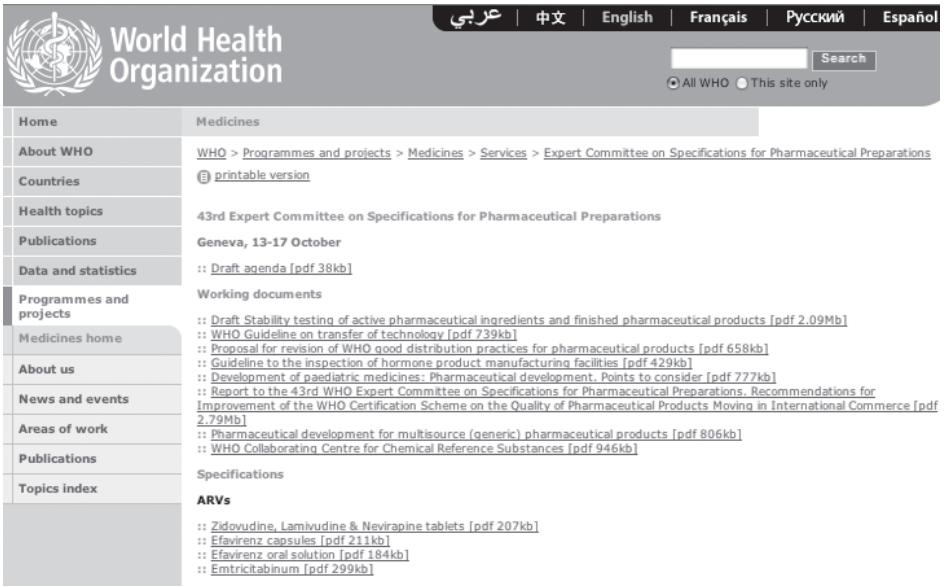
The main global quality assurance guidelines under current development were the following:

— update of procedures for prequalification of medicines;
— transfer of technology;

— global stability testing requirements for active pharmaceutical ingredients and finished pharmaceutical products;
— updates and revision of good manufacturing practices (GMP) texts;
— guidance on medicines for children;
— guidelines on the pharmaceutical development of generics.

He concluded his presentation by expressing his appreciation for the contributions made by the members of the Expert Committee and for the constructive recommendations.

Figure 2
Working documents on the WHO medicines web site



Dr Sabine Kopp**,** Secretary of the WHO Expert Committee on Specifications for Pharmaceutical Preparations, explained the administrative process of appointment of experts and the working procedures related to the Expert Committee meeting. The working documents for each Expert Committee meeting were available on the WHO medicines web site (see Figure 2). She said that the Expert Committee was an official advisory body to the Director-General of WHO and was governed through rules and procedures. The reports of the WHO Expert Committee contained a summary of the discussions, recommendations to WHO and its Member States, and included newly adopted guidelines. The report of the Expert Committee was presented to the WHO Governing Bodies for final comments, endorsement and implementation by Member States and constituted WHO technical guidance. The development of a set of WHO guidelines was mainly based on recommendations included in World Health Assembly

resolutions, Executive Board resolutions to the Director-General based on advice from experts, ICDRA, other WHO programmes and clusters or the recommendations proposed by the Committee itself.

The Expert Committee consultative process involved several steps, i.e. preliminary consultation and drafting, worldwide circulation of a first draft working document for comments, revision of the draft, discussion of the draft by the WHO Expert Committee and finally, once adopted, publication in the Expert Committee report as an annex, and submission to the WHO Governing Bodies and recommendation to Member States for implementation. Partners in the Expert Committee on Specifications for Pharmaceutical Preparations included: national and regional authorities; international organizations (e.g. UNAIDS, United Nations Population Fund (UNFPA), United Nations Children's Fund (UNICEF), the World Bank, WIPO, World Trade Organization (WTO) and World Customs Organization (WCO)); international professional associations; nongovernmental organizations (including consumer associations, Médecins sans Frontières); the pharmaceutical industry (including IFPMA, IGPA, WSMI, FIP and the World Medical Association (WMA)); members of the WHO Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations; specialists from all quality assurance-related areas, including regulatory and academic, and from the pharmaceutical industry; WHO Collaborating Centres – usually national quality control laboratories; pharmacopoeia commissions and secretariats; national institutions and institutes; and regional and interregional regulatory harmonization groups (such as the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and the Association of Southeast Asian Nations (ASEAN)).

Celebration of 60th anniversary

On the occasion of the 60th anniversary of the World Health Organization, the WHO Expert Committee on Specifications for Pharmaceutical Preparations was able to look back on its existence and activities even before that date.

The Secretary informed the members of the Expert Committee that the first meeting of this Expert Committee, named "Unification of Pharmacopoeias" at that time, was held from 13 to 17 October 1947 in the Palais des Nations in Geneva, Switzerland. The report of that meeting was issued in the Official Records of WHO (no. 8, p. 54) and was presented to the Interim Commission of WHO at its 4th session. Already at that time one of the recommendations was, inter alia, to include preparations in *The International Pharmacopoeia* that had been standardized by the Expert Committee on Biological Standardization. Two further meetings were held from 31 May to 5 June 1948 and from 15 to 23 October 1948 in the Palais des Nations. The reports from these two meetings were also published in the WHO Official Records. The 4th Expert Committee meeting was held on 20–30 April 1949. The report of that meeting constituted the very first WHO Technical Report in January 1950. Thus the Expert Committee was looking back on a history of more than 60 years!

2. General policy

2.1 Collaboration with international organizations and agencies

2.1.1 *The Global Fund to Fight AIDS, Tuberculosis and Malaria*

The Expert Committee was informed that the main objective of the Global Fund to Fight AIDS, Tuberculosis and Malaria was to allow access to and continued availability of quality-assured medicines and health products to fight AIDS, malaria and tuberculosis. The Global Fund is a financial institution and about 30% of grant funds are spent on procurement of medicines and health products. It does not conduct any procurement activities for pharmaceutical products, and the principal recipient (PR) is responsible for ensuring adherence to Global Fund quality assurance and quality control (QA/QC) requirements, following decisions of the Global Fund Board. The Global Fund's Pharmaceutical Supply and Management (PSM) policies are: to procure quality-assured products at the lowest price; to adhere to national and international laws; and to conduct procurement in a transparent and competitive manner.

The Governing Board, at its 3rd meeting held in October 2002, devised a Quality Assurance Policy which classified pharmaceuticals into multisource products and single- and limited-source products. The policy had been updated many times since then, the main revisions occurring in 2005, 2007 and 2008.

The Global Fund Quality Assurance Policy, which was currently under revision, defines multisource products as products generally off-patent and products for which quality standards were publicly available (*The International Pharmacopoeia* (Ph.Int.), *British Pharmacopoeia* (BP) and *United States Pharmacopeia* (USP)) before October 2002.

All products – single-source, multisource and limited-source – must meet criteria approved by the Board and must comply with quality standards and requirements of the national medicines regulatory authority in the recipient country.

In addition, quality assurance criteria for selection of single-source and limited-source products included a number of options starting with products prequalified by WHO (option A) and products authorized by a stringent regulatory authority (option B). Further options, currently identified as C(i) and C(ii) were part of ongoing discussions.

The percentage of prequalified products purchased with Global Fund resources had increased from 578 million units (54%) in 2006 to 2218 million units (63%) in 2007. In all cases, pharmaceutical products purchased with Global Fund resources are subject to the monitoring of product quality standards prescribed by the Global Fund. The precise testing

processes for the various categories of products made available under Global Fund resources were explained. In the quality monitoring of multisource and option A or B products, for example, the PRs must systematically draw random samples of pharmaceutical products for quality control testing to monitor compliance with quality standards. For multisource products for which public standards are available, samples should be sent to WHO-recognized laboratories in cases where the national medicines regulatory authority has no capacity for testing. For single-source or limited-source products categorized as option A products, samples should be sent to WHO-recognized laboratories participating in the WHO Prequalification Project if the national medicines regulatory authority has no capacity for testing. The use of pharmacopoeial methods (Ph.Int., BP or USP), when available, was encouraged. In cases where this was not possible, manufacturers' validated methods and specifications were to be used. Items to be tested and reported include appearance, identification, assay and impurities, dissolution or disintegration, content uniformity or weight variation, pH, microbial limits (for solution), sterility and presence of bacterial endotoxin.

The Global Fund works closely with the WHO Prequalification Programme to update and revise its quality assurance policy and to achieve its mission. It encourages the purchase of products prequalified by WHO and national medicines regulatory authorities to expedite registration of finished products purchased with Global Fund resources by accepting WHO prequalification inspection and supporting dossiers in lieu of national requirements.

Additional information about procurement can be found on the Global Fund web site: http://www.theglobalfund.org/en/.

2.1.2 *Pharmacopoeial Discussion Group*

An update on the activities of the Pharmacopoeial Discussion Group (PDG) (which consists of the European Pharmacopoeia (PhEur), Japanese Pharmacopoeia (JP) and United States Pharmacopeia (USP)) was presented to the Expert Committee. The Committee noted that the PDG met in association with the Expert Working Groups of the ICH.

Harmonization had been achieved on nine of the 11 general chapters identified by the ICH Quality Guideline entitled *Specifications: test procedures and acceptance criteria for new drug substances and new drug products: chemical substances (including decision trees)* (Q6A). Minor revisions for general chapters, in response to user comments, were signed off on "Tests for specified micro-organisms, microbial enumeration tests". In addition, PDG had signed off a minor revision of the chapter on "Bulk and tapped density".

New items for sign-off included excipient monographs on magnesium stearate, polysorbate 80 and stearic acid. Valuable input from the

pharmaceutical industry facilitated this outcome. In addition, revisions to monographs on talc, benzyl alcohol, lactose anhydrous and lactose monohydrate were signed off. At the time of the meeting of the Expert Committee, 25 of the 35 general chapters and 39 of the 62 excipient monographs had been harmonized.

The PDG considered process improvements and identified the following next steps and action items for immediate implementation: establishment of a small working group to monitor and communicate on PDG topics on a regular basis; follow-up on the PDG work programme; keeping activities on track; including selected experts in the communications as appropriate when a topic reaches an impasse or in other exceptional cases; moving towards a common online repository of PDG information and the use of up-to-date technology for the exchange of such information; and continuing to include "process improvement" as a standing agenda topic.

Interactions between PDG and the ICH Expert Working Group on "Evaluation and recommendation of pharmacopoeial texts for use in the ICH regions" (Q4B) continued to make progress.

Following recent, serious problems with heparin, the three pharmacopoeias of the PDG had all taken emergency measures to react to the safety issue; the revisions undertaken by each pharmacopoeia followed the same general direction.

At the Heparin Workshop, held on 19–20 June 2008 in Strasbourg, which was organized by the European Directorate for the Quality of Medicines and HealthCare (EDQM), the National Institute for Biological Standards and Control (NIBSC) and USP, the experience gained by official control laboratories and industries was discussed with the aim of improving the analytical test methods. The three pharmacopoeias agreed to work collaboratively to optimize their respective heparin monographs.

The Expert Committee noted the current status of Q6A general chapters. Text submitted to Q4B included "Residue on ignition", "Extractable volume", "Particulate matter", "Disintegration", "Uniformity of dosage units", "Microbial contamination", "Dissolution", "Sterility" and "Bacterial endotoxins". The PDG was proposing two chapters on colour determination (visual inspection and instrumental) and Q4B was considering the proposal.

Possible future activities of the PDG included "Analytical sieving (PDG Stage 6)", "Bulk density and tapped density (PDG Stage 6)", "Heavy metals (PDG Stage 2)", "X-ray powder diffraction (PDG Stage 6)", "Chromatography", "pH", "Spectrophotometry (including near infrared)" and "Water determination".

2.1.3 *European Directorate for the Quality of Medicines and HealthCare*

In 2007 the European Directorate for the Quality of Medicines and HealthCare (EDQM) expanded its activities to integrate those of the Council of Europe concerned with blood transfusion and organ transplantation. In 2008 further activities in the area of combating counterfeits, pharmaceutical care and definition of the legal status of medicines were transferred. As of January 2009 EDQM would also be responsible for the Council of Europe activities in the field of cosmetics and food packaging.

EDQM collaborates with WHO in a number of areas including the following.

- *The External Quality Assurance Assessment Scheme (EQAAS)* which is a proficiency testing scheme for national medicines control laboratories in the six WHO regions. The samples are prepared and the results analysed by EDQM on behalf of WHO. The fourth phase of the Scheme is in progress and studies have been completed on water determination by Karl Fischer titration, dissolution testing and high-performance liquid chromatography (HPLC) assay. The final report is awaited for study 4 on volumetric titration and samples for study 5 will be distributed at the beginning of 2009.
- *Cooperation between the Certification Unit of EDQM and sharing of information on inspections of manufacturing sites.* A WHO staff member has participated in assessing submissions for the EDQM Certification Scheme.
- *EDQM staff have contributed to various WHO workshops in quality assurance*, e.g. in Morocco for francophone African countries and in the United Republic of Tanzania for anglophone African countries in 2007. A joint EDQM/WHO workshop was also held in Vienna, Austria in 2007. WHO has been informed of and invited to send delegates to EDQM Official Medicines Control Laboratory (OMCL) workshops on quality assurance subjects.

Following the discovery of adulterated heparin on the world market, the European Pharmacopoeia Commission adopted, at its 131st Session in June 2008, a rapid revision of the heparin monographs in consultation with the manufacturers of heparin and in collaboration with other pharmacopoeias.

The Commission also instructed its Group of Experts No. 6 to further revise the monograph and to include a test for the limitation of naturally occurring contaminants such as dermatan sulfate and chondroitin sulfate at appropriate levels. In the meantime, the OMCL network, in an effort to assist the competent authorities, was conducting an interlaboratory trial with a panel of heparin samples.

2.1.4 *European Medicines Agency*

The Expert Committee noted the updates presented on the activities of the European Medicines Agency (EMEA) Inspections Sector, specifically EudraGMP (the European Community database containing information on all manufacturing and importation authorizations issued by European Economic Area (EEA) competent authorities). EudraGMP contains information on GMP certificates, which Member States issue following each GMP inspection. Information on inspections in countries outside the EEA and any inspections of active substances and certain excipients are included in this database. It is intended to also include information on non-compliance, a planning tool for GMP inspections outside the EEA and alerting mechanisms in the EudraGMP.

EEA competent authorities have full read/write access to the EudraGMP database. Access to the general public with the exception of any information of commercially and/or personally confidential nature was planned.

The Committee noted the status of various European Union GMP guidelines, for example *GMP for Radiopharmaceuticals*.

2.1.5 *International Pharmaceutical Federation*

The Committee was provided with an overview of activities on International Pharmaceutical Federation (FIP)/WHO guidelines on Good pharmacy practice (GPP) in community and hospital settings. The Committee noted that so far five publications had been produced and widely distributed: *Good pharmacy practice in community and hospital settings*; *Standards for quality of pharmacy services*; *GPP in developing countries*; *Recommendations for step-wise implementation*; and *Developing pharmacy practice: A focus on patient care*.

It was also noted that FIP had a three-year pilot project on GPP covering the period 2005–2007. The project in Moldova, Mongolia, Thailand, Uruguay and Viet Nam focused on the development of national technical groups; collaboration between WHO, pharmaceutical associations, universities and ministries of health; tailor-made programmes targeting priority needs of the profession; strengthening of existing policies, legislation, culture and strategies; and use of the FIP global network.

FIP organized a regional conference on GPP policy and plans in Bangkok on 27–29 June 2007, attended by 56 pharmacists from 15 countries representing community practice, government, academia and national pharmaceutical associations. The following six priority areas emerged:

— changing perception of the role of the pharmacist among pharmacists themselves;

— improving the quality of pharmacy practice;
— documentation and dissemination of the value and benefits of pharmacy in the supply chain for society and for the patients;
— raising public awareness of the added value of the role of the pharmacist and the pharmacy;
— the role of pharmaceutical associations and regional forums; and
— education and continuing education.

A similar conference was also organized in Yogyakarta, Indonesia in August 2008 in collaboration with the WHO Regional Office for South-East Asia and the FIP South East Asia Pharmaceutical Forum. The purpose of the conference was to review GPP implementation policy and plans. Representatives from Bangladesh, Bhutan, India, Indonesia, Maldives, Myanmar, Nepal, Sri Lanka and Thailand presented their reports at the conference.

The FIP Expert Consultation on Standards of Quality of Pharmacy Services took place on 3 September 2008 in Basel, Switzerland. Fifty invited participants representing WHO, FIP, national pharmaceutical associations and other international agencies (Management Sciences for Health, and Ecumenical Pharmaceutical Network) attended the consultation. The objectives were to: understand the background and development history of the FIP/WHO guidelines on GPP; identify key issues that needed to be considered in the revision of the FIP/WHO Guidelines on GPP; and discuss enabling factors essential for developing and implementing GPP standards in community, hospitals and other patient care settings. Key issues discussed included**:** interprofessional collaborative practice in the health care team; quality management systems of pharmacies and pharmacy practice in the community and in hospital settings; and strengthening awareness of the need for more comprehensive pharmaceutical workforce planning, especially on education and training capacity. The consultation identified a number of focus areas for further consideration.

The Committee also noted the intention of FIP to update the FIP/WHO joint document on *Good pharmacy practice in community and hospital pharmacy settings* (in: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-fifth report.* WHO Technical Report Series, No. 885, 1999, Annex 7) and looked forward to contributing to the review processes in 2009. The revised joint document would be presented to the forty-fourth meeting of the Expert Committee.

2.1.6 *United Nations Children's Fund*

The Expert Committee was briefed on the role of the Supply Division of the United Nations Children's Fund (UNICEF). The Supply Division was responsible for overseeing UNICEF's global procurement and logistics

operation, to procure supplies on behalf of UNICEF and procurement services partners, and to ensure that high quality, good value supplies reached children and their families quickly. Its role was to maintain the highest ethical standards for procurement, provide technical support to UNICEF offices and procurement services partners globally, share procurement expertise with development partners and innovate to find ever-better supply solutions for children.

UNICEF collaborates in partnership with other United Nations agencies (WHO, United Nations Population Fund (UNFPA), Office of the United Nations High Commissioner for Refugees (UNHCR), Joint United Nations Programme on HIV/AIDS (UNAIDS), UNITAID, United Nations Office for Project Services (UNOPS) and United Nations Development Programme (UNDP)), donor organizations (the World Bank, African Development Bank (ADB), the Global Fund to fight AIDS, Tuberculosis and Malaria, the Global Alliance for Vaccines and Immunization (GAVI), the Roll Back Malaria Partnership (RBM), Medécins sans Frontières (MSF), Oxfam, International Red Cross and Red Crescent Committee (ICRC)), international associations (Pharmaceutical Inspection Co-operation Scheme (PIC/S)) and universities (Columbia, USA, and Oxford, England). The total value of procured commodities for 2007 was 1.4 billion US dollars. Over 80% of goods procured were strategic commodities such as vaccines and other pharmaceuticals.

UNICEF's quality system is based on division and centre procedures which are available electronically on the UNICEF intranet. ISO 9000:2001 was to be implemented in 2008–2009. The quality system for GMP inspections is in accordance with PIC/S quality system requirements for GMP inspectorates. The WHO Model Quality Assurance (QA) system for procurement agencies is based on assessment of documentation and inspection of manufacturers for compliance with WHO GMP guidelines. The product questionnaire is the same as the one in the WHO Model QA System (WHO Technical Report Series, No. 937).

GMP inspection is carried out by UNICEF or a representative selected by UNICEF and contract manufacture is accepted only if the subcontractor is also approved by UNICEF. The objective of GMP inspection by UNICEF is to check compliance with WHO GMP guidelines. Between 2003 and 2007 UNICEF carried out 118 GMP inspections and 41 (35%) of the companies failed the inspection.

Prequalification of essential medicines is carried out in connection with an invitation to bid (ITB) by the HIV/Health Center. Companies desiring to participate in the bid are required to complete an interagency questionnaire and forward supporting documentation to UNICEF. A supply agreement is made with the company providing the "best offer" of an assured quality but

with one to two back-up suppliers. When procuring vaccines, HIV/AIDS, malaria and tuberculosis products, it is necessary for these to be prequalified by WHO and listed on the WHO web site, and suppliers have to confirm to UNICEF that products are identical to those assessed by WHO/UNICEF.

2.1.7 *World Intellectual Property Organization*

The Expert Committee was informed about the recent developments in the collaboration between the World Intellectual Property Organization (WIPO) and WHO in the field of International Nonproprietary Names (INN) for pharmaceutical products.

The issue of INNs for pharmaceutical products had been discussed several times in different forums at WIPO, by the Standing Committee on the Law of Trademarks, Industrial Designs and Geographical Indications (SCT). This forum discusses issues concerning the progressive international development of the law of trademarks, industrial designs and geographical indications, including harmonization of national laws and procedures. Participation in the SCT was open to all Member States of WIPO and to intergovernmental and nongovernmental organizations in the capacity of observers.

Discussions within the SCT had led to the conclusion that there was a need to improve the availability of the lists of INNs to industrial property offices responsible for granting requests on trademarks. As a result, several measures had been put in place in 2007 to improve the accessibility of the lists of proposed and recommended INNs by the national and regional industrial property offices of WIPO Member States. The measures taken included the distribution to all national and regional industrial property offices of WIPO Member States, by the International Bureau of WIPO, of a CD-ROM containing lists of all proposed and recommended INNs to date.

At its 19th session in July 2008, the members of the SCT continued to discuss the relationship between INNs and trademarks and shared their experience on the examination of trademark applications against conflicting INNs or versus a word containing a stem. The discussion was based on a background document which had been prepared by WHO. In addition, a WHO representative attended the session and made a presentation concerning the application of the relevant WHO resolutions relating to the non-appropriation of proposed and recommended INNs. WHO's participation at the previous session of the Committee was found to have been extremely useful, as it allowed members of the SCT to raise queries and clarify doubts, particularly over the importance of INN stems.

The major outcome of the discussion at the SCT of July 2008 was that there was still a need for better accessibility to the list of INNs for industrial property offices, inter alia those in charge of registering trademarks. It was

agreed that WIPO would continue to circulate information concerning the publication of new lists of proposed and recommended INNs by way of paper circular and, in addition, by sending an e-mail alert to all offices of SCT members and to SCT observers who had subscribed to the SCT electronic forum. Furthermore, the SCT requested the WIPO Secretariat to explore, together with WHO, the possibilities of developing a publicly-searchable database for INNs. WIPO would work with the INN Programme to look at potential ways of further improving the accessibility of the INN database for industrial property offices.

The Expert Committee was grateful for the support from WIPO for the protection of INNs and was pleased to note the progress made.

2.1.8 *The World Bank*

The Committee was provided with an update on the work of the World Bank. It noted that the strategic directions for pharmaceutical sector work at the World Bank were based on the principle "Better health outcomes through improved health systems". Consequently the pharmaceutical sector operated as part of the health system, since access to and appropriate use of medicines was an essential element of a functioning health system. Areas of interest where the health, nutrition and population (HNP) sector was in a good position to provide support were promoting availability by improving procurement, improving the supply chain, ensuring affordability by financing procurement, improving purchasing efficiency and price, improving acceptability by improving medicine regulation, promoting transparency of rules and decisions, and promoting rational prescribing and use. The support provided was based on skills available, leveraging potential by and for other activities or partnerships, areas not well covered by other agencies, high impact on outcomes and measurable results.

The pharmaceutical expert in HNP operates within the framework of general health systems development work with a focus on good governance and management practices in the pharmaceutical sector (covering financing, purchasing efficiency, pricing, selection, procurement, supply chain management and rational use of medicines). It considers public as well as private sector solutions and also provides regulatory support relevant to the above areas.

Linkage to WHO technical committees was important because the procurement of medicines under World Bank-financed projects faced capacity challenges: critical expertise on technical issues specific for pharmaceuticals was lacking in both the World Bank and its clients. It also enabled the World Bank to better understand the standards and procedures for quality assurance of medicines.

2.1.9 *International Conference on Harmonisation*

The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) brings together the regulatory authorities of Europe, Japan and the United States of America. The ICH Steering Committee and its expert working groups met in Portland, USA in June 2008. The main achievements of this meeting are outlined below.

A new guideline entitled "Development safety update reports" (E2F) was to be released for consultation. This guideline would harmonize the requirements for annual reporting of clinical trials to the regulators in the three ICH regions. This would provide an additional level of protection for patients participating in clinical trials and would facilitate work sharing among global regulators.

Pharmacogenomic biomarkers were increasingly being used to aid medicine development to support approvals of pharmaceutical products. In order to promote more rapid and efficient qualification of biomarkers, a new expert working group had been formed to develop data standards and formats for use in all the ICH regions – ICH Guideline E16: "Genomic biomarkers related to drug response: context, structure and format of qualification submissions".

A new guideline had been adopted: ICH Q10 "Pharmaceutical quality systems" which would complement existing GMP with modern quality systems elements. This guideline addresses the life-cycle of the product and the process.

Two new working groups had started their work: the Implementation Working Group Q8, 9 and 10 with the scope to facilitate a harmonized implementation of the new quality paradigm within the three regions, as defined in the three above-mentioned guidelines; and an Expert Working Group (EWG) Q11: "Development and manufacture of drug substances (chemical and biotechnological/biological entities)".

Significant progress had been made in Portland on harmonization of pharmacopoeial monographs from Europe, Japan and the USA: two documents had been finalized and four additional documents had reached step 2 for consultation.

As part of a continuing effort to disseminate ICH guidelines, the ICH Steering Committee had supported the development of a library of training materials and presentations on ICH topics. The library would be made available to the public on the ICH web site where materials from recent ICH-endorsed training events were already posted.

2.1.10 *Medicines for children*

The Expert Committee recalled the discussion held during its forty-second meeting concerning new WHO initiatives in relation to medicines for children.

The 60th World Health Assembly (WHA) in May 2007 adopted a resolution on "Better medicines for children". Article 2 of this WHA Resolution requested the Director-General: "(2) to ensure that all relevant WHO programmes, including but not limited to that on essential medicines, contribute to making safe and effective medicines as widely available for children as for adults"; and "(3) to promote the development of international norms and standards for quality and safety of formulations for children, and of the regulatory capacity to apply them".

The Executive Board at its 121st meeting approved a Subcommittee on Selection and Use of Essential Medicines to develop a list of essential medicines for children.

The Subcommittee had met twice (in July 2007 and September 2008) and the Expert Committee on the Selection and Use of Essential Medicines met in October 2007 to review the report of the first meeting. The report of that meeting (WHO Technical Report Series, No. 950) had been published and contained the first WHO Model List of Essential Medicines for Children. In developing the list the Subcommittee and Expert Committee had taken account of the priority diseases identified in the resolution and the treatment guidelines published by WHO. A number of important gaps in research and products had been identified during this process, including the need for appropriate fixed-dose combination medicines for the treatment of tuberculosis in children.

The Subcommittee for Children of the WHO Subcommittee of the Expert Committee on the Selection and Use of Essential Medicines, at its 2008 meeting, recommended that further work was needed to develop and maintain the Essential Medicines List for Children, but noted that this could be accomplished by an appropriately constituted Expert Committee rather than the Subcommittee. The report of the Subcommittee would be considered at the meeting of the Expert Committee in March 2009 and would include an updated Essential Medicines List for Children.

With respect to *The International Pharmacopoeia*, several monographs for specific paediatric formulations had already been adopted and would be included in the Second Supplement to *The International Pharmacopoeia*, 4th Edition. A number of new drafts would be discussed during this Expert Committee meeting (see WHO Technical Report Series, No. 953).

The Expert Committee recognized that dosage form monographs in *The International Pharmacopoeia* were generally designed to cover a range of strengths. In principal, therefore, they could accommodate both adult and paediatric products. Thus, where a children's medicine was developed by simply providing a lower strength of an adult formulation (e.g. a capsule, tablet or injection) which was the subject of a monograph in *The*

International Pharmacopoeia, the children's medicine would be covered by that monograph. In such cases the strength(s) available for paediatric use could be added under Additional information.

WHO was preparing a brainstorming consultation with partners on innovative paediatric formulations in preparation for a wider consultative process in this area.

WHO had launched a new initiative on 6 December 2007: "Make medicines child size". This was a global campaign spearheaded by WHO to raise awareness and speed up action to address the need for improved availability of and access to safe child-specific medicines for all children under the age of 15 years.

To achieve this goal more research was needed, more medicines needed to be developed and improved access measures were essential. At present, many medicines were not specifically developed for children nor were they available in suitable dosages or forms; those that were available often did not reach the children who needed them the most. The "make medicines child size" campaign was an effort to change that reality.

Further information could be found on the WHO web site: http://www.who.int/childmedicines/en/index.html.

During the 13th International Conference of Drug Regulatory Authorities (ICDRA) meeting held in Bern, Switzerland on 16–19 September 2008, recommendations were made which emanated from the pre-conference (see section 2.1.12).

The Expert Committee took note of the numerous activities related to medicines for children carried out in WHO, and recommended continuation of the close collaboration between the various related Expert Committees, especially between this Committee and the WHO Expert Committee on the Selection and Use of Essential Medicines and its Subcommittee on Essential Medicines for Children.

2.1.11 *Counterfeit medicines*

The International Medical Products Anti-Counterfeiting Taskforce (IMPACT) is a voluntary coalition of stakeholders that has the purpose of coordinating international activities aimed at combating counterfeit medical products. The broad spectrum of IMPACT stakeholders' mandates, roles, interests and experience reflects the fact that combating the counterfeiting of medical products cannot be successfully achieved by the health sector alone, but requires the coordinated effort and effective collaboration of the health sector, enforcement, border control, justice (at all administrative levels), as well as the private sector (manufacturers, importers, distributors, health

professionals, media, patients and consumers, and other organized groups of the civil society).

IMPACT is led by WHO, which acts as the Secretariat, to keep the focus on the public health implications of counterfeiting rather than on intellectual property-related aspects. Its outputs include recommendations, policy advice, and reference and training materials that reflect the consensus reached among IMPACT stakeholders.

To accomplish its mandate IMPACT focuses on the following five key areas:

Legislative and regulatory infrastructure. In most countries national legislation is often not equipped to deal with the extremely serious consequences of counterfeit medicines and penalties for counterfeiters are too light to act as deterrents. Stronger legislation clearly identifying counterfeiting medical products as a crime will help to empower regulators, police, customs officials and the judiciary. IMPACT stakeholders have reviewed existing legislative instruments and have developed "Principles and elements for national legislation against counterfeit medical products" covering administrative, civil and penal aspects of legislation aimed at combating counterfeit medical products. This document aims to assist Member States in establishing, complementing or updating national or regional legislation or regulation regarding counterfeit medical products. It is available at http://www.who.int/entity/impact/events/FinalPrinciplesforLegislation.pdf. The text was to be disseminated and promoted during 2008 in order to provide support to countries that wished to strengthen their legislative infrastructure.

Regulatory implementation. IMPACT stakeholders were working on ways to help national authorities to take action and implement legislative and regulatory measures on counterfeit medical products. These include a broad variety of activities such as guidance for improving control on importation, exportation and distribution of medical products; tools to assess national situations and needs; model approaches to procedures for managing cases of suspected counterfeit products; models for establishing effective exchange of information at the national and international levels; and for establishing effective coordination among health authorities, police, customs, judiciary, manufacturers, distributors and health professionals to ensure proper detection, regulation, control, investigation and prosecution. IMPACT will develop projects to help countries with weak regulatory systems strengthen them by improving collaboration and drawing from the experience, capacity and resources of all IMPACT stakeholders.

Enforcement. By working with INTERPOL, the World Customs Organization and a network of enforcement officers, the Permanent Forum on International

Pharmaceutical Crime, IMPACT aims to improve contact and mutual understanding among enforcement officials of different countries to improve coordination of operations and exchange of information. IMPACT is also a tool by which enforcement officers can establish communication with health authorities and other stakeholders. A guide to investigating counterfeiting of medical products and other pharmaceutical crimes has been prepared for IMPACT by the Permanent Forum on International Pharmaceutical Crime. The guide will be used in courses for the training of regulatory and enforcement officers. The two complementary goals that IMPACT wants to pursue with its training courses are to provide training and to contribute to creating the conditions for improved collaboration between health and enforcement authorities in this very specific area. Building on the work done by the Council of Europe's Ad hoc Group on Counterfeit Medicines, IMPACT is also developing a "Model for a network of single points of contact (SPOC)" which is aimed at facilitating operational collaboration at the international level as well as streamlining collaboration among the different national institutions and other stakeholders involved in investigating and taking proper timely action when confronted with a case of a counterfeit medical product.

WHO, INTERPOL and the Secretariat of the Association of Southeast Asian Nations have launched a collaborative project for regulatory and enforcement authorities of all countries in the Mekong subregion: Cambodia, People's Republic of China, Lao People's Democratic Republic, Myanmar, Thailand and Viet Nam. The project, based on previous experience, aims to disrupt the manufacture and trade of counterfeit antimalarial agents and antibiotics through intensified cross-border collaboration.

Technology. IMPACT is helping to disseminate information useful for assessing technologies aimed at preventing, deterring or detecting counterfeit medicinal products. This assessment takes into account cost, scalability, specific country needs and situations, feasibility and regulatory implications. This work has led to the following conclusions:

- There is no one technology that is applicable worldwide; different approaches are needed.
- In developing countries the priority is to strengthen the capacity to tackle the informal trade in medicines such as at street markets or through smuggling and other unregulated or illegal activities.
- Countries should implement technologies appropriate to their situation and give preference to those that are compatible across borders.
- Although it has been proposed as a promising solution, there are many weaknesses in radio-frequency identification (RFID) (including cost, privacy concerns and logistics throughout the distribution system). IMPACT consensus is that full implementation of RFID can only be envisaged in the distant future; as a consequence, the most realistic

alternative to enable tracking and tracing medical products along the supply chain is the use of two-dimensional barcode labels.
- The Working Group's view is that authentication of medicines should only go as far as the pharmacist and that the burden of verifying that a product is authentic must not fall on patients.

Communication. IMPACT has drawn up a communication strategy for creating awareness of the risks created by counterfeit medical products in the supply systems, supporting policy objectives and increasing the commitment of those who can influence change. Model materials have been prepared to create awareness among, and foster cooperation of, health professionals. Other materials aimed at enforcement officers are being developed.

IMPACT is assisting Member States to estimate the prevalence of counterfeit medical products and is strengthening international information networks to exchange information and issue alerts for transmission from country to country. Increased public information is essential for patients, dispensers and doctors, who have a right to know if there are suspect goods on the market, but who must also contribute to detecting counterfeits by reporting and helping to investigate suspicious cases. Special initiatives are being prepared to make Internet users aware of the risks they run when purchasing medicines from unknown sources and to alert and inform people in extremely disadvantaged areas. IMPACT's vision is that all counterfeit medical products will be eradicated from the supply chain by 2015. A communications campaign is required to create awareness and increase commitment from those who can influence change throughout the medicines supply chain. Different levels of engagement are required from the various stakeholders. This entails addressing, with specific strategies and goals, government institutions, industry (manufacturers and wholesalers), health care professionals, patients and the media. IMPACT is also working at extending to all regions the availability of the web-based Rapid Alert System developed by WHO's Regional Office for the Western Pacific.

The Committee also noted that three related events were planned before the end of 2008. An interregional meeting on combating counterfeit medical products would be held in Abuja, Nigeria in October; an IMPACT ad hoc Working Group on Counterfeit Medical Devices was to be held in Bonn, Germany in November; and the IMPACT General Meeting would be held in Hammamet, Tunisia in December. More information was available on the web site (http://www.who.int/impact/).

2.1.12 *International Conference of Drug Regulatory Authorities*

The International Conference of Drug Regulatory Authorities (ICDRA) was organized for the first time in 1980 by WHO, and was intended to promote collaboration among the national medicines regulatory authorities of WHO

Member States. The Conference was also intended to assist in coordinating the work of the various authorities and thus enhance the safety, efficacy and quality of medicines.

The 13th ICDRA was hosted by the Swiss Agency for Therapeutic Products (SwissMedic) and was held in Bern, Switzerland from 16 to 19 September 2008. More than 200 regulators from over 100 countries participated in the meeting.

The Conference followed a similar format to those of previous ICDRAs. There were plenaries addressing topics of general interest as well as workshops focusing on more specific items, two of each running in parallel. An interesting and varied programme was set up by the Programme Committee. For more detailed information, please refer to the Conference web site (www.icdra.ch).

Participation at the main Conference was restricted to representatives of national medicines regulatory authorities.

Pre-conference: better medicines for children – the way forward

The pre-conference was dedicated to the topic "Medicines for children". On the first day topics such as clinical trials in children, dosage and formulations of choice, off-label use, distribution and stability issues were on the agenda. The second day was split into two parallel tracks, one continuing on general topics regarding medicines for children, and the other looking specifically at biological medicinal products for paediatric use. Some 240 experts participated actively in this two-day meeting.

In addition to representatives from national medicines regulatory authorities, participation at the pre-conference was open to representatives from the pharmaceutical industry, nongovernmental organizations and academia.

More information on the programme, the report and the recommendations of the ICDRA can be obtained from the ICDRA web site.

2.1.13 *Regulatory support*

The Expert Committee was updated on the activities of QSM in the area of regulatory support. The mission of QSM in regulatory support was to enhance the capacity of effective national and regional regulatory systems to contribute to universal access to medicines of assured safety, quality and efficacy. Core functions included collecting and analysing evidence on the situation of medicines regulatory systems worldwide; providing support to countries and regions for strengthening medicines regulation; facilitating communication and promoting harmonization among national medicines regulatory authorities; developing and continuously improving internal

capacities and developing and maintaining comprehensive databases on national medicines regulatory authorities.

The process of country support involved assessing medicines regulatory systems to identify needs, developing institutional plans, and providing financial support and capacity building. During 2008 two training workshops had been held to promote a self-assessment tool. This tool had been used for harmonization purposes in two WHO regions. So far, 44 assessments had been performed on 40 regulatory systems with the involvement of various WHO regional offices.

In the area of country support QSM, in close collaboration with the capacity building team from the WHO Prequalification Programme and the WHO Immunization, Vaccines and Biologicals Department's Initiative for Vaccine Research, had organized training programmes to strengthen national capacities in information management, inspection, quality control laboratories and marketing authorizations, and to promote good regulatory practices by providing guidelines, tools and technical assistance.

Regional support involved provision of technical assistance to harmonization initiatives and supporting participation of regulators in harmonization meetings such as the Southern African Development Community (SADC), East African Community (EAC) and the Caribbean Community (CARICOM). The regulatory support programme also provided financial support to harmonization initiatives in Africa.

The Regulatory Support Programme had been active in promoting WHO norms and guidance and harmonization of regulatory requirements with subregional economic blocs, improving communication among national medicines regulatory authorities through networking, sharing of information and regulatory decisions (specific work on registration packages was intended for regulators).

It had also been active in reviewing the assessment tool, providing feedback on implementation of existing WHO guidance, developing training materials, developing internal procedures, developing and maintaining technical competence of regulatory staff and enhancing technical cooperation with partners and with other WHO areas.

Future work would include improving feedback and identification of needs for guidance, developing second-level guidance, establishing a pool of regulatory experts for training purposes and supporting the computerization of national medicines regulatory authorities (WHO Model System for Computer-assisted Drug Registration (SIAMED)). The programme aspired to set up a network of centres of excellence to serve as training centres, design new intervention mechanisms for supporting activities and new concepts for conducting day-to-day work. Introducing a capability maturity model approach would help to visualize the stage of development and

maturity of national medicines regulatory authorities, and to identify areas of priority support and to develop support strategies.

The work of the Programme was financially supported by the European Community. The representative of the World Bank suggested further collaboration with WHO in this area.

3. Joint session with the Expert Committee on Biological Standardization

During the meeting, a joint session was held with the Expert Committee on Biological Standardization (ECBS) at which a number of matters of common interest, set out below, were discussed.

The Expert Committee on Specifications for Pharmaceutical Preparations recommends holding a joint session with the Expert Committee on Biological Standardization again in 2009, when items of joint interest to the two Committees would be chosen for discussion.

3.1 Transition from biological to chemical assay

A paper on the transition from biological to chemical assay for the quality assurance of medicines had been discussed by both Expert Committees in October 2007. Both Committees had agreed that there was a need to develop guidance in this area and had recognized that the implications of such a transition might be complicated by the consideration of labelling and dose regimens (see also section 4.4.2 of this report).

The transition from use of a biological assay to use of a chemical assay method was an evolutionary step, based on scientific evaluation. Once the transition was completed, it was usual to use an appropriate chemical reference substance, such as an International Chemical Reference Substance, in place of the International Standard, defined in International Units (IU). This was the case, for example, for many antibiotics. At the joint meeting it was recognized, however, that once this analytical transition was complete, there might still be a need to maintain labelling of certain finished products in IU, for example, insulin and oxytocin. It was agreed that, in relevant cases, the retention of the IU should be uncoupled from the scientific considerations relating to the analytical methodology. The strength of a finished product had to be stated in the same terms as those used for the dosage. The information on the product label was intended primarily for the users of the medicine, including clinicians and patients. Changing the way the strength of a medicine was expressed had implications for patient safety, especially because of the potential for medication errors. In cases where it was deemed necessary to continue to label products in biological units for the purposes of dosage, a mechanism should be found for WHO to

maintain the IU. This might be done, for example, by providing an official WHO statement of the equivalence between weight and unitage.

It was recommended that an informal consultation with participants from both Expert Committees should be convened to consider the provision of:

— guidance (in the form of a flexible framework) for managing future transitions;
— clarification concerning product labelling for the small number of long-established hormones, such as insulin and oxytocin, for which the analytical transition was complete or nearing completion.

It was further suggested that interested parties and stakeholders should be consulted prior to any decision being taken, especially regarding changes in labelling.

3.2 International Nonproprietary Names

A review of the work plan and progress of the Programme on International Nonproprietary Names (INN) was presented. An increasing number of applications for naming biologicals was being received and additional advice in this area was now available. New stems had been added to those used in the selection of INNs including –cept for receptor molecules, native or modified (a preceding infix should designate the target). An INN Working Group on Nomenclature for Monoclonal Antibodies (mAb) was held in October 2008 and the draft recommendations of this meeting were presented. The work related to the INN Programme was a good example of close collaboration between the two WHO Expert Committees, the World Intellectual Property Organization (WIPO) and the World Customs Organization (WCO). Information available on the INN web site and in the INN Cumulative List on CD-ROM was outlined (see also section 15.2 of this report for more details).

3.3 Quality assurance – good manufacturing practices for biologicals

The two Expert Committees endorsed collaboration in the area of quality assurance. In order to define a strategy for revision of good manufacturing practice (GMP) in the field of biologicals, a series of workshops assembling regulators and manufacturers of biological products had been conducted to gather information on the users' needs for the interpretation and implementation of GMP (see also section 7.1 for more details).

3.4 Quality control parameters and their relevance to International Standards

A presentation was given on the relevance of quality control parameters to meeting the WHO International Standards for biologicals. A number of

parameters were controlled during filling, as set out in the *Recommendations for the preparation, characterization and establishment of international and other biological reference standards*. Studies had been performed (document WHO/BS/08.2096) to investigate the effects of formulation, drying time and residual oxygen on rates of degradation. The recommendation of less than 1% residual oxygen might be over-cautious and further studies had been initiated. Drying to a low residual dry weight appeared to be correlated with high residual moisture and also led to problems with the nature of the cake of material obtained. Optimal selection of the formulation and freeze-drying cycle might be equally important for ensuring long-term stability. Filling under "clean" conditions was sufficient for reference materials and full aseptic manufacture was considered unnecessary. Problems with sterility usually arose from the quality of the material for filling rather than the process itself. The introduction of newer, non-destructive methods, such as near infrared for determining moisture and laser infrared for oxygen content should offer useful control of quality.

3.5 Pharmaceutical cold chain – distribution of temperature-sensitive vaccines

Satisfactory distribution of vaccines that are sensitive to temperature was a key factor in ensuring that vaccination programmes achieved their objectives. Although a number of documents addressing this topic from the perspectives of both pharmaceuticals and biologicals were available, most originated from industry (including the food industry). The absence of guidance from a regulatory perspective was seen as a gap to be filled. A task force had been established by WHO, its members drawn from countries in many of WHO's Member States, together with a secretariat from Quality Safety and Standards (QSS), Quality and Safety: Medicines (QSM) and regional offices, to review existing documents, identify overlapping and conflicting areas and aspects that were missing. The intention was to draw up guidance on minimum recommendations, particularly for handling and distribution of temperature-sensitive vaccines, for review by the Expert Committee on Biological Standards in 2009 and subsequent publication.

4. Quality control – specifications and tests

4.1 The International Pharmacopoeia

The Committee was pleased to note that the First Supplement to the Fourth Edition of *The International Pharmacopoeia* had recently been published in both book form and electronically (as a replacement for the CD-ROM of the 4th Edition and via a link on the Medicines web site: http://www.who.int/phint), and that work was under way on the Second Supplement. The monographs adopted by the Expert Committee in October 2007 were ready

for inclusion in the Second Supplement; the final texts of these monographs were already available on the WHO Medicines web site (http://www.who.int/medicines/publications/pharmacopoeia/overview/en/index.html). The final texts for the monographs adopted during this meeting would be made available once the editorial work was completed.

4.2 Current work plan and future work programme

The Committee noted the good progress that had been made with respect to the current work plan as well as the update highlighting the remaining monographs. Responding to the new programme that had been agreed by the Expert Committee in October 2007, this Expert Committee endorsed the proposal to give high priority to a first group of six active pharmaceutical ingredients (APIs) and 36 dosage forms as listed below. This list focused in particular on high priority medicines for children and included items from the first List of Essential Medicines for Children (October 2007), from WHO guidelines (for example, for the Integrated Management of Childhood Illness) and those identified by UNICEF. The Committee believed that awarding priorities in this way reflected the needs of WHO programmes and of partner organizations. Such collaboration inside and outside WHO was important in order to meet WHO's goals with respect to the health of children, especially in developing countries.

New work programme

Analgesics, antipyretics

— paracetamol oral solution/suspension
— morphine oral solution

Anti-epileptics

— carbamazepine oral liquid
— chewable carbamazepine tablets
— phenobarbital oral liquid
— phenytoin oral liquid
— chewable phenytoin tablets
— valproic acid oral liquid
— crushable valproic acid tablets

Anti-infective medicines

Antibacterial agents

— amoxicillin oral suspension
— ceftriaxone sodium
— ceftriaxone injection
— doxycycline dispersible tablets

— levofloxacin
— levofloxacin tablets
— sulfamethoxazole/trimethoprim tablets
— sulfamethoxazole/trimethoprim injection
— sulfamethoxazole/trimethoprim oral liquid

Antiprotozoal, antifungal and antimycobacterial agents

— fluconazole
— fluconazole capsules
— fluconazole injection
— fluconazole oral liquid
— metronidazole oral liquid
— pyrimethamine tablets

Anthelminthics

— albendazole chewable tablets
— ivermectin
— ivermectin tablets
— levamisole tablets
— pyrantel chewable tablets
— pyrantel oral liquid

Oral rehydration therapy: zinc supplementation

Further to the adoption of monographs for zinc sulfate and the associated dosage forms, UNICEF had expressed interest in specifications for equivalent dosage forms containing one of the other soluble zinc salts (acetate or gluconate):

— zinc acetate
— zinc gluconate
— paediatric zinc acetate tablets
— paediatric zinc acetate oral solution
— paediatric zinc gluconate tablets
— paediatric zinc gluconate oral solution

Vitamin A deficiency

UNICEF had expressed interest in pharmacopoeial specifications for oral dosage forms containing retinol concentrate, oily form. Vitamin A supplementation was supported by several initiatives of WHO and partner organizations:

— retinol capsules
— paediatric retinol oral solution

Large-volume parenterals

— glucose intravenous infusion
— sodium chloride intravenous infusion
— sodium chloride and glucose intravenous infusion.

4.3 Specifications for medicines, including children's medicines

The members of the Committee were reminded that the clearly-defined steps followed in the development of new monographs (see Box 1) were available on the WHO Medicines web site. In addition a "schedule for the adoption process" outlining the development history of a draft monograph was included in each working document circulated for comment. After adoption of a text presented to the Expert Committee, all changes agreed during the discussion leading to adoption were incorporated by the Secretariat together with any editorial points. Where necessary, the Secretariat was also requested to take account of any further comments that might still be received owing to comment deadlines for recirculated texts (Step 12 and beyond) falling shortly after the meeting. In all cases the Secretariat confirmed the amended text by correspondence with the relevant experts or collaborating laboratory before making it available on the WHO Medicines web site. These "final texts" were included on the web site to provide users, such as prequalification assessors and manufacturers, with the approved specifications in advance of the next publication date. The "final texts" on the web site for the monographs adopted at the October 2007 meeting, for example, were prefaced with the following wording:

"This monograph was adopted at the Forty-second WHO Expert Committee on Specifications for Pharmaceutical Preparations in October 2007 for addition to the 4th Edition of *The International Pharmacopoeia.*

The Expert Committee strongly endorsed the steps taken by the Secretariat to ensure wide consultation and transparency during monograph development and to make the adopted texts available in a timely manner. As noted during discussion of the work programme, provision of monographs in *The International Pharmacopoeia* provided the quality dimension for the medicines (included on the basis of efficacy and safety) in the WHO Lists of Essential Medicines and in WHO treatment guidelines. As emphasized by a number of speakers during the meeting, major WHO programmes, such as Prequalification (funded by the Bill & Melinda Gates Foundation and UNITAID) and others funded or managed by partner organizations such as UNICEF and the Global Fund to fight AIDS, Tuberculosis and Malaria, relied heavily upon the quality specifications of *The International Pharmacopoeia*. The Committee was pleased to note that, in addition to the monographs for which a text was presented at this meeting, the development of a number of other texts was in progress as indicated on the WHO Medicines web site.

Box 1. Steps followed in the development of new monographs

- Step 1: Identification of specific pharmaceutical products for which quality control (QC) specifications need to be developed, confirmation by all WHO parties concerned (including Department of Essential Medicines and Pharmaceutical Policies (EMP), specific disease programmes and the Prequalification Programme).
- Step 2: Provision of contact details from manufacturers of the above products in collaboration with all parties concerned.
- Step 3: Contact manufacturers for provision of QC specifications and samples.
- Step 4: Identify and contact QC laboratories for collaboration in the project (2–3 laboratories depending on how many pharmaceutical products have been identified in Step 1).
- Step 5: Prepare the contract for drafting the specifications and undertaking the necessary laboratory work.
- Step 6: Search for information on QC specifications available in the public domain.
- Step 7: Conduct laboratory testing, development and validation of QC specifications.
- Step 8: Support WHO Collaborating Centre in the establishment of International Chemical Reference Substances.
- Step 9: Follow the consultative process, mailing of draft specifications to Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations and other specialists.
- Step 10: Discussion of comments with contract laboratories, WHO Collaborating Centres, and additional laboratory testing to verify and/or validate specifications.
- Step 11: Consultation to discuss the comments and test results received as feedback.
- Step 12: Recirculation for comments.
- Step 13: As Step 10.
- Step 14: Present the drafts to the WHO Expert Committee on Specifications for Pharmaceutical Preparations for possible formal adoption; if not adopted, repeat Steps 11–13 as often as necessary.

4.3.1 *Medicines for HIV and related conditions*

The following monographs were adopted subject to minor modifications and inclusion of comments.

API:

— emtricitabine

Dosage forms:

— efavirenz capsules
— efavirenz oral solution
— zidovudine, lamivudine and nevirapine tablets.

The following monographs were adopted subject to minor modifications and inclusion of comments and to final written confirmation from the members of the Expert Committee by correspondence:

— nevirapine tablets
— nevirapine oral suspension
— nevirapine (as a consequence of the preparation of new monographs for dosage forms).

4.3.2 *Antimalarial medicines*

The following monographs were adopted subject to minor modifications and inclusion of comments:

Dosage forms

— artemether and lumefantrine oral suspension
— chloroquine sulfate oral solution
— quinine sulfate tablets.

The Committee was pleased to note that the development of a number of other monographs was in progress, for example, for amodiaquine hydrochloride tablets, as well as the revision of the monographs for artemisinin derivatives (see 4.4.3).

4.3.3 *Antituberculosis drugs*

The following monographs were adopted subject to minor modifications and inclusion of comments:

API

— cycloserine

Dosage forms

— cycloserine capsules
— ethambutol hydrochloride tablets (revision of published monograph).

4.3.4 *Other medicines*

The following monographs were adopted subject to minor modifications and inclusion of comments:

APIs

— mebendazole (revision of published monograph)
— oseltamivir phosphate

Dosage form

— chewable mebendazole tablets (revision of published monograph for mebendazole tablets).

4.4 Revision of texts of The International Pharmacopoeia

4.4.1 *Heparin*

The Committee was aware that, since February 2008, national medicines regulatory authorities (NMRAs) and WHO had issued international alerts, warning letters to health professionals and information about recalls regarding contaminated heparin sodium injections.

As noted in section 2.1.2, the PDG initiated discussions among experts and their decision-making bodies on how best to improve the test specifications to enable users to test for contamination of the finished products and starting materials concerned. In the meantime they had carried out a rapid revision of the monographs in their respective pharmacopoeias.

The Expert Committee agreed that the corresponding amendments should be made to the relevant monographs in *The International Pharmacopoeia*. These amendments would be published in the Second Supplement to the Fourth Edition and in the interim would be made available in this report and on the WHO Medicines web site. The following wording was adopted for the monographs for heparin calcium and heparin sodium:

Additional information. *Amend to read*:

> **"Additional information.** Heparin calcium/sodium is moderately hygroscopic."

Add the following section after Definition:

> **"Manufacture.** Heparin calcium/sodium is prepared from the lungs of oxen or from the intestinal mucosa of oxen, pigs or sheep. *All stages of production and sourcing are governed by a suitable quality assurance system.*
>
> The method of manufacture is designed to minimize or eliminate microbial contamination and substances lowering blood pressure *and to ensure freedom from contaminants such as over-sulfated glycosaminoglycans. The method is validated inter alia to demonstrate that, if tested, the substance would comply with the following tests.*
>
> ***Nuclear magnetic resonance spectrometry.*** *The ^{1}H NMR spectrum obtained with a frequency of at least 300 MHz complies with the specifications approved by the appropriate national or regional regulatory authority.*
>
> ***Capillary electrophoresis.*** *The electrophoretogram obtained complies with the specifications approved by the appropriate national or regional regulatory authority."*

The Expert Committee also adopted the following addition to the first paragraph of the General Notice on General requirements:

The requirements in monographs have been designed to provide appropriate control of potential impurities rather than to provide against all possible contaminants or adulterants. Material found to contain a contaminant or adulterant not detectable by means of the prescribed tests is not of pharmacopoeial quality if the nature or amount of the foreign substance found is incompatible with good manufacturing or good pharmaceutical practice.

4.4.2 *Antibiotics*

As agreed by the Expert Committee, the Secretariat was carrying out a review of those monographs for antibiotics which specified a microbiological assay with the aim of replacing this method by a chromatographic method, where possible. This was in line with the transition from biological to chemical assay (see also section 3.1). Priority had been given to those antibiotics for which the relevant biological reference material had been disestablished, since revision of these texts was urgent.

The International Standards/Reference Preparations necessary to support a microbiological assay and to define an International Unit (IU) for a number of antibiotics had been discontinued during recent years. For example, the first International Standard for amikacin (50600 IU/ampoule), established in 1953, was discontinued in 2001 (at the 52nd meeting of the Expert Committee on Biological Standardization; WHO Technical Report Series, No. 924).

The European Directorate for the Quality of Medicines & HealthCare (EDQM) was now responsible for the WHO International Standards for Antibiotics (ISA) for those antibiotics for which there was still a need for microbiological assay. There was no entry in the relevant EDQM online database for amikacin, amikacin sulfate, chlortetracycline hydrochloride, doxycycline hyclate, oxytetracycline, paromomycin, tetracycline and tetracycline hydrochloride for which the monographs in Volume 1 of the Fourth Edition of *The International Pharmacopoeia* specified a microbiological assay.

The Expert Committee agreed that these monographs should be revised to replace the biological assay with high-performance liquid chromatography (HPLC). It was noted that a revised monograph for doxycycline hyclate, in which reliance was placed on a liquid chromatographic assay, had recently been published in the First Supplement.

For the tetracyclines the Secretariat would prepare draft revisions based on established pharmacopoeial methods; these texts would be circulated in accordance with the usual consultative procedure. Further laboratory work would be needed, however, for amikacin, amikacin sulfate and paramomycin.

4.4.3 *Antimalarials: artemisinin derivatives*

Monographs for artemisinin and derivatives (artemether, artemotil, artenimol and artesunate and their respective dosage forms) had first been published in 2003 in Volume 5 of the Third Edition of *The International Pharmacopoeia*. Members recalled that certain aspects of these monographs were revised before inclusion in the Fourth Edition. They appreciated that, since publication of the Fourth Edition, the WHO Secretariat had focused resources on the development of new monographs for the fixed-dose combination preparations in line with WHO policy for combination therapy for malaria. Monographs for lumefantrine and for artemether and lumefantrine tablets had been adopted by the Expert Committee in 2007 and the monograph for artemether and lumefantrine oral suspension at this meeting (see section 4.3.2). While monotherapy was no longer prescribed, the monographs for the monocomponent dosage forms were still relevant since single-component tablets could be co-packaged to provide combination therapy.

The Expert Committee was informed that, owing to the importance of the published monographs for the APIs and the monocomponent dosage forms and their wide usage, a large amount of user feedback and comments had been received from, for example, the WHO External Quality Assurance Assessment Scheme, WHO Prequalification assessors and inspectors, national quality control laboratories and especially manufacturers. It was clear from the comments received and from the development work carried out on the new monographs that further revision of the published monographs was needed, in particular with respect to the chromatographic tests for Related substances and Assay. The Expert Committee, therefore, recommended that the Secretariat, in liaison with the collaborating laboratory, should review all the comments received and prepare a document to be circulated for comment, which covered all the monographs.

Members commented that the feedback received on these monographs demonstrated not only the importance of the quality specifications published in *The International Pharmacopoeia* but also the interdependence and the constructive dialogue between the various components of the overall quality assurance system supported by WHO and its partners.

4.4.4 *Excipients*

Following up on previous Expert Committee recommendations, the WHO Secretariat had looked into the revision of the excipients monographs included in *The International Pharmacopoeia*.

A preliminary review was discussed during an informal consultation on specifications for medicines and quality control laboratory issues held in June 2008. The participants at that consultation had noted the efforts to revise monographs of *The International Pharmacopoeia* in line with

Expert Committee recommendations, by consulting PDG-"harmonized" monographs and methods. They further recognized that a major challenge lay in the general methods being different. In addition, in the different pharmacopoeias, the functionality tests were included as requirements or as recommendations. It was also noted that many of the PDG excipients monographs were harmonized by attribute and that the PDG parties might in future make additional efforts towards full harmonization.

It was noted that the Secretariat had held a meeting with representatives of the International Pharmaceutical Excipients Council (IPEC) and was currently awaiting their feedback regarding a proposal for setting priorities for the existing *International Pharmacopoeia* monographs.

The Expert Committee recommended that in continuing this process of revising the excipients monographs included in *The International Pharmacopoeia*:

— the WHO Secretariat should closely monitor recent efforts by PDG parties towards full harmonization of the PDG "signed-off" excipients monographs; and
— the WHO Secretariat should collaborate with IPEC towards priority setting and harmonization when revising the existing monographs.

4.5 General monographs for dosage forms and associated method texts

The Expert Committee noted that the revision work on general monographs for dosage forms and associated method texts was continuing but that, as yet, texts were not available for discussion.

4.6 Radiopharmaceuticals

WHO and the International Atomic Energy Agency (IAEA), a specialized agency of the United Nations system, had been working jointly on specifications for radiopharmaceuticals since 2001. Following consultation and discussion, it had been agreed that this work would include inter alia revision of the general monograph in *The International Pharmacopoeia* and the preparation of monographs for individual radiopharmaceuticals. The representative from IAEA informed the Committee that Article II of the Statutes of the IAEA stated that: "The Agency shall seek to accelerate and enlarge the contribution of atomic energy to peace, health and prosperity throughout the world". He explained that the quality of radiopharmaceuticals was important for accuracy of diagnosis and reproducibility of quantitative data from nuclear investigation. Quality was also an important determinant of safety (with respect to both pharmaceutical and radiation aspects). He emphasized that what was needed by the international community was a set of individual monographs for medically relevant radiopharmaceuticals.

There was a sense of urgency to review, update and compile individual monographs at an international level. Having outlined the joint work carried out since October 2007, he concluded by saying that IAEA appreciated the excellent support from the WHO Secretariat and from the Expert Committee.

The Committee took note of the extensive collaborative work that had been carried out by WHO and IAEA since the presentation at the Expert Committee meeting in October 2007 of the texts circulated for comment. This included an informal meeting between WHO and IAEA in March 2008 during which all technical comments received had been considered and agreement reached on the structure and format of the texts. Discussion had also taken place at the informal consultation on specifications for medicines and quality control laboratory issues in June 2008. The Expert Committee agreed that radiopharmaceuticals were unique medicines containing radioisotopes which were used in major clinical areas for diagnosis and/or therapy. It recognized the importance of providing specifications in *The International Pharmacopoeia* for this special category of pharmaceutical preparation and noted that the individual preparations were those to which priority had been awarded by IAEA in 2005.

4.6.1 *General monograph and related texts*

It was noted that the WHO Secretariat had remodelled the general text as presented in October 2007. In so doing the Secretariat had endeavoured to conform to a pharmacopoeial monograph approach, while taking due account of the special nature of radiopharmaceuticals. Following the discussion with IAEA in March 2008 three separate documents had been prepared and discussed at the informal consultation on specifications for medicines and quality control laboratory issues held in June 2008.

The agreed changes had been made and the texts sent out again to relevant WHO and IAEA experts for further comments and confirmation of the technical content. Revised texts had been prepared, taking into account the comments received.

The following texts were adopted subject to minor modifications:

— general monograph
— methods of analysis
— supplementary information.

4.6.2 *Individual monographs*

In parallel with the development of the general texts, a set of 30 individual draft monographs for radiopharmaceutical preparations had been presented

in October 2007. It was noted that to facilitate the adaptation of these texts to the format and style of *The International Pharmacopoeia*, the WHO Secretariat had prepared a "skeleton text" using one of the draft monographs as an example to indicate the format, layout and editorial style that would be used. During the discussion with IAEA in March 2008, certain general points had been agreed concerning the content, format and style of the monographs. The WHO Secretariat had then begun the process of revising the individual texts. A number of revised draft monographs had been prepared and discussed at the informal consultation in June 2008.

The agreed changes had been made to these texts and the relevant texts sent to WHO and IAEA experts for further comment and confirmation. Revised texts had been prepared taking into account the comments received.

The following monographs were adopted subject to minor modifications:

— fludeoxyglucose (^{18}F) injection
— gallium citrate (^{67}Ga) injection
— technetium (^{99m}Tc) pentetate complex injection
— sodium pertechnetate (^{99m}Tc) injection (fission).

The following monographs were adopted subject to minor modifications and final confirmation by IAEA:

— iobenguane (^{123}I) injection
— sodium iodide (^{131}I) injection
— sodium iodide (^{131}I) solution
— sodium pertechnetate (^{99m}Tc) injection (non-fission)
— thallous chloride (^{201}Tl) injection.

As a result of the extensive work in collaboration with IAEA and of the need for *International Pharmacopoeia* specifications, the following monographs were also adopted subject to final scrutiny of the reformatted texts by a small working group composed of experts from both WHO and IAEA:

— iobenguane (^{131}I) injection
— samarium ethylene diamine tetramethylene phosphonate complex (^{153}Sm) injection
— sodium iodide (^{131}I) capsules
— sodium iothalamate (^{125}I) injection
— sodium phosphate (^{32}P) injection
— strontium chloride (^{89}Sr) injection
— technetium (^{99m}Tc) bicisate complex injection
— technetium (^{99m}Tc) exametazime complex injection
— technetium (^{99m}Tc) labelled macrosalb (^{99m}Tc MAA) injection
— technetium (^{99m}Tc) mebrofenin complex injection

— technetium (^{99m}Tc) mertiatide injection
— technetium (^{99m}Tc) methylene diphosphonate (MDP) complex injection
— technetium (^{99m}Tc) nanocolloid injection
— technetium (^{99m}Tc) pyrophoshate tin complex injection
— technetium (^{99m}Tc) sestamibi complex injection
— technetium (^{99m}Tc) succimer complex injection
— technetium (^{99m}Tc) sulfur colloid injection
— technetium (^{99m}Tc) tetrofosmin complex injection
— technetium (^{99m}Tc) tin colloidal injection
— yttrium silicate (^{90}Y) colloid injection.

The Expert Committee noted that further draft individual monographs were in preparation by IAEA; once received these would be circulated for comment in the usual way. Meanwhile, it was agreed that further consideration needed to be given to how quality specifications for technetium (^{99m}Tc)-labelled red blood cells might best be provided. A draft text for this radiopharmaceutical preparation had been one of the 30 included in the document presented in October 2007. This diagnostic radiopharmaceutical preparation was, however, prepared from an autologous sample of whole blood. Neither this starting material nor any blood products were currently included in *The International Pharmacopoeia*. Such materials were normally the responsibility of the Expert Committee on Biological Standardization or were dealt with through the Blood Regulators Network for which WHO provided the Secretariat.

5. Quality control – International Reference materials (International Chemical Reference Substances and International Infrared Reference Spectra)

5.1 Annual reports of the WHO Collaborating Centre

The Committee noted with appreciation the work of the WHO Collaborating Centre for Chemical Reference Substances as presented in its report for 2007. It was noted that the number of International Chemical Reference Substances (ICRS) distributed from the Centre in 2007 was 2332 which was an increase from the 1579 reported in 2006. The most frequently requested substances included artesunate, artemether, artemisinin, efavirenz and prednisolone.

The Expert Committee adopted the report for 2007 and noted the further progress made in 2008. In particular it was pleased to note that the analytical work had recently been completed for the reference substance needed to support the newly adopted monograph for oseltamivir phosphate. It emphasized that the work carried out by the Centre was essential to support the monographs of *The International Pharmacopoeia* and expressed its appreciation of the continuing support of the Government of Sweden. Annex 1 included the 2007

list of all ICRS available from the Collaborating Centre (see the Centre's web site for the current list: http://www.apl.apoteket.se/who).

5.2 Adoption of new International Chemical Reference Substances

Seven International Chemical Reference Substances were established in 2007, including the following five new substances:

— abacavir sulfate for system suitability
— amoxicillin trihydrate
— lamivudine for system suitability
— norethisterone enantate
— zidovudine impurity B

and the following replacements:

— levothyroxine sodium
— paracetamol.

The Expert Committee adopted the above ICRS.

5.3 International Infrared Reference Spectra

The Expert Committee noted that 125 reference spectra prepared by the Collaborating Centre had been included in the First Supplement to the Fourth Edition of *The International Pharmacopoeia* and that so far 30 additional reference spectra were available for inclusion in the Second Supplement. As noted at the forty-second meeting of the Committee, adoption of an ICRS included adoption of the relevant infrared reference spectrum as presented in the relevant analytical report. Thus the spectra to be published in the Second Supplement had already been adopted. The Expert Committee, therefore, endorsed their publication.

6. Quality control – national laboratories

6.1 External Quality Assurance Assessment Scheme

With a view to continuing the promotion of quality assurance in pharmaceutical quality control laboratories in WHO Member States, four test series in phase 4 of the proficiency testing scheme had taken place, with the fifth and final procedure still to be carried out. Some 50 laboratories from all six WHO regions were currently participating in the Scheme.

This External Quality Assurance Assessment Scheme (EQAAS) aimed to give each laboratory the opportunity to measure its performance through a confidential system of testing of blind samples and to determine its ability to perform a given analytical procedure within a network of governmental control laboratories.

In this fourth phase, performance was being evaluated in the five following analytical procedures:

— titration
— water content by Karl-Fischer titration
— dissolution test
— determination of glucose by polarimetry
— HPLC assay.

The Expert Committee discussed mechanisms to promote continuous improvement of the performance of the laboratories and recommended inclusion of standardized protocols, communication via an established web site or discussion forum, capacity building and educational opportunities. The Committee considered that it might be helpful if these suggestions could be implemented on a regional basis in order to enhance the collaboration of the laboratories.

The Committee was informed that increased capacity building was being included in the new activities relating to prequalification of quality control laboratories (see section 12).

The WHO Secretariat informed the Expert Committee that workshops had been held with participants from more than 20 WHO Member States, which had been organized in collaboration with the WHO Regional Offices for Africa and for the Eastern Mediterranean and with EDQM, namely in Morocco and in the United Republic of Tanzania. Additional training programmes were also being held in the WHO Region for the Americas.

The Committee noted the final reports on the first and second tests and the preliminary reports on the third and fourth tests carried out in phase 4 of the Scheme. The test results obtained when performing the water determination by Karl-Fischer titration seemed to show an improvement compared to the results of the previous proficiency testing scheme.

During the course of the past year three further test series had been completed. The final report (of the first and second series) and the preliminary reports (of the third series) were included in the documentation provided at the meeting of the Expert Committee. The fourth series had just been completed and an oral update was given. The results of the second and third test series had been discussed during the informal consultation on specifications for medicines and quality control laboratory issues in June 2008.

The participants took note of the following results.

Second series on dissolution testing (isoniazid tablets). In general the results were good; the large majority of the laboratories reported satisfactory results.

Third series on assay of tablets by liquid chromatography (zidovudine and lamivudine tablets). In general the results reported were very good. Taking both substances together, 88% (37 out of 42) of the laboratories reported satisfactory results.

Fourth series on assay by titration on quinine dihydrochloride injections. A preliminary report given orally showed that 46 out of 49 laboratories had reported satisfactory results.

The Committee recognized that many partners – as well as the national quality control laboratories actually participating – were directly and indirectly involved in this external assessment scheme, including WHO Collaborating Centres, UNICEF, colleagues in the Prequalification Programme, and WHO regional and country offices. It expressed thanks both to UNICEF for the provision of samples and to the WHO Collaborating Centre in Sweden for the provision of ICRS. Furthermore it recommended that the WHO Secretariat take actions:

— to foresee the need for extra samples for additional quality assurance investigations in a future phase;
— to study further the available alternatives when deliveries of samples were hampered by customs and/or other national challenges;
— to trigger a fast-track revision process when an *International Pharmacopoeia* specification used within the Scheme could be improved; and
— to consider adding key questions to trigger additional feedback from the participating quality control laboratories on performances.

The Expert Committee reinforced the need for:

— training using "hands-on" workshops to enhance the effects of the EQAAS; and
— a link with capacity projects.

In view of the positive impact and feedback regarding this WHO External Quality Assurance Assessment Scheme for national quality control laboratories, the experts strongly recommended that the Secretariat prepare a new phase to continue this most useful activity once the fifth test series had been finalized.

6.2 WHO good practices for national quality control laboratories

The WHO Expert Committee adopted in its thirty-sixth report in 1999 a revised version of the *WHO Good practices for national pharmaceutical control laboratories* (WHO Technical Report Series, No. 902, 2002, Annex 3) (http://whqlibdoc.who.int/trs/WHO_TRS_902.pdf#page=37).

During the inspections carried out when prequalifying laboratories, the inspectors had noticed that some of the text of these guidelines might benefit from improvement and clarification.

Within the procedure for prequalification of a quality control laboratory, compliance with the following WHO standards was assessed:

— good practices for national pharmaceutical control laboratories (GPCL);
— good manufacturing practices (GMP) as recommended by WHO for such laboratories.

The relevant WHO standards are published under the title *WHO good manufacturing practices: main principles for pharmaceutical products*. 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.

Inspectors found that laboratories traditionally did not consult the GMP guide. To facilitate the implementation of WHO standards in practice and the inspections and audits carried out in accordance with the prequalification procedure for quality control laboratories, it was deemed useful to add the most important parts directly to the GPCL guidelines and to add references to the relevant part of the GMP guide.

In considering the possible improvement of the guidelines, the following activities were carried out:

— review of observations made in laboratories during inspections, in particular repeatedly occurring deficiencies in several laboratories;
— review of references indicating the clauses from the guides relevant to the observation in question, as provided by inspectors during inspections; and
— detailed comparison of GPCL with ISO 17025.

Based on these reviews, the following areas were identified in which amendment or clarification could help laboratories to improve the implementation of WHO standards in practice:

— control of documentation and document changes;
— internal audits;
— corrective and preventive measures;
— cleaning procedure;
— qualification of equipment;
— purchasing services and supplies; and
— subcontracting of tests.

According to the title, the WHO guidelines on *Good practices for national pharmaceutical control laboratories* were mainly pertinent to national

quality control laboratories, indicating that similar principles would also be applicable to pharmaceutical quality control laboratories. However, the prequalification procedure was open for any laboratory (private, governmental or nongovernmental). In the future, therefore, to avoid confusion, it was considered that it would be useful to make the guidelines more generally applicable, to modify the title accordingly and stress the specifics of national quality control laboratories within the guidance text.

Once the GPCL guidelines have been revised, the guidelines for preparing a laboratory information file (WHO Technical Report Series, No. 917, 2004, Annex 5) should also be revised accordingly.

In light of the above, the Committee recommended that the WHO Secretariat initiate the process of revision of these good practices.

7. Quality assurance – good manufacturing practices

7.1 Good manufacturing practices for biologicals

The Committee supported collaboration between the two Expert Committees (Specifications for Pharmaceutical Preparations, and Biological Standardization) in the area of GMP for biologicals.

The Committee was informed that, in order to define a strategy for the revision, a series of workshops assembling regulators and manufacturers of biological products had been conducted to gather information on the users' needs for the interpretation and implementation of GMP. Based on a gap analysis, it was recommended that a biologicals-specific core section should be provided, in which the requirements common to all biologicals would be covered, and that a series of technical appendices covering specific topics would then be added as necessary.

The core set of requirements would include the procurement of biological starting materials; avoiding contamination of products through facility design, validation and qualification of inherently variable biological processes; stability concerns for labile biological materials; quality control and quality assurance for biological products; risk analysis tools for biological processes; and procedures for inspection of manufacturers of biologicals.

The Committee was reminded that the WHO GMP for biologicals was used for prequalification by the WHO Immunization, Vaccines and Biologicals Department. An oral update was given.

The Expert Committee took note of this update.

The new text was planned to be used in connection with the other WHO good practices adopted by the WHO Expert Committee on Specifications for Pharmaceutical Preparations in this area, which were available in printed

form, on CD-ROM together with training modules and a training video, and on the WHO web site (http://www.who.int/medicines/areas/quality_safety/quality_assurance/production/en/index.html).

7.2 Guidance on the inspection of hormone product manufacturing facilities

The working document on *Guideline to the inspection of hormone product manufacturing facilities* was presented to the Expert Committee together with a summary of the comments received.

This guideline was intended to set out the design parameters and inspection criteria applicable to facilities handling hormone products. Its primary focus was on the air-conditioning and ventilation systems of such facilities. The need for this guideline had been expressed by colleagues carrying out inspections within the context of the Prequalification Programme and by numerous participants in the training sessions organized by WHO, as well as being noted in queries received by the WHO Secretariat.

This guideline was to be read in conjunction with other WHO GMP guidelines such as those covering building finishes and general services installations. This draft guideline currently dealt only with criteria which were not covered in the other WHO GMP guidelines.

The areas in which this guideline could be applied were all zones where the handling of hormone products could lead to a hazardous situation. This included research and development facilities, and facilities engaged in API manufacturing, storage, finished product manufacturing, including packing, and product distribution. The collective general term used in the guideline for all these different aspects was "hormone facilities". Although this document related to hormone products, the principles it contained could be applied to other hazardous products for which containment was required.

The Expert Committee acknowledged its previous recommendation to provide guidance in this area. Based on the various comments received, discussion about the scope of the guide took place. It was stressed that the text should focus on pharmaceuticals and not repeat a guideline on environmental issues in accordance with WHO's task to assist Member States in providing guidance on health and safety issues. It was agreed that a small expert group be formed to review all the comments received and to propose a new draft version for wide circulation for comments in line with the usual working procedure of the Expert Committee. The outcome would then be presented to the next meeting of the Expert Committee.

8. Quality Assurance – new approaches and risk analysis

8.1 Information sharing and collaboration

Strategies on how best to cope with the increasing need for inspections by national and regional bodies had been discussed in many forums. This topic had also been discussed during several WHO consultations and at previous meetings of the WHO Expert Committee on Specifications for Pharmaceutical Preparations. During the forty-second meeting of the Expert Committee, this topic was raised, indicating that this might be a possible subject for a session in the programme of the 13th ICDRA.

This session was agreed upon in accordance with the points highlighted in this report by the ICDRA Planning Committee. The workshop was entitled "GMP inspections: impact of information sharing and risk management". (For details see the 13th ICDRA, information available at http://www.icdra.ch/.) The titles of the presentations were: Risk management of GMP inspections: example Australia; Coping with increasing need for inspections: ASEAN initiatives; and What is EMEA's approach in GMP inspections?

A growing demand for inspection had led many WHO Member States to use a model to assess the risk and the strategies for coping with it. Supporting elements were sufficient numbers of competent auditors, effective management, appropriate legislation and an effective quality management system. Other aspects to be taken into account included:

— range of products;
— types of manufacturers;
— history of compliance;
— recalls;
— complaints;
— external intelligence; and
— results of tests.

Factors that could be controlled, e.g. audit frequency, and those that were consequences of product failure, depended on product whereas the probability of a product defect depended on compliance with GMP.

Based on the information available, a risk rating could be performed for the various products to be inspected. Compliance classified according to a set of criteria → matrix produced including all factors → determining the frequency of inspection. In case of unacceptable GMP compliance, risk assessment could be performed by an independent review panel on a case-by-case basis. The risk should be managed on a continuous basis.

Another approach to reducing the number of inspections required was the use of mutual recognition agreements (MRAs). In the Association of Southeast

Asian Nations (ASEAN), for example, an MRA on GMP was under legal review by all Member States and would be finalized at the end of 2008. It foresaw that the number of audits would be reduced, that GMP certificates would be accepted, and GMP reports issued by the Inspections Services listed in the MRA. Products currently covered were prescription and non-prescription medicinal products. The challenges included the different legal infrastructures in the various Member States and implementation of the GMP code and global cooperation, as well as the involvement of the pharmaceutical industry.

The European regulatory system, i.e. the centralized and decentralized procedure, included more than 40 national competent authorities for national medicines regulatory authorities for medicines for human and veterinary use. The European Medicines Agency (EMEA) focused on coordination in areas of inspection. European Union (EU) inspectors were the national inspectors of all EU Member States. All medicines manufactured outside the EU had to be imported by an "authorized" manufacturing or importation site. All inspections performed by the European Economic Area (EEA) were valid in all EU and EEA Member States. Authorized manufacturers of finished pharmaceutical products (FPPs) were expected to audit API manufacturers (see also section 2.1.4).

Most inspections coordinated by EMEA were performed outside the EU and took due consideration of the signed MRAs. The number of inspections had increased both within EU national inspectorates and EMEA-coordinated ones. Due to scarce resources, increased global operations were necessary. Nowadays most manufacture took place outside the EU and new models were needed to control the situation. The situation called for improving efficiency and new guidance together with improved communication, transparency and increased European and international collaboration. Examples of collaboration are those with MRA parties, EDQM, WHO and confidentiality arrangements with some states.

The EMEA had developed a new database, EudraGMP, a community GMP database, to which MRA partners and partners in confidentiality agreements would have access. This database included negative reports and links between marketing authorization information. The EudraGMP database was intended to facilitate communication and part of it would be available to the public. Confidentiality arrangements had been signed between EMEA and the United States Food and Drug Administration (USFDA), which included pilot joint inspections within and outside the USA and EU countries for APIs.

The examples discussed during the ICDRA session summarized above clearly indicated that to save scarce resources there should be a move from local to global efforts together with harmonization of approaches.

During this ICDRA workshop the following recommendations were made.

Member States should:

1. Work towards ensuring quality, efficacy and safety of drugs while making efforts to contain escalating costs of drug prices by minimizing duplication of inspection activities through:
   — better networking;
   — improved information sharing;
   — enhanced collaboration;
   — increased mutual trust and confidence.
2. Promote efficient use of inspectorate resources through use of a risk management approach in GMP inspections, especially for overseas manufacturers, by taking advantage of information available from other national medicines regulatory authorities.
3. Collaborate with WHO Member States and the WHO Medicines Prequalification Programme to share information about dates, purpose of inspection and major outcomes.
4. Encourage manufacturers to actively collaborate in information sharing among national, regional and international bodies involved in inspections.
5. Increase availability of non-confidential information on the web sites of interested authorities and on "protected" sites to which national authorities have access.

WHO should:

- Promote and enable networking and information sharing among national, regional and other relevant authorities involved in inspections.

The ICDRA plenary session fully endorsed the above recommendations and emphasized the importance of trust-building among the national authorities.

The Head of Inspection in WHO's Prequalification Programme gave an overview of the various efforts WHO was making to build synergies and reduce the number of inspections. WHO collaborated with many parties, especially when organizing inspections carried out within its remit of the various inspection activities relating to the Prequalification Programme. Trust was being built through joint inspections and many training activities. In addition the members of the Expert Committee were reminded about the availability of public inspection reports (PIRs) from the inspections carried out within the context of the Prequalification Programme.

The Committee commended WHO for its efforts and recommended continuing with further trust-building in this area. They further requested that:

— a risk-based approach be attempted based on the sharing of information;
— better cooperation on a regional basis be considered; and
— information on databases be made available where possible.

8.2 WHO guideline on transfer of technology

The working document on the *WHO Guideline on transfer of technology* was presented to the Expert Committee.

The scope of this new working document was to give guidance in principle and to provide general recommendations on the activities necessary to conduct a successful intra-site or inter-site transfer of technology. The intention was to address the basic requirements for a successful transfer in order to satisfy any regulatory authority. Transfer of processes to an alternative site occurred at some stage in the life-cycle of most pharmaceutical products, from preclinical development through clinical studies, scale-up and launch, to the post-approval phase. The processes usually transferred were those of manufacturing investigational pharmaceutical products for clinical trials as part of research and development, manufacturing APIs, manufacturing and packaging of established FPPs and/or performing analytical testing.

The recommendations provided in this guideline applied to transfer of all analytical methods and all dosage forms. Particularly close control of certain aspects would be required for complex formulations such as sterile products, metred-dose aerosols and clinical trials supplies. WHO guidance on the manufacture of specific pharmaceutical products would be useful in this regard.

The Expert Committee made various remarks and recommendations on the matter, including the following:

- The guide should address the case of possible shortage of supplies when transfer takes place.
- The responsibility of the sending unit needs to be stressed.
- GMP guidelines could be the way to ensure transfer of responsibility from the sending unit to the receiving unit.
- The guide should address the case of national quality control laboratories where there was no sending unit.
- The Committee recommended that an informal consultation be held to discuss the numerous comments received on this draft WHO guideline and that the revision following the informal consultation be circulated again widely for further comment.

9. Quality assurance – distribution and trade of pharmaceuticals

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

The WHO Certification Scheme for finished pharmaceutical products was an international voluntary agreement to provide assurance to countries participating in the Scheme, about the quality of pharmaceutical products

moving in international commerce (World Health Assembly resolutions WHA22.50 (1969), WHA28.65 (1975), WHA41.18 (1988), WHA45.29 (1992) and WHA50.3 (1997)). The primary document of the Scheme was the Certificate of Pharmaceutical Product (CPP).

The Expert Committee discussed the report of the consultation on the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce which was held from 22 to 24 July 2008. The consultation was held further to a recommendation made by the Expert Committee at its forty-second meeting based on the changing environment, including the rapid globalization of the pharmaceutical manufacturing sector coupled with changes in the make-up of both the regulators and the groups involved in procurement. Moreover, legislation had recently been put in place in various countries and regions to assess products manufactured in these countries or regions and produced for "export only", for which there was currently no adequate provision in the Scheme.

The participants at the consultation discussed the recommendations made on working document QAS/07.240 (*Proposal for improvement of the WHO Certification Scheme*) and the comments received. They acknowledged the value of the Certification Scheme but also recognized that it had some limitations. This proposal identified limitations and put forward recommendations to address them. The consultation group was of the opinion that implementation of these recommendations would strengthen the Scheme and improve compliance with its goals towards quality medicines circulating in international commerce. A draft report for presentation to the Expert Committee on Specifications for Pharmaceutical Preparations at its forty-third meeting was prepared by the consultation group. This report was circulated for comment before being presented to the Expert Committee in its final form.

The recommendations from the consultation were also reported to the 13th ICDRA in September 2008 for information and possible comments.

Feedback from the International Federation of Pharmaceutical Manufacturers and Associations/European Federation of Pharmaceutical Industries and Associations (IFPMA/EFPIA) was reported to the Expert Committee, which noted that the pharmaceutical industry regarded the WHO Certification Scheme as a very important tool.

The Expert Committee endorsed the following recommendations:

1. The WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce should be revised.
2. The proposal for revision of the Scheme and modification of the guidelines should be discussed by the relevant WHO Governing

Bodies – the Executive Board and the World Health Assembly – and in consultation with WHO's Legal Counsel.

3. In the interim a question and answer paper should be prepared on the function of the Scheme.

9.2 WHO good distribution practices for pharmaceutical products (proposal for revision by the International Medical Products Anti-Counterfeiting Taskforce (IMPACT) partnership)

Following the adoption of the WHO guidelines for good distribution practices (GDP) by the fortieth WHO Expert Committee on Specifications for Pharmaceutical Preparations in October 2005: http://whqlibdoc.who.int/trs/WHO_TRS_937_eng.pdf (WHO Technical Report Series, No. 937, 2006, Annex 5, p. 191) these guidelines had been revised by the International Medical Products Anti-Counterfeiting Taskforce (IMPACT) partnership.

IMPACT met in Bonn, Germany in November 2006, and decided that the existing GDP should be revisited and, if necessary, amendments proposed with the specific aim of improving the security of the distribution chain vis-à-vis counterfeits. This decision was based on the consideration that in highly regulated countries, counterfeit medicines reached patients through the regulated distribution chain.

A first draft was prepared and circulated (in March 2007) to all the members of the IMPACT Regulatory Implementation Working Group (IRIWG). The IRIWG met in Washington, DC from 23 to 25 April 2007, when it discussed the draft and recommended amendments. A revised draft was circulated among IRIWG members until a final draft was made available on WHO's web site for further comments. All IMPACT members (which included the NMRAs of 60 WHO Member States as well as the other stakeholders mentioned above) were encouraged to comment. Comments were also welcomed from other sources but no specific action was taken to initiate such comments. The draft was further revised and finalized at the IMPACT General Meeting held in Lisbon, Portugal in December 2007. This text was then circulated in accordance with the usual procedure by mailing it to all parties collaborating in the standard-setting process of this Expert Committee.

The working document entitled *Proposal for revision: WHO good distribution practices for pharmaceutical products* was presented to the Expert Committee, as were the comments made by the IRIWG.

This document laid down guidelines for the distribution of pharmaceutical products. Depending on national and regional legislation on pharmaceuticals, this guide might equally apply to medicinal products for humans and for veterinary use. The main principles to secure the distribution chain established in this document might also be relevant to medical devices.

The Expert Committee agreed that further discussion was necessary and that a joint expert group be formed with specialists from the IMPACT expert working group and members of the WHO Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations to review the comments and revise the proposal in line with the usual consultative procedure.

10. Quality assurance – stability

The revised working document on *Draft Stability testing of active pharmaceutical ingredients and finished pharmaceutical products* was presented to the Expert Committee.

A brief history of this guidance document and the various related discussions held in the past by this Expert Committee were given as an introduction to this agenda item.

The Committee started to work in the area of stability in 1988. Eight years later the first WHO guidelines on stability testing requirements were finalized. The process of consultation was long mainly because, at the same time, the International Conference on Harmonisation (ICH) was also developing its guidance in this area for new chemical entities and products. The WHO experts advised strongly at that time that the ICH discussion be observed in order to harmonize the testing conditions and to avoid recommending different stability testing conditions.

The WHO Stability guidelines at that time focused on well-established pharmaceutical products, i.e. "generic products" in conventional dosage forms, as this was considered to be the priority. The world at that time was considered to be divided into four climatic zones: *Zone I:* temperate; *Zone II*: subtropical, with possible high humidity; *Zone III*: hot/dry; and *Zone IV*: hot/humid. It was important for WHO to consider especially the "hot-dry" and "hot-humid" conditions. The storage conditions were derived from references and calculated data.

In 1996, the testing condition chosen for Zone IV was 30 ˚C/70% relative humidity (RH). In 2000, ICH requested a modification of the standard condition for Zone IV. This proposal, to change the condition from 30 ˚C/70% RH to 30 ˚C/60% RH, was submitted to the WHO consultation process, but in the end was not found acceptable to the WHO experts. In 2001, a new proposal was received to modify both the ICH and the WHO guidelines for Zone IV to 65% RH instead of 70% RH. Again, this proposal was widely circulated for comments and was found to be acceptable by most experts. The WHO testing conditions for Zone IV were subsequently modified to 30 ˚C /65% RH following a decision by the WHO Expert Committee. Some Member States had raised the concern that this condition would not be applicable in their

countries; therefore, the WHO experts included a provision for transportation and storage conditions when outside these criteria.

In 2003, ICH Q1F (Stability data package for registration applications in climatic zones III and IV) was signed off by all ICH partners and the conditions were in line with those discussed by WHO's Expert Committee. In 2004, a number of meetings were held in the ASEAN region to discuss its stability testing conditions. In January 2004, new conditions, based on real meteorological data, were proposed in ASEAN. These new conditions for Zone IV were 30 ˚C/75% RH. Many discussions were subsequently triggered at international level and these new conditions found acceptance in other parts of the world, e.g. Brazil.

At its meeting in October 2004, the WHO Expert Committee recommended further discussion at an international level because the so-called Zone IV was now defined with two conditions. In December 2004 a meeting was organized by WHO in Geneva. The outcome was three options and a plea to all WHO Member States and all interested parties to express which of the three conditions they would find acceptable. In October 2005 the Expert Committee reviewed the feedback received and discussed and recommended two different zones within Zone IV, i.e. Zone IVA and IVB, in order to avoid creating another, third set of conditions at WHO level. Each WHO Member State was asked to indicate which condition(s) would be applicable in its territory.

Further to developments in 2006, ICH withdrew its Q1F. The guideline was withdrawn owing to the divergence in global stability testing requirements and the definition of the storage conditions in the climatic zones III and IV. It was left to the individual regions and to WHO to define the respective stability testing conditions for those regions. It was also decided that the intermediate conditions would be retained to facilitate the harmonization process and avoid another set of conditions.

The ICDRA key recommendations on stability testing made during its 12th meeting (2006) included the following:

- WHO Member States should identify their stability testing conditions to facilitate import to and export from their countries.
- WHO Member States should make information available to WHO regarding the stability conditions to be applied within their markets.
- WHO should make available country information to facilitate its accessibility to manufacturers and to any interested party in any part of the world.

At the beginning of 2006 guidelines were developed by the WHO Eastern Mediterranean Region during the WHO/EMRO Consultation on Regional Guidelines on Stability Studies of Medicines and Biologicals, Jeddah, Saudi Arabia; the final draft was adopted by the EMR Regional Committee.

A discussion subsequently took place during the fortieth meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations in October 2006 regarding possible adoption of WHO/EMRO guidelines to serve as global guidelines, and it was decided that they be circulated for comments. WHO also corresponded with major regional harmonization groups requesting conditions in their regions or countries, to follow up on the recommendations of both the Expert Committee and ICDRA. Two rounds of circulation and revisions of working documents subsequently took place in 2006–2008.

An informal consultation on stability studies in a global environment took place in Cairo, Egypt, from 19 to 21 August 2008 to review all comments received on the third version of this working document. The meeting was jointly organized by EMRO and WHO headquarters in order to revise the text again in light of the numerous comments received following its wide circulation. A new draft (QAS/06.179/Rev.3) was subsequently circulated and presented to ICDRA (2008) in Bern, Switzerland.

During circulation of the third draft many new comments had been received. To avoid a never-ending process, the Committee recognized that it was very difficult to incorporate all of the, often contradictory, remarks and adopted the view that a less than ideal guideline was still better than a non-published one.

While applying this view, careful consideration was given to all the comments submitted to the Expert Committee. After a lengthy discussion, decisions were made on the controversial issues. As a compromise, the table(s) of labelling statements connected to testing conditions were removed from the main text and added as annexes to the draft guideline in order to avoid any misunderstanding as to their non-mandatory character, and to facilitate revision of these annexes should new information become available.

It was stressed that the national and regional regulatory authorities would decide on the stability testing requirements as well as on the storage conditions given on the label. The importance of Annex 2, specifying the stability testing conditions actually employed in WHO Member States was emphasized. To complete the table in Annex 2: Stability conditions for WHO Member States by Region, the various regional regulatory harmonization groups and IFPMA would again be contacted for their input.

The guidelines were adopted, subject to the inclusion of the changes discussed being overseen by a small working group composed of members of this Expert Committee (Annex 2).

11. Prequalification of priority essential medicines and devices

11.1 Prequalification Programme managed by WHO

The Prequalification Programme, set up in 2001, is a service provided by WHO to facilitate access to medicines for HIV/AIDS, malaria and tuberculosis, which met unified standards of quality, safety and efficacy. From the outset, the Programme was supported by UNAIDS, UNICEF, UNFPA and the World Bank as a concrete contribution to the United Nations priority goal of addressing widespread diseases in countries with limited access to quality medicines. The standards and guidelines developed by the Expert Committee were implemented within this Programme.

The Committee was provided with an update on the Prequalification Programme activities in 2008 (see also Table 1).

The two major developments in the Programme were:

1. Introduction of the Notice of Concern procedure after inspections at manufacturers of prequalified medicines and research organizations indicated a significant failure of the quality management system or non-compliance with GMP (or good clinical practices or good laboratory practices as relevant), resulting in inadequate assurance of product quality.
2. Implementation of the biowaiver concept, i.e. in selected cases the efficacy and safety part of the dossier (application) was approved based on evidence of equivalence other than through in vivo equivalence testing.

Table 1
Statistics on Prequalification Programme in 2007 and 2008 (January–August)

	2007 (whole year)	2008 (January–August)
List of prequalified medicinal products		
Medicinal products prequalified	21	28
Total number of prequalified products	156	184
Number of product dossiers submitted	90	66
Number of dossiers accepted for evaluation	59	47
Dossier assessment		
Assessment sessions in Copenhagen	6	4
Total number of assessment reports	**463**	**487**
Assessment reports on HIV/AIDS products	298	356
Assessment reports on TB products	100	49
Assessment reports on malaria products	54	63
Assessment reports on reproductive health products	11	19

	2007 (whole year)	2008 (January–August)
Inspections	**45**	**40**
Sites of manufacture of finished products	26	17
Sites of manufacture of APIs	6	7
Contract research organizations	13	16
Quality control laboratories		
Number of laboratories submitting applications	7	12
Number of laboratories inspected and pre-audited	7	5
Number of laboratories prequalified	1	3
Training workshops		
Total number of training courses	13	9
Number of participants	510	350
Technical assistance missions	10	7

11.2 Procedure for prequalification of pharmaceutical products

The revised working document on *Procedure for prequalification of medicinal products* was presented to the Expert Committee. The Committee adopted the procedure subject to reverting to the current WHO nomenclature, including the use of "pharmaceutical products" in the title (Annex 3). The Committee noted that the procedure discussed would need to receive final clearance by the WHO Legal Counsel.

12. Prequalification of quality control laboratories

The prequalification of quality control laboratories is undertaken by WHO together with UNICEF, UNAIDS, UNFPA and UNITAID and with the support of the World Bank. The procedure started in 2004 when participation was limited to laboratories in Africa. In September 2007, the third Invitation for Expression of Interest (EOI) (http://www.who.int/prequal/info_applicants/eoi/EOI-QCLabsV3.pdf) was published without regional limitation. There were now six prequalified laboratories (five in Africa and one in India) and a further 25 laboratories at various stages of the prequalification procedure (18 in Africa and seven from the rest of the world). Of the 31 laboratories in the prequalification procedure, 23 were national quality control laboratories.

In terms of capacity building, WHO had provided technical assistance to five laboratories, and three training programmes for laboratory staff were organized in 2007.

Surveillance testing of pharmaceutical products

To monitor the quality of prequalified medicines supplied, to contribute to quality control of other products procured by United Nations agencies and to contribute to quality control of products, sampling and testing projects were organized if requested by Member States. These projects were conducted in close cooperation with NMRAs and thus contributed to capacity building activities. In 2007, projects on testing of artemether/lumefantrine tablets and generic products containing nelfinavir mesilate were finalized.

Currently there were three projects in progress, which focused on antimalarials, paediatric and second-line antiretrovirals and antituberculosis products.

13. Prequalification of active pharmaceutical ingredients

13.1 Procedure for prequalification of active pharmaceutical ingredients

The need for quality assurance of APIs, as requested by Member States, was discussed by the WHO Expert Committee on Specifications for Pharmaceutical Preparations at its fortieth and forty-first meetings. This need had also been endorsed in the recommendations of the 12th ICDRA in April 2006.

In response, the draft procedure for prequalification of APIs was drawn up by the WHO Prequalification Programme and presented to the Expert Committee at its forty-second meeting in October 2007. The Committee at that time had endorsed, in principle, the proposed approach as distributed for comments and noted that the revised draft would be presented to the Committee at its next meeting.

The revised working document on the *Procedure for assessing the acceptability, in principle, of active pharmaceutical ingredients for use in pharmaceutical products* was presented to the Expert Committee at its forty-third meeting. The Committee adopted the procedure, subject to consideration of comments received after the meeting of the Expert Committee but before the deadline of 28 October 2008 (Annex 4).

The Committee noted that the procedure discussed would need to receive clearance by the WHO Legal Counsel.

14. Regulatory guidance

14.1 Specific regulatory guidance on paediatric medicines

Based on recommendations made by the Expert Committee at its forty-second meeting, a paper was prepared to provide guidance on the formulation of

paediatric medicines. The guidance focused on suitable dosage forms for children of different ages, on formulation excipients and on some specific dosage forms.

This work was closely related to other current activities of the WHO Expert Committee on the Selection and Use of Essential Medicines and its Subcommittee for Children (see also section 2.1.11).

Following the WHO–International Pharmaceutical Federation (FIP) pilot training workshop for manufacturers on pharmaceutical development (with an emphasis on paediatric medicines), which was held in South Africa in April 2007, a first draft on points to be considered was prepared and circulated as working document QAS/08.257: *Development of paediatric medicines: pharmaceutical development. Points to consider*, which was presented to the Expert Committee.

It was recognized that while guidance on extemporaneous "manipulative" formulations would be needed until appropriate new dosage forms became available, this might be better addressed in a separate document. The main focus would be on providing advice to NMRAs rather than to manufacturers. A new draft would, therefore, be prepared, focusing more on the regulatory aspects and circulated in accordance with the usual consultative procedure. Consideration should be given to developing a second guidance document dealing with the extemporaneous "manipulative" formulations.

The Committee also recognized the need for medicines specific for children as well as for promoting the development of novel dosage forms for children. Further discussions would be needed on the best mechanism for this, and approaches considered could include a multifaceted one.

14.2 Guidelines for pharmaceutical development of generics

Based on the discussion during the forty-second meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations of October 2007, triggered by a concept paper, the working document on *Pharmaceutical development for multisource (generic) pharmaceutical products* was prepared, circulated for comments and the outcome presented to the Expert Committee.

These guidelines were intended to provide guidance on the contents of the pharmaceutical development section both for the applicants for marketing authorizations and for NMRAs for generic medicines, i.e. to complement the guidance given in the ICH Q8 guideline (Pharmaceutical development) for innovative medicines.

The comments received were presented and discussed. It was recognized that few comments had been received from concerned manufacturers and few from NMRAs outside the ICH region. Following the discussion, the

Committee agreed that the guidelines needed to be developed to provide general guidance for all multisource products, and not only for those covered by the Prequalification Programme.

The Expert Committee also agreed that further discussion was necessary and recommended that an expert group be formed to review comments and revise this document in line with the usual consultative procedure. This discussion would need to take place in close collaboration with the group revising the document entitled: *Development of paediatric medicines: pharmaceutical development. Points to consider.*

14.3 Quality of herbal and complementary medicines

The representative of the Traditional Medicine Programme gave an oral presentation which updated the Committee on the Programme's progress and future activities. The Committee was pleased to note that the World Conference on Traditional Medicine would take place in November 2008; the publication of WHO guidelines on assessing the quality of herbal medicines with reference to contaminants and residues in 2007; and the expansion of the network of the International Regulatory Cooperation for Herbal Medicines (IRCH).

14.4 List of comparator products

Following up on the recommendations of previous Expert Committees the WHO Secretariat updated the Committee on the steps undertaken to revise the previously published list in: *Guidance on the selection of comparator pharmaceutical products for equivalence assessment of interchangeable multisource (generic) products*.

An update of the above-mentioned guidance was needed following revision of the Model List of Essential Medicines, taking into account comments received when a proposed update had been circulated previously as working document QAS/05.143 in 2006.

In collaboration with IFPMA, the WHO Secretariat had again circulated the current draft list of comparators to the contact persons at pharmaceutical companies for verification of the entries made by their companies.

The Expert Committee took note of this update and confirmed its decision to put this list on the web site as a "living" document.

15. Nomenclature, terminology and databases

15.1 Quality assurance terminology

The database, available on the WHO quality assurance web site: http://www.who.int/medicines/areas/quality_safety/quality_assurance/en/ was presented

to the Committee. The Committee emphasized the importance of this database during the preparation of guidelines as it would ensure consistency in the terms used in all quality assurance-related WHO guidance documents.

15.2 International Nonproprietary Names

The Expert Committee was informed of the work plan and progress of the International Nonproprietary Names (INN) Programme. Since October 2007, i.e. the previous meeting of the Expert Committee, lists 98 and 99 of proposed INN and lists 58 and 59 of recommended INN had been published, bringing the total to 130 new proposed INN and 136 new recommended INN.

The following new stems had been added to those used in the selection of INN:

(INN Working Document 08.237, Addendum 3 to *The use of stems in the selection of International Nonproprietary Names (INN) for pharmaceutical substances* (WHO/PSM/QSM/2006.3).)

*-azepide**	*CCK (cholecystokinin) antagonists, benzodiazepine derivatives*
-cept	*receptor molecules, native or modified (a preceding infix should designate the target)*
-ciguat	guanylate cyclase activators and stimulators

Under gli antihyperglycaemics

- gliptin	dipeptidyl aminopeptidase–IV inhibitors

Under imod immunomodulators, both stimulant/suppressive and stimulant

-mapimod	mitogen-activated protein (MAP) kinase inhibitors

Under imus immunosuppressants (other than antineoplastics)

-rolimus	immunosuppressants, rapamycin derivatives
-mulin	antibacterials, pleuromulin derivatives
-nabant	cannabinoid receptors antagonists
-pris-	steroidal compounds acting on progesterone receptors (excluding *-gest-* compounds)
tril/trilat	*endopeptidase inhibitors*

Under vir antivirals (undefined group)

-viroc	CCR5 (Chemokine CC motif receptor 5) receptor antagonists

** already existing stem whose definition has been amended.*

The pre-stems were newly available on the web site at: http://www.who.int/medicines/services/inn/en/.

It was anticipated that the new database would soon go live. New functionality would include online access to the INN selection process for the INN experts.

An INN Working Group on Nomenclature for Monoclonal Antibodies (mAb) met in October 2008. The draft recommendations of this meeting were presented to the Committee. The work related to the INN Programme was a good example of close collaboration with the WHO Expert Committee on Biological Standardization, the World Intellectual Property Organization and the World Customs Organization.

The Committee was also informed about the information available on the INN web site and on the INN Cumulative List on CD-ROM.

The Expert Committee took note of this update.

15.3 Pharmacopoeial references

The Expert Committee was updated on the activities relating to the further development of a pharmacopoeial reference database which was currently being reformatted and validated. There were plans to begin a pilot phase in 2009. This database was intended to be made available to the Expert Committee members, members of the Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations and to Prequalification Programme experts and staff.

16. Miscellaneous

16.1 Draft WHO Medicines Strategy 2008–2013

Late in 2007 the Director-General announced her intention to combine the Department of Medicines Policy and Standards and the Department of Technical Cooperation for Essential Drugs and Traditional Medicine. This merger was now complete and a single Department of Essential Medicines and Pharmaceutical Policies was taking shape.

This renewed focus offered an opportunity to fully link the global normative and policy functions with a programme of tailor-made technical support to Member States. More information about the work of the Department as well as the updated *Who is Who in WHO essential medicines and pharmaceutical policies* may be found on the web site (http://www.who.int/medicines/en/).

Over the past decade, WHO's activities in the field of medicines had been guided by the WHO Medicines Strategies for 2000–2003 and 2004–2007. Based on these good experiences and to ensure a strong foundation for the

new Department, a third WHO Medicines Strategy within the scope of WHO's Medium-Term Strategic Plan for 2008–2013 was developed.

The Strategy document was not intended to repeat existing information on the global pharmaceutical situation or past achievements. It summarized the changes that had occurred since 2003 and the key challenges after 2008. The Strategy presented major strategic directions and approaches but did not include operational details or work plans.

The current draft of the WHO Medicines Strategy 2008–2013 was shared with the Expert Committee for its review and comments.

16.2 Follow-up activities on "biowaiver"

An update on the follow-up activities on "biowaiver" was given to the Expert Committee. The FIP-BPS Special Interest Group (SIG) Biopharmaceutics Classification System had started to collect publicly available information for essential medical drug products based on the Biopharmaceutical Classification System (BCS). This activity was supported by WHO and referred to the FDA Guidance on possible biowaivers for class 1 drugs of the BCS. The information collected was critically reviewed and published in the form of monographs in the *Journal of Pharmaceutical Sciences*. The monographs were also made available on the FIP web site under the web pages of the BCS (http://www.fip.org/www/, free access).

By the time of the meeting, more than 20 monographs had been published and more data on class 1 (and class 3) drugs would follow. The selection of possible drug candidates was based on the WHO Model List of Essential Medicines in order to especially assist developing countries in obtaining approval by means of a biowaiver of generic drug products belonging to BCS Class 1.

These "monographs" were essentially literature reviews, which gathered and organized relevant data to be taken into consideration in deciding whether a biowaiver could be recommended for a new formulation of a specific API. The items discussed were: solubility, pharmacokinetics and permeability; dissolution of dosage forms; the therapeutic use and therapeutic window of the API; data on interactions with excipients; and problems with bioavailability and/or bioequivalence.

The monographs had no formal regulatory status, but represented the best scientific opinions available at the time of compilation. They were published in the *Journal of Pharmaceutical Science* but could also be downloaded free of charge by clicking on the API of interest on the FIP web site (http://www.fip.org/www/) . It was foreseen that the monographs would be updated with addenda if new data became available.

The list of "biowaiver monographs" currently available and in print included:

— acetaminophen = paracetamol
— acetazolamide
— aciclovir
— atenolol
— amitriptyline hydrochloride
— cimetidine
— chloroquine phosphate
— chloroquine sulfate
— chloroquine hydrochloride
— diclofenac potassium (accepted for publication)
— diclofenac sodium (accepted for publication)
— ethambutol dihydrochloride
— ibuprofen
— isoniazid
— metoclopramide HCl
— prednisolone
— prednisone
— propranolol hydrochloride
— pyrazinamide
— quinidine sulfate
— ranitidine hydrochloride
— rifampicin
— verapamil hydrochloride.

16.3 Promotional brochure

The promotional brochure entitled *Quality assurance of pharmaceuticals: meeting a major public health challenge* had been printed in 2006. This brochure on the WHO Expert Committee on Specifications for Pharmaceutical Preparations was appreciated by the Committee. It strongly recommended updating the brochure to include recent information about the outcomes of this Expert Committee.

16.4 Model quality assurance system for procurement agencies

The model quality assurance system for procurement agencies (MQAS), which was originally published as an annex to the fortieth report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations (WHO Technical Report Series, No. 937), had now been adopted as an interagency guide.

The Expert Committee was informed that Appendix 6 (questionnaire) of the MQAS had been revised by the interagency group. In addition, the

Committee was informed about the current practices of some procurement agencies which used the risk assessment approach when purchasing FPPs for medicines for which no prequalified FPPs existed.

The Committee noted the positive use of its work and the feedback on the implementation of the MQAS.

17. Summary and recommendations

On the occasion of the 60th anniversary of the World Health Organization, the WHO Expert Committee on Specifications for Pharmaceutical Preparations was able to look back on its existence and activities even before that date. The first meeting of this Expert Committee, which was named "Unification of Pharmacopoeias" at that time, was held in 1947. Two further meetings were held in 1948, and the reports of these three meetings were all published in the WHO Official Records. The fourth Expert Committee meeting was held in 1949. The report of that meeting constituted the very first Technical Report of WHO in January 1950. Thus the Expert Committee was looking back on a history of more than 60 years!

Since the inception of this WHO Expert Committee, its members have worked towards making available clear, independent and practical recommendations, written and physical standards, as well as international guidelines for quality medicines. Standards in the area of quality assurance for medicines are developed by the Committee through a wide international consensus-building process.

The activities discussed during this Expert Committee have broad inter-cluster and intra-cluster relationships and links. There are joint activities, specifically with the WHO Expert Committees on Biological Standardization and on the Selection and Use of Essential Medicines. In addition, the Committee serves to develop specific additional guidance and specifications, as needed, for the various medicines recommended by WHO Programmes.

Regarding implementation from a wider perspective, the international guidelines, specifications and nomenclature developed under the aegis of this Committee serve all Member States, international organizations, United Nations agencies, regional and interregional harmonization efforts, and underpin important initiatives, including the prequalification of medicines, the Roll Back Malaria Programme, Stop TB, essential medicines and medicines for children. The advice and recommendations provided by this Expert Committee are intended to help national and regional authorities and procurement agencies – as well as major international bodies and institutions, such as the Global Fund to Fight AIDS, Tuberculosis and Malaria, and international organizations such as UNICEF – to combat circulation of

substandard medicines and to work towards ensuring access to quality medicines.

This Committee also serves the United Nations Programme on Prequalification of Medicines managed and operated by WHO, as this Programme could not function without the guidelines, standards and specifications adopted by this Committee after passage through its rigorous, international and wide consultative process. The major advantage for this Committee is that, as a result of implementing these guidelines and specifications, practical suggestions for potential revision or the need for additional guidance are communicated to the Expert Committee.

In conclusion, the Expert Committee gives recommendations and provides independent international standards and guidelines in the area of quality assurance for implementation by WHO Member States, international organizations, United Nations agencies, regional and interregional harmonization efforts, as well as WHO's medicines-related programmes and initiatives. Making resources available for these activities is, therefore, very cost-effective.

The following new guidelines were adopted and recommended for use

- List of available International Chemical Reference Substances and International Infrared Reference Spectra (Annex 1)
- Stability testing of active pharmaceutical ingredients and finished pharmaceutical products (Annex 2)
- Procedure for prequalification of pharmaceutical products (Annex 3)
- Procedure for assessing the acceptability, in principle, of active pharmaceutical ingredients for use in pharmaceutical products (Annex 4)

The following monographs were adopted for inclusion in *The International Pharmacopoeia*:

- *for antiretroviral medicines*:
  - — efavirenz capsules
  - — efavirenz oral solution
  - — emtricitabine
  - — nevirapine
  - — nevirapine oral suspension
  - — nevirapine tablets
  - — zidovudine, lamivudine and nevirapine tablets;
- *for antimalarial medicines*:
  - — artemether and lumefantrine oral suspension
  - — chloroquine sulfate oral solution
  - — quinine sulfate tablets;
- *for antituberculosis medicines*:

— cycloserine
— cycloserine capsules
— ethambutol hydrochloride tablets;

- *other medicines*:
  — mebendazole
  — oseltamivir phosphate
  — chewable mebendazole tablets;

- *radiopharmaceuticals*:
  — fludeoxyglucose (^{18}F) injection
  — gallium citrate (^{67}Ga) injection
  — technetium (^{99m}Tc) pentetate complex injection
  — sodium pertechnetate (^{99m}Tc) injection (fission);

- *the following monographs were adopted subject to minor modifications and final confirmation by IAEA*:
  — iobenguane (^{123}I) injection
  — sodium iodide (^{131}I) injection
  — sodium iodide (^{131}I) solution
  — sodium pertechnetate (^{99m}Tc) injection (non-fission)
  — thallous chloride (^{201}Tl) injection.

The Committee adopted the following new ICRS:

— abacavir sulfate for system suitability
— amoxicillin trihydrate
— lamivudine for system suitability
— norethisterone enantate
— zidovudine impurity B.

Replacement reference standards:

— levothyroxine sodium
— paracetamol.

In addition to the above, the Committee adopted:

- the work plan for future development of monographs for inclusion in *The International Pharmacopoeia* to be posted on the WHO web site;
- 30 International Infrared Reference Spectra for publication on the WHO web site and in the Second Supplement to *The International Pharmacopoeia*.

A joint session was organized between the WHO Expert Committee on Specifications for Pharmaceutical Preparations and the WHO Expert Committee on Biological Standardization. The following topics were covered in that special session and will be followed up in accordance with the remit of each Expert Committee:

— regulatory oversight of the distribution chain for temperature-sensitive vaccines/pharmaceuticals;
— quality control parameters and relevance to WHO International Standards;
— moving from biological to chemical references standards;
— International Nonproprietary Names (INN) for pharmaceutical substances;
— good manufacturing practices for biologicals;
— stability testing.

The following recommendations were made in the various quality assurance-related areas. Progress on the suggested actions should be reported to the next Expert Committee.

The underlying principle is that the development of specifications and guidelines would be carried out using the established international consultative process.

Organizational

- Update the promotional brochure entitled *Quality assurance of pharmaceuticals: meeting a major public health challenge* to include recent information and outcomes of this Expert Committee.

The International Pharmacopoeia

- Continue development of specifications for medicines in accordance with the work plan adopted at this meeting.
- Continue the efforts of international collaboration in relation to the revision and inclusion of new monographs for excipients.
- Continue the preparatory work on the Second and Third Supplements to *The International Pharmacopoeia,* Fourth edition, in printed and in electronic form (CD-ROM and online).
- Continue collaboration with the International Atomic Energy Agency (IAEA) with a view to replacement of monographs for radiopharmaceuticals.

International Reference Standards

- In collaboration with the WHO Expert Committee on Biological Standardization, elaborate a draft policy for cases where a transition from biological to chemical reference preparations may be appropriate in the future. Discuss this topic and related issues in a second joint session with the Expert Committee on Biological Standardization.

International Chemical Reference Substances (ICRS)

- Continue promoting the use of ICRS through various activities, including a promotional offer to national authorities and improvements to the Collaborating Centre's web site.

External Quality Assurance Assessment Scheme

- Continue the External Quality Assurance Assessment Scheme (EQAAS) for national quality control laboratories and investigate the possibility of starting a new test phase.
- Organize further "hands-on" quality control laboratory workshops to enhance the effects of the EQAAS for national quality control laboratories.
- Link up with capacity projects in target countries through greater involvement of the WHO regional offices with regard to capacity building for those laboratories with doubtful or unsatisfactory results.
- Trigger a fast-track revision process when an *International Pharmacopoeia* specification used within the Scheme could be improved.

National laboratories

- Continue the process of revision of the current *WHO good practices for national quality control laboratories* and broaden its scope to cover all laboratories engaged in quality control of medicines.

Good manufacturing practices and manufacture

- Follow-up on the revision process for good manufacturing practices (GMP) for biologicals currently taking place under the aegis of the Expert Committee on Biological Standardization.
- Continue the development of the *Guidelines on the inspection of hormone product manufacturing facilities*.
- Follow-up on development in the area of blood products and their derivatives.

Transfer of technology

- Continue the development of the *WHO guidelines on transfer of technology*, giving special consideration to the responsibilities of the sending and receiving units and any potential shortages of supplies during a transfer.

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

- Discuss further measures and steps to be taken regarding the WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce in consultation with WHO Member States and the WHO Legal Counsel.
- Continue developments for improvement of the Scheme.
- Prepare "questions and answers" on the functioning of the Scheme.

WHO Good distribution practices for pharmaceutical products

- Continue the process of revision of the *WHO good distribution practices for pharmaceutical products*.

Regulatory guidance

- Continue advancement of the *Development of paediatric medicines: pharmaceutical development. Points to consider*.
- Continue the development of the *Pharmaceutical development for multisource (generic) pharmaceutical products*.

Regulatory burden and inspections

- In view of the regulatory burden with regard to increasing numbers of inspections, promote:
  - — and enable networking and information sharing among national, regional and other relevant authorities involved in inspections;
  - — a risk-based approach in selection of inspections based on the sharing of information;
  - — better cooperation on a regional basis; and
  - — sharing information on databases where possible.

Development of medicines, including "child-size"

- Continue cooperation with the different WHO departments working on clinical and quality aspects of paediatric formulations, specifically with respect to advancing the development of paediatric formulations.

International comparator products

- Continue the update of the *Guidance on the selection of comparator pharmaceutical products for equivalence assessment of interchangeable multisource (generic) products* and its list of international comparator products and make it available on the web site as a "living" document.

WHO databases

- Maintain the consolidated database on nomenclature used in WHO quality assurance and identify preferred terms when various definitions have been published at different times.
- Make the pharmacopoeial reference database available in a pilot phase to Expert Advisory Panel members, prequalification assessors, those involved in development of monographs for *The International Pharmacopoeia* and, upon request, to national quality control laboratories.
- Maintain the INN database and continue to make it available on the web.

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Professor E. Adams, Labo voor Farmaceutische Analyse, Leuven, Belgium; Professor I. Addae-Mensah, University of Ghana, Legon, Ghana; Ms R. Ahmad, Centre for Product Registration, National Pharmaceutical Control Bureau, Ministry of Health, Petaling Jaya, Malaysia; Mrs S. Ahmed Jaffar, Directorate General of Pharmaceutical Affairs and Drugs Control, Ministry of Health, and Office of the WHO Representative, Muscat, Oman; Dr R. Andrews, Medicines and Healthcare products Regulatory Agency, London, England; Dr H. Arentsen, Regulatory Intelligence and Policy Specialist, Regulatory Development Strategy, H. Lundbeck A/S, Copenhagen-Valby, Denmark; Dr C. Athlan, Quality Reviewer, Swissmedic, Bern, Switzerland; Dr O.P. Baula, Deputy Director, State Pharmacological Center, Ministry of Health, Kiev, Ukraine; Professor S.A. Bawazir, Vice-President, Saudi Food and Drug Authority, Head of Drug Sector, Riyadh, Saudi Arabia; Dr R.P. Best, President and CEO, International Society for Pharmaceutical Engineering, Tampa, FL, USA; Dr L. Bigger, Regulatory and Scientific Affairs, International Federation of Pharmaceutical Manufacturers and Associations, Geneva, Switzerland; Professor C.F. Bittencourt, Farmacopéia Brasileira, Universidade Federal de Santa Maria, Santa Maria, RS, Brazil; Professor R. Boudet-Dalbin, Faculté de Pharmacie, Laboratoire de Chimie Thérapeutique, Paris, France; Dr S.K. Branch, Acting Group Manager, Special Populations Group, Medicines and Healthcare products Regulatory Agency, London, England; Dr E. Brendel, Bayer HealthCare AG, Elberfeld, Germany; Mr C. Brown, Inspections Enforcement and Standards Division, Medicines and Healthcare products Regulatory Agency, London, England; Dr F. Burnett, Managing Director, Pharmaceutical Procurement Service, Organization of Eastern Caribbean States, Casties, St Lucia; Dr. D. Calam, Wiltshire, England; Dr A. Castro, Regulatory Affairs Director and Senior Pharmacist, Roche Servicios SA, Heredia, Costa Rica; Mr Xuanhao Chan, Project Manager, International Pharmaceutical Federation, The Hague, Netherlands; Dr B. Chapart, Pharma Review Manager, Global Analytical Development, Sanofi-Aventis Pharma, Anthony, France; Ms I. Clamou, Assistant Manager, Scientific,Technical and Regulatory Affairs, European Federation of Pharmaceutical Industries and Associations,

Brussels, Belgium; Dr M. Cooke, Senior Manager, Global Quality, Operations, AstraZeneca, England; Dr C. Craft, Member, United States Pharmacopeia International Health Expert Committee, Rockville, MD, USA; Professor T. Dekker, Research Institute for Industrial Pharmacy, North-West University, Potchefstroom, South Africa; Dr M. Derecque-Pois, Director General, European Association of Pharmaceutical Full-line Wholesalers, Brussels, Belgium; Professor J.B. Dressman, Institut für Pharmazeutische Technologie, Biozentrum, Johann Wolfgang Goethe-Universität, Frankfurt am Main, Germany; Dr A.T. Ducca, Senior Director, Regulatory Affairs and Healthcare Policy, Healthcare Distribution Management Association, Arlington, VA, USA; Dr S. Durand-Stamatiadis, Director, Information and Communication, World Self-Medication Industry, Ferney-Voltaire, France; Dr E. Ehrin, Director, Centrallaboratoriet, ACL, Apoteket AB, Kungens Kurva, Sweden; Dr E. Fefer, Member, United States Pharmacopeia International Health Expert Committee, Rockville, MD, USA; Dr M. Garvin, Senior Director, Scientific and Regulatory Affairs, Pharmaceutical Research and Manufacturers of America, Washington, DC, USA; Dr M. Guazzaroni Jacobs, Director, Quality and Regulatory Policy, Pfizer Inc., New York, NY, USA; Ms N.M. Guerrero-Rivas, Instituto Especializado de Análisis, Estafeta Universitaria, Panamá, Panama; Dr N. Hamilton, Industrial Quality and Compliance, Industrial Affairs, Sanofi Aventis, West Malling, Kent, England; Dr S. Harada, International Affairs Division, Minister's Secretariat, Ministry of Health, Labour and Welfare, Tokyo, Japan; Dr G.W. Heddell, Director, Inspection Enforcement & Standards Division, Medicines and Healthcare products Regulatory Agency, London, England; Dr D. Hege-Voelksen, Swissmedic, Bern, Switzerland; Professor J. Hoogmartens, Labo voor Farmaceutische Analyse, Leuven, Belgium; Dr K. Hoppu, Director, Poison Information Centre, Helsinki University Central Hospital, Helsinki, Finland; Dr Kim Huynh-Ba, USA; Dr N. Ibrahim, National Pharmaceutical Control Bureau, Ministry of Health, Jalan University, Petaling Jaya, Indonesia; Dr R. Jähnke, Global Pharma Health Fund e.V., Frankfurt, Germany; Dr M. James, GlaxoSmithKline, Brentford, Middlesex, England; Professor Jin Shaohong, Executive Deputy Director, National Institute for the Control of Pharmaceutical and Biological Products, Ministry of Public Health, Beijing, People's Republic of China; Dr P. Jones, Director, Analytical Control, Pharmaceutical Sciences, Pfizer Global R&D, Sandwich, Kent, England; Dr M. Kaplan, Director, Institute for Standardization and Control of Pharmaceuticals, Jerusalem, Israel; Dr A.M. Kaukonen, National Agency for Medicines, Helsinki, Finland; Dr H. Köszegi-Szalai, Head, Department for Quality Assessment and Control, National Institute of Pharmacy, Budapest, Hungary; Dr A. Krauss, Principal Scientist, Chemist Laboratory, Therapeutic Goods Administration Laboratories, Woden, Australian Capital Territory, Australia; Professor H.G. Kristensen, Vedbaek, Denmark; Professor S. Läer, Institut für Klinische Pharmazie und Pharmakotherapie, Heinrich-Heine-Universität, Düsseldorf, Germany; Ms Low Min Yong, Director, Pharmaceutical Division, Applied Sciences Group, Health Sciences Authority, Singapore; Reverend J.Y. Martey, Head, Laboratory Services, Quality Control Laboratory, Food and Drugs Board, Accra, Ghana; Dr T. Massa, Vice President, Global Regulatory Sciences – Chemistry, Manufacturing and Control, Bristol-Myers Squibb, USA; Dr A. Mechkovski, Moscow, Russian Federation; Dr D. Mehta, Vigilance and Risk Management of Medicines, Medicines and Healthcare products Regulatory Agency, London, England; Dr J.H.McB. Miller, Strasbourg, France; Dr J.A. Molzon,

Associate Director for International Programs, Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, MD, USA; Dr I. Moore, Product and Quality Assurance Manager, Croda Europe Ltd, Snaith, England; Dr K. Morimoto, Expert, Office of Review Management, Review Planning Division, Pharmaceutical and Medical Devices Agency, Tokyo, Japan; Dr O. Morin, Regulatory and Scientific Affairs, International Federation of Pharmaceutical Manufacturers and Associations, Geneva, Switzerland; Dr A.E. Muhairwe, Executive Secretary and Registrar, National Drug Authority, Kampala, Uganda; Dr T. Nunn, Clinical Director of Pharmacy, Royal Liverpool Children's NHS Trust and Associate Director, Medicines for Children Research Network, University of Liverpool, Liverpool, England; Dr A. Nyrup, Specialist, DFP QA Logistics and Manufacturing Development, Novo Nordisk, Gentofte, Denmark; Dr A. Ojoo, United Nations Children's Fund, New York, NY, USA; Dr S. Parra, Acting Manager, Generic Drug Quality Division 1, Bureau of Pharmaceutical Sciences, Therapeutic Products Directorate, Health Canada, Ottawa, Canada; Dr J. Pogány, Budapest, Hungary; Dr J.-L. Robert, Laboratoire National de Santé, Luxembourg; Dr A. Pontén-Engelhardt, Head of Stability Management, Global Quality, Operations, AstraZeneca, Södertälje, Sweden; Ms A. Poompanich, Bangkok, Thailand; Dr S. Rönninger, Global Quality Manager, F. Hoffmann-La Roche, Basel, Switzerland; Dr C. Sánchez, CECMED, Havana, Cuba; Dr L.M. Santos, Scientific Liaison – International Health, The United States Pharmacopeia, Rockville, MD, USA; Dr A. Seiter, Member, United States Pharmacopeia International Health Expert Committee, Rockville, MD, USA; Dr U. Shah, Formulation Research Fellow, Cheshire, Merseyside & North Wales LRN, Medicines for Children Research Network, Royal Liverpool Children's NHS Trust, Liverpool, England; Dr M. Sigonda, Director-General, Tanzania Food and Drugs Authority, Dar-es-Salaam, United Republic of Tanzania; Dr S. Singh, Professor and Head, Department of Pharmaceutical Analysis, National Institute of Pharmaceutical Education and Research, Nagar, Punjab, India; Dr G.N. Singh, Secretary-cum-Scientific Director, Government of India, Ministry of Health and Family Welfare, Central Indian Pharmacopoeia Laboratory, Ghaziabad, India; Ms K. Sinivuo, Senior Researcher and Secretary, National Agency for Medicines, Helsinki, Finland; Dr L. Slamet, Deputy for Therapeutic Product & Narcotic, Psychotropic and Addictive Substance Control, National Agency of Drug and Food Control, Jakarta, Indonesia; Dr C. Sokhan, Deputy Director, Department of Drug and Food, Phnom Penh, Cambodia; Dr L. Stoppa, Agenzia Italiana del Farmaco, Rome, Italy; Dr D. Teitz, Manager, Bristol-Myers Squibb Company, New Brunswick, NJ, USA; Dr B.B. Thapa, Chief Drug Administrator, Department of Drug Administration, Ministry of Health and Population, Kathmandu, Nepal; Dr R. X. Torano, Pharmacopoeial Intelligence and Advocacy Specialist, GlaxoSmithKline, Brentford, Middlesex, England; Ms M. Treebamroong, Senior Pharmacist, Drug Quality and Safety, Department of Medical Sciences, Bureau of Drug and Narcotic, Ministry of Public Health, Nonthaburi, Thailand; Mr R. Tribe, Holder, Australian Capital Territory, Australia; Dr C. Tuleu, Senior Lecturer and Deputy Director, Department of Pharmaceutics and Centre for Paediatric Pharmacy Research, School of Pharmacy, University of London, London, England; Dr A.R.T. Utami, National Agency for Drugs and Food Control, Jakarta Pusat, Indonesia; Mrs M. Vallender, Editor-in-Chief, British Pharmacopoeia Commission Secretariat, London, England; Mr P. van der Hoeven, APIC Secretary General and Cefic Manager, Active

Pharmaceutical Ingredients Committee, European Chemical Industry Council, Brussels, Belgium; Dr L. Virgili, USA; Professor Wang Ping, Deputy Director, China Pharmacopoeia Committee, Beijing, People's Republic of China; Dr G. Wang'ang'a, Head, Microbiological and Medical Devices Units, National Quality Control Laboratory, Nairobi, Kenya; Dr A. Ward, Regulatory Affairs, Avecia Vaccines, Billingham, England; Dr W. Watson, Associate Manager, CMC Regulatory Affairs, Gilead Sciences International, Cambridge, England; Dr D.E. Webber, Director-General, World Self-Medication Industry, Ferney-Voltaire, France; Professor W. Wieniawski, Polish Pharmaceutical Society, Warsaw, Poland; Mr E. Wondemagegnehu, Addis Ababa, Ethiopia; Dr B. Wright, Group Manager, GMP/GDP, North East Region, Medicines Inspectorate, Medicines and Healthcare products Regulatory Agency, York, England; Professor Yang Zhong-Yuan, Guangzhou Municipal Institute for Drug Control, Guangzhou, People's Republic of China; Dr M. Zahn, Keltern, Germany; Dr Hua Zhang, GMP Department Head, Center for Certification & Evaluation, Shanghai Food and Drug Administration, Shanghai, People's Republic of China; Professor Zhong-Yuan Yang, Member, United States Pharmacopeia International Health Expert Committee, Rockville, MD, USA.

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Annex 1

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

General information

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

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

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

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

The stability of the International Chemical Reference Substances kept at the Collaborating Centre is monitored by regular re-examination and any material that has deteriorated is replaced by new batches when necessary. Lists giving control numbers for the current batches are issued in the annual reports from the Centre and new lists may also be obtained on request.

Ordering information

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

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

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

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

The invoice number must be quoted when payment is made.

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

It is regretted that payment by letter of credit (L/C) cannot be accepted.

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

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

The administration charge of US$ 10 covers the cost for **handling and dispatch by airmail** (small parcel or air parcel post). If **registered airmail**

or **express airmail** is required, an extra charge is added. If safe delivery is possible by means of airmail, this ought to be preferred as it is much less expensive for all parties.

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

Available International Chemical Reference Substances

Catalogue number	Reference substance	Package size	Control number
9931422	abacavir sulfate	100 mg	106238
9931552	abacavir sulfate for system suitability	10 mg	107244
9930375	*p*-acetamidobenzalazine	25 mg	290042
9930202	acetazolamide	100 mg	186128
9930204	allopurinol	100 mg	287049
9930206	amidotrizoic acid	100 mg	196205
9930191	2-amino-5-nitrothiazole	25 mg	186131
9930194	3-aminopyrazole-4-carboxamide hemisulfate	100 mg	172050
9930193	3-amino-2,4,6-triiodobenzoic acid	100 mg	196206
9930208	amitriptyline hydrochloride	100 mg	181101
9930209	amodiaquine hydrochloride	200 mg	192160
9931426	amoxicillin trihydrate	100 mg	106242
9930210	amphotericin B	400 mg	191153
9930211	ampicillin (anhydrous)	200 mg	390001
9930212	ampicillin sodium	200 mg	388002
9930213	ampicillin trihydrate	200 mg	274003
9930214	anhydrotetracycline hydrochloride	25 mg	206096
9931408	artemether	100 mg	103225
9931406	artemisinin	100 mg	103222
9931407	artemotil	100 mg	103226
9931410	artenimol	100 mg	103223
9931409	artesunate	100 mg	103224
9930215	atropine sulfate	100 mg	183111
9930216	azathioprine	100 mg	172060
9930218	bacitracin zinc	200 mg	192174
9930219	beclometasone dipropionate	200 mg	192175
9930225	benzylpenicillin potassium	200 mg	180099
9930226	benzylpenicillin sodium	200 mg	280047
9930227	bephenium hydroxynaphthoate	100 mg	183112
9930228	betamethasone	100 mg	183113

Catalogue number	Reference substance	Package size	Control number
9930229	betamethasone sodium phosphate	100 mg	196203
9930230	betamethasone valerate	100 mg	190145
9930233	bupivacaine hydrochloride	100 mg	289054
9930234	caffeine	100 mg	181102
9930236	calcium folinate (leucovorin calcium)	100 mg	194188
9930237	captopril	100 mg	197214
9930238	captopril disulfide	25 mg	198216
9930239	carbamazepine	100 mg	189143
9930240	carbenicillin monosodium	200 mg	383043
9930241	chloramphenicol	200 mg	486004
9930242	chloramphenicol palmitate	1 g	286072
9930243	chloramphenicol palmitate (polymorph A)	200 mg	175073
9930199	5-chloro-2-methylaminobenzophenone	100 mg	172061
9930245	chloroquine sulfate	200 mg	195201
9930190	2-(4-chloro-3-sulfamoylbenzoyl)benzoic acid	50 mg	181106
9930246	chlorphenamine hydrogen maleate	100 mg	182109
9930247	chlorpromazine hydrochloride	100 mg	178080
9930248	chlortalidone	100 mg	183114
9930249	chlortetracycline hydrochloride	200 mg	187138
9930250	cimetidine	100 mg	190150
9930256	ciprofloxacin hydrochloride	400 mg	197210
9930252	ciprofloxacin by-compound A	20 mg	198220
9930253	ciprofloxacin desfluoro-compound	20 mg	198219
9930255	ciprofloxacin fluoroquinolonic acid	20 mg	198217
9930258	cisplatin	100 mg	197207
9930259	clomifene citrate	100 mg	187136
	clomifene citrate Z-isomer *see* zuclomifene		
9930261	cloxacillin sodium	200 mg	274005
9930263	cortisone acetate	100 mg	167006
9930265	dapsone	100 mg	183115
9930266	desoxycortone acetate	100 mg	167007
9930267	dexamethasone	100 mg	388008
9930268	dexamethasone acetate	100 mg	288009
9930269	dexamethasone phosphoric acid	100 mg	192161
9930270	dexamethasone sodium phosphate	100 mg	192158
9930282	diazoxide	100 mg	181103

Catalogue number	Reference substance	Package size	Control number
9930283	dicloxacillin sodium	200 mg	174071
9930285	dicoumarol	100 mg	178077
9931413	didanosine	10 mg	104228
9931414	didanosine for system suitability	10 mg	104230
9930287	diethylcarbamazine dihydrogen citrate	100 mg	181100
9930288	digitoxin	100 mg	277010
9930289	digoxin	100 mg	587011
9930290	dopamine hydrochloride	100 mg	192159
9930292	doxorubicin hydrochloride	100 mg	196202
9930294	emetine hydrochloride	100 mg	187134
9931411	efavirenz	100 mg	104229
9930197	4-epianhydrotetracycline hydrochloride	25 mg	306097
9930198	4-epitetracycline hydrochloride	25 mg	306098
9930295	ergocalciferol (vitamin D_2)	500 mg	190147
9930296	ergometrine hydrogen maleate	50 mg	277012
9930297	ergotamine tartrate	50 mg	385013
9930298	erythromycin	250 mg	191154
9930299	erythromycin B	25 mg	205186
9930300	erythromycin C	25 mg	194187
9930301	estradiol benzoate	100 mg	167014
9930302	estrone	100 mg	279015
9930304	ethambutol hydrochloride	100 mg	179081
9930305	ethinylestradiol	100 mg	301016
9930306	ethisterone	100 mg	167017
9930307	ethosuximide	100 mg	179088
9930309	flucloxacillin sodium	200 mg	195194
9930310	flucytosine	100 mg	184121
9930311	fludrocortisone acetate	200 mg	195199
9930312	fluorouracil	100 mg	184122
9930313	fluphenazine decanoate dihydrochloride	100 mg	182107
9930314	fluphenazine enantate dihydrochloride	100 mg	182108
9930315	fluphenazine hydrochloride	100 mg	176076
9930316	folic acid	100 mg	388019
9930195	3-formylrifamycin	200 mg	202149
9930355	framycetin sulfate (neomycin B sulfate)	200 mg	193178
9930318	furosemide	100 mg	171044

Catalogue number	Reference substance	Package size	Control number
9930319	gentamicin sulfate	100 mg	205183
9930322	griseofulvin	200 mg	280040
9930323	haloperidol	100 mg	172063
9930324	hydrochlorothiazide	100 mg	179087
9930325	hydrocortisone	100 mg	283020
9930326	hydrocortisone acetate	100 mg	280021
9930327	hydrocortisone sodium succinate	200 mg	194184
9930188	(–)-3-(4-hydroxy-3-methoxyphenyl)-2-hydrazino-2-methylalanine (3-*o*-methylcarbidopa)	25 mg	193180
9930189	(–)-3-(4-hydroxy-3-methoxyphenyl)-2-methylalanine (3-*o*-methylmethyldopa)	25 mg	179085
9930328	ibuprofen	100 mg	183117
9930329	imipramine hydrochloride	100 mg	172064
9931415	indinavir	100 mg	105231
9930330	indometacin	100 mg	178078
9930331	isoniazid	100 mg	185124
9930332	kanamycin monosulfate	12 mg	197211
9931416	lamivudine	100 mg	105232
9931553	lamivudine for system suitability	10 mg	107246
9930333	lanatoside C	100 mg	281022
9930334	levodopa	100 mg	295065
9930335	levonorgestrel	200 mg	194182
9930336	levothyroxine sodium	50 mg	207144
9930337	lidocaine	100 mg	181104
9930338	lidocaine hydrochloride	100 mg	181105
9930339	liothyronine sodium	50 mg	193179
9930340	loperamide hydrochloride	100 mg	194185
9930341	mebendazole	200 mg	195195
9930454	medroxyprogesterone acetate	100 mg	106241
	Melting point reference substances		
9930217	azobenzene (69 °C)	1 g	192168

Catalogue number	Reference substance	Package size	Control number
9930438	vanillin (83 °C)	1 g	299169
9930222	benzil (96 °C)	1 g	294170
9930201	acetanilide (116 °C)	1 g	297171
9930380	phenacetin (136 °C)	1 g	297172
9930221	benzanilide (165 °C)	1 g	192173
9930422	sulfanilamide (166 °C)	1 g	192162
9930423	sulfapyridine (193 °C)	1 g	192163
9930286	dicyanodiamide (210 °C)	1 g	192164
9930411	saccharin (229 °C)	1 g	202165
9930235	caffeine (237 °C)	1 g	299166
9930382	phenolphthalein (263 °C)	1 g	299167
9930345	methotrexate	100 mg	194193
	3-*o*-methylcarbidopa *see* (–)-3-(4-hydroxy-3-methoxyphenyl)-2-hydrazino-2-methylalanine		
	3-*o*-methylmethyldopa *see* (–)-3-(4-hydroxy-3-methoxyphenyl)-2-methylalanine		
9930346	methyldopa	100 mg	179084
9930347	methyltestosterone	100 mg	167023
9930348	meticillin sodium	200 mg	274024
9930350	metronidazole	100 mg	183118
9930351	nafcillin sodium	200 mg	272025
9931417	nelfinavir mesilate	100 mg	105233
	neomycin B sulfate *see* framycetin sulfate		
9930356	neostigmine metilsulfate	100 mg	187135
9931412	nevirapine anhydrous	100 mg	104227
9931423	nevirapine impurity B	10 mg	106239
9930357	nicotinamide	100 mg	200090
9930358	nicotinic acid	100 mg	179091
9930359	nifurtimox	100 mg	194189
9930360	niridazole	200 mg	186129
9930361	niridazole-chlorethylcarboxamide	25 mg	186130
9930366	norethisterone	100 mg	186132
9930367	norethisterone acetate		185123
9972123	norethisterone enantate	50 mg	107243
9930369	nystatin	200 mg	405152
9930371	ouabain	100 mg	283026

Catalogue number	Reference substance	Package size	Control number
9930372	oxacillin sodium	200 mg	382027
9930373	oxytetracycline dihydrate	200 mg	189142
9930374	oxytetracycline hydrochloride	200 mg	189141
9930376	papaverine hydrochloride	100 mg	185127
9930377	paracetamol	100 mg	195198
9930378	paromomycin sulfate	75 mg	195197
9930383	phenoxymethylpenicillin	200 mg	179082
9930384	phenoxymethylpenicillin calcium	200 mg	179083
9930385	phenoxymethylpenicillin potassium	200 mg	176075
9930387	phenytoin	100 mg	179089
9930388	piperazine adipate	100 mg	197212
9930389	piperazine citrate	100 mg	197213
9930390	praziquantel	100 mg	194191
9930391	prednisolone	100 mg	389029
9930392	prednisolone acetate	100 mg	289030
9930393	prednisolone hemisuccinate	200 mg	195196
9930394	prednisolone sodium phosphate	200 mg	194190
9930395	prednisone	100 mg	167031
9930396	prednisone acetate	100 mg	169032
9930397	probenecid	100 mg	192156
9930398	procaine hydrochloride	100 mg	183119
9930399	procarbazine hydrochloride	100 mg	184120
9930400	progesterone	100 mg	167033
9930402	propranolol hydrochloride	100 mg	187139
9930403	propylthiouracil	100 mg	185126
9930404	pyrantel embonate (pyrantel pamoate)	500 mg	192157
9931424	pyrazinamide	100 mg	106240
9930405	pyridostigmine bromide	100 mg	182110
9930406	reserpine	100 mg	186133
9930408	riboflavin	250 mg	382035
9930409	rifampicin	300 mg	203151
9930410	rifampicin quinone	200 mg	202148
9931421	ritonavir	100 mg	105237
9931418	saquinavir mesilate	100 mg	105234
9930412	sodium amidotrizoate	100 mg	198221

Catalogue number	Reference substance	Package size	Control number
9930413	sodium cromoglicate	100 mg	188140
9930415	spectinomycin hydrochloride	200 mg	193176
9931419	stavudine	100 mg	105235
9930416	streptomycin sulfate	100 mg	197215
9930417	sulfacetamide	100 mg	196200
9930419	sulfamethoxazole	100 mg	179092
9930420	sulfamethoxypyridazine	100 mg	178079
9930421	sulfanilamide	100 mg	179094
9930424	sulfasalazine	100 mg	191155
9930425	tamoxifen citrate	100 mg	196208
9930426	tamoxifen *E*-isomer	10 mg	205209
9930427	testosterone enantate	200 mg	194192
9930428	testosterone propionate	100 mg	167036
9930429	tetracycline hydrochloride	200 mg	205095
9930430	thioacetazone	100 mg	171046
9930196	4,4'-thiodianiline	50 mg	183116
	thyroxine sodium *see* levothyroxine sodium		
9930431	tolbutamide	100 mg	179086
9930432	tolnaftate	100 mg	176074
9930433	toluene-2-sulfonamide	100 mg	196204
9930434	trimethadione	200 mg	185125
9930435	trimethoprim	100 mg	179093
9930439	warfarin	100 mg	168041
9931420	zidovudine	100 mg	105236
9931554	zidovudine impurity B	10 mg	107247
9930260	zuclomifene	50 mg	187137

List of available International Infrared Reference Spectra

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

The current price is US$ 5 for a single spectrum and US$ 200 for a set of 50 spectra, including a hardcover binder. The binder can be ordered separately for US$ 10. An administrative charge of US$ 10 is added to each order to cover costs for handling and dispatch by airmail or air parcel post.

Orders should be sent to:
WHO Collaborating Centre for Chemical Reference Substances
Apoteket AB
Produktion & Laboratorier
Farmaci/Centrallaboratoriet (ACL)
Prismavägen 2
SE-141 75 Kungens Kurva
Sweden
Fax: + 46 8 740 60 40
e-mail: who.apl@apoteket.se
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The following International Infrared Reference Spectra are available from the Centre:

aceclidine salicylate
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allopurinol
amiloride hydrochloride
amitriptyline hydrochloride
ampicillin trihydrate

beclometasone dipropionate
benzylpenicillin potassium
biperiden
biperiden hydrochloride
bupivacaine hydrochloride

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

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

erythromycin ethylsuccinate
erythromycin stearate
etacrynic acid
ethionamide
ethosuximide

furosemide

gallamine triethiodide
glibenclamide

haloperidol
hydrochlorothiazide

ibuprofen
imipramine hydrochloride
indometacin
isoniazid

lidocaine
lidocaine hydrochloride
lindane

metronidazole
miconazole nitrate

niclosamide
nicotinamide
noscapine

oxamniquine

papaverine hydrochloride
phenobarbital
phenoxymethylpenicillin calcium
phenytoin
primaquine phosphate
propylthiouracil
protionamide
pyrimethamine

salbutamol
salbutamol sulfate
sulfadimidine
sulfadoxine
sulfamethoxazole
sulfamethoxypyridazine

tiabendazole
trihexyphenidyl hydrochloride
trimethoprim

valproic acid
verapamil hydrochloride

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Annex 2

Stability testing of active pharmaceutical ingredients and finished pharmaceutical products

1. Introduction

1.1 Objectives of these guidelines

These guidelines seek to exemplify the core stability data package required for registration of active pharmaceutical ingredients (APIs) and finished pharmaceutical products (FPPs), replacing the previous WHO guidelines in this area (*1*,*2*). However, alternative approaches can be used when they are scientifically justified. Further guidance can be found in International Conference on Harmonisation (ICH) guidelines (*3*) and in the WHO *guidelines on the active pharmaceutical ingredient master file procedure* (*4*).

It is recommended that these guidelines should also be applied to products that are already being marketed, with allowance for an appropriate transition period, e.g. upon re-registration or upon re-evaluation.

1.2 Scope of these guidelines

These guidelines apply to new and existing APIs and address information to be submitted in original and subsequent applications for marketing authorization of their related FPP for human use. These guidelines are not applicable to stability testing for biologicals (for details on vaccines please see *WHO guidelines for stability evaluation of vaccines* (*5*)).

1.3 General principles

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. In fixed-dose combination FPPs (FDCs) the interaction between two or more APIs also has to be considered.

As a result of stability testing a re-test period for the API (in exceptional cases, e.g. for unstable APIs, a shelf-life is given) or a shelf-life for the FPP can be established and storage conditions can be recommended.

Various analyses have been done to identify suitable testing conditions for WHO Member States based on climatic data and are published in the literature (*6–9*) on the basis of which each Member State can make its decision on long-term (real-time) stability testing conditions. Those Member States that have notified WHO of the long-term stability testing conditions they require when requesting a marketing authorization are listed in Appendix 1.

2. Guidelines

2.1 Active pharmaceutical ingredient

2.1.1 *General*

Information on the stability of the API is an integral part of the systematic approach to stability evaluation. Potential attributes to be tested on an API during stability testing are listed in the examples of testing parameters (Appendix 2).

The re-test period or shelf-life assigned to the API by the API manufacturer should be derived from stability testing data.

2.1.2 *Stress testing*

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.

For an API the following approaches may be used:

— when available, it is acceptable to provide the relevant data published in the scientific literature to support the identified degradation products and pathways;
— when no data are available, stress testing should be performed.

Stress testing may be carried out on a single batch of the API. It should include the effect of temperature (in 10 °C increments (e.g. 50 °C, 60 °C, etc.) above the temperature used for accelerated testing), humidity (e.g. 75% relative humidity (RH) or greater) and, where appropriate, oxidation and photolysis on the API. The testing should also evaluate the susceptibility of the API to hydrolysis across a justified range of pH values when in solution or suspension (*10*).

Assessing the necessity for photostability testing should be an integral part of a stress testing strategy. More details can be found in other guidelines (*3*).

Results from these studies will form an integral part of the information provided to regulatory authorities.

2.1.3 *Selection of batches*

Data from stability studies on at least three primary batches of the API should normally be provided. The batches should be manufactured to a minimum of pilot scale by the same synthesis route as production batches, and using a method of manufacture and procedure that simulates the final process to be used for production batches. The overall quality of the batches

of API placed on stability studies should be representative of the quality of the material to be made on a production scale.

For existing active substances that are known to be stable, data from at least two primary batches should be provided.

2.1.4 *Container closure system*

The stability studies should be conducted on the API packaged in a container closure system that is the same as, or simulates, the packaging proposed for storage and distribution.

2.1.5 *Specification*

Stability studies should include testing of those attributes of the API that are susceptible to change during storage and are likely to influence quality, safety and/or efficacy. The testing should cover, as appropriate, the physical, chemical, biological and microbiological attributes. A guide as to the potential attributes to be tested in the stability studies is provided in Appendix 2.

Validated stability-indicating analytical procedures should be applied. Whether and to what extent replication should be performed will depend on the results from validation studies (*11*).

2.1.6 *Testing frequency*

For long-term studies, frequency of testing should be sufficient to establish the stability profile of the API.

For APIs with a proposed re-test period or shelf-life of at least 12 months, the frequency of testing at the long-term storage condition should normally be every three months over the first year, every six months over the second year, and annually thereafter throughout the proposed re-test period or shelf-life.

At the accelerated storage condition, a minimum of three time points, including the initial and final time points (e.g. 0, 3 and 6 months), from a six-month study is recommended. Where it is expected (based on development experience) that results from accelerated studies are likely to approach significant change criteria, increased testing should be conducted either by adding samples at the final time point or by including a fourth time point in the study design. When testing at the intermediate storage condition is called for as a result of significant change at the accelerated storage condition, a minimum of four time points, including the initial and final time points (e.g. 0, 6, 9 and 12 months), from a 12-month study is recommended.

2.1.7 *Storage conditions*

In general an API should be evaluated under storage conditions (with appropriate tolerances) that test its thermal stability and, if applicable, its

sensitivity to moisture. The storage conditions and the lengths of studies chosen should be sufficient to cover storage and shipment.

Storage condition tolerances are defined as the acceptable variations in temperature and relative humidity of storage facilities for stability studies. The equipment used should be capable of controlling the storage conditions within the ranges defined in these guidelines. The storage conditions should be monitored and recorded. Short-term environmental changes due to opening the doors of the storage facility are accepted as unavoidable. The effect of excursions due to equipment failure should be assessed, addressed and reported if judged to affect stability results. Excursions that exceed the defined tolerances for more than 24 hours should be described in the study report and their effects assessed.

The long-term testing should normally take place over a minimum of 12 months for the number of batches specified in section 2.1.3 at the time of submission, and should be continued for a period of time sufficient to cover the proposed re-test period or shelf-life. For existing substances that are known to be stable, data covering a minimum of six months may be submitted. Additional data accumulated during the assessment period of the registration application should be submitted to the authorities upon request. Data from the accelerated storage condition and, if appropriate, from the intermediate storage condition can be used to evaluate the effect of short-term excursions outside the label storage conditions (such as might occur during shipping).

Long-term, accelerated and, where appropriate, intermediate storage conditions for APIs are detailed in sections 2.1.7.1–2.1.7.3. The general case applies if the API is not specifically covered by a subsequent section. Alternative storage conditions can be used if justified.

If long-term studies are conducted at 25 °C ± 2 °C/60% RH ± 5% RH and "significant change" occurs at any time during six months' testing at the accelerated storage condition, additional testing at the intermediate storage condition should be conducted and evaluated against significant change criteria. In this case, testing at the intermediate storage condition should include all long-term tests, unless otherwise justified, and the initial application should include a minimum of six months' data from a 12-month study at the intermediate storage condition.

"Significant change" for an API is defined as failure to meet its specification.

2.1.7.1 ***General case***

Study	Storage condition	Minimum time period covered by data at submission
Long-term[a]	25 °C ± 2 °C/60% RH ± 5% RH or 30 °C ± 2 °C/65% RH ± 5% RH or 30 °C ± 2 °C/75% RH ± 5% RH	12 months or 6 months as described in point 2.1.7
Intermediate[b]	30 °C ± 2 °C/65% RH ± 5% RH	6 months
Accelerated	40 °C ± 2 °C/75% RH ± 5% RH	6 months

[a] Whether long-term stability studies are performed at 25 °C ± 2 °C/60% RH ± 5% RH or 30 °C ± 2 °C/65% RH ± 5% RH or 30 °C ± 2 °C/75% RH ± 5% RH is determined by the climatic condition under which the API is intended to be stored (see Appendix 1). Testing at a more severe long-term condition can be an alternative to testing condition, i.e. 25 °C/60% RH or 30 °C/65% RH.

[b] If 30 °C ± 2 °C/65% RH ± 5% RH or 30 °C ± 2 °C/75% RH ± 5% RH is the long-term condition there is no intermediate condition.

2.1.7.2 ***Active pharmaceutical ingredients intended for storage in a refrigerator***

Study	Storage condition	Minimum time period covered by data at submission
Long-term	5 °C ± 3 °C	12 months
Accelerated[a]	25 °C ± 2 °C/60% RH ± 5% RH or 30 °C ± 2 °C/65% RH ± 5% RH or 30 °C ± 2 °C/75% RH ± 5% RH	6 months

[a] Whether accelerated stability studies are performed at 25 ± 2 °C/60% RH ± 5% RH or 30 °C ± 2 °C/65% RH ± 5% RH or 30 °C ± 2 °C/75% RH ± 5% RH is based on a risk-based evaluation. Testing at a more severe long-term condition can be an alternative to storage testing at 25 °C/60%RH or 30 °C/65%RH.

Data on refrigerated storage should be assessed according to the evaluation section of these guidelines, except where explicitly noted below.

If significant change occurs between three and six months' testing at the accelerated storage condition, the proposed re-test period should be based on the data available at the long-term storage condition.

If significant change occurs within the first three months' testing at the accelerated storage condition a discussion should be provided to address the effect of short-term excursions outside the label storage condition, e.g. during shipping or handling. This discussion can be supported, if appropriate, by further testing on a single batch of the API for a period shorter than three months but with more frequent testing than usual. It is considered unnecessary to continue to test an API for the whole six months when a significant change has occurred within the first three months.

2.1.7.3 ***Active pharmaceutical ingredients intended for storage in a freezer***

Study	Storage condition	Minimum time period covered by data at submission
Long-term	-20 °C ± 5 °C	12 months

In the rare case of any API of non-biological origin being intended for storage in a freezer, the re-test period or shelf-life should be based on the long-term data obtained at the long-term storage condition. In the absence of an accelerated storage condition for APIs intended to be stored in a freezer, testing on a single batch at an elevated temperature (e.g. 5 °C ± 3 °C or 25 °C ± 2 °C or 30 °C ± 2 °C) for an appropriate time period should be conducted to address the effect of short-term excursions outside the proposed label storage condition, e.g. during shipping or handling.

2.1.7.4 ***Active pharmaceutical ingredients intended for storage below -20°C***

APIs intended for storage below -20 °C should be treated on a case-by-case basis.

2.1.8 *Stability commitment*

When the available long-term stability data on primary batches do not cover the proposed re-test period granted at the time of approval, a commitment should be made to continue the stability studies post-approval in order to firmly establish the re-test period or shelf-life.

Where the submission includes long-term stability data on the number of production batches specified in section 2.1.3 covering the proposed re-test period, a post-approval commitment is considered unnecessary. Otherwise one of the following commitments should be made:

- If the submission includes data from stability studies on the number of production batches specified in section 2.1.3, a commitment should be made to continue these studies through the proposed re-test period.
- If the submission includes data from stability studies on fewer than the number of production batches specified in section 2.1.3, a commitment should be made to continue these studies through the proposed re-test period and to place additional production batches, to a total of at least three, in long-term stability studies through the proposed re-test period.
- If the submission does not include stability data on production batches, a commitment should be made to place the first two or three production batches (see section 2.1.3) on long-term stability studies through the proposed re-test period.

The stability protocol used for long-term studies for the stability commitment should be the same as that for the primary batches, unless otherwise scientifically justified.

2.1.9 *Evaluation*

The purpose of the stability study is to establish, based on testing a minimum of the number of batches specified in section 2.1.3, unless otherwise justified and authorized, of the API and evaluating the stability information (including, as appropriate, results of the physical, chemical, biological and microbiological tests), a re-test period applicable to all future batches of the API manufactured under similar circumstances. The degree of variability of individual batches affects the confidence that a future production batch will remain within specification throughout the assigned re-test period.

The data may show so little degradation and so little variability that it is apparent from looking at them that the requested re-test period will be granted. Under these circumstances it is normally unnecessary to go through the statistical analysis; providing a justification for the omission should be sufficient.

An approach for analysing the data on a quantitative attribute that is expected to change with time is to determine the time at which the 95% one-sided confidence limit for the mean curve intersects the acceptance criterion. If analysis shows that the batch-to-batch variability is small, it is advantageous to combine the data into one overall estimate. This can be done by first applying appropriate statistical tests (e.g. p values for level of significance of rejection of more than 0.25) to the slopes of the regression lines and zero time intercepts for the individual batches. If it is inappropriate to combine data from several batches, the overall re-test period should be based on the minimum time a batch can be expected to remain within acceptance criteria.

The nature of any degradation relationship will determine whether the data should be transformed for linear regression analysis. Usually the relationship can be represented by a linear, quadratic or cubic function on an arithmetic or logarithmic scale. As far as possible, the choice of model should be justified by a physical and/or chemical rationale and should also take into account the amount of available data (parsimony principle to ensure a robust prediction). Statistical methods should be employed to test the goodness of fit of the data on all batches and combined batches (where appropriate) to the assumed degradation line or curve.

Limited extrapolation of the long-term data from the long-term storage condition beyond the observed range to extend the re-test period can be undertaken if justified. This justification should be based on what is known about the mechanism of degradation, the results of testing under accelerated conditions, the goodness of fit of any mathematical model, batch size and existence of supporting stability data. However, this extrapolation assumes that the same degradation relationship will continue to apply beyond the observed data.

Any evaluation should cover not only the assay but also the levels of degradation products and other appropriate attributes. Where appropriate, attention should be paid to reviewing the adequacy of evaluation linked to FPP stability and degradation "behaviour" during the testing.

2.1.10 *Statements and labelling*

A storage statement should be established for display on the label based on the stability evaluation of the API. Where applicable specific instructions should be provided, particularly for APIs that cannot tolerate freezing or excursions in temperature. Terms such as "ambient conditions" or "room temperature" should be avoided.

The recommended labelling statements for use if supported by the stability studies are provided in Appendix 3.

A re-test period should be derived from the stability information, and a re-test date should be displayed on the container label if appropriate.

2.1.11 *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, and can be expected to remain, within specifications under the storage conditions indicated on the label, within the re-test period in all future batches.

The ongoing stability programme should be described in a written protocol and the results presented in a formal report.

The protocol for an ongoing stability programme should extend to the end of the re-test period and shelf-life 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); and
— other applicable parameters specific to the API.

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 (*12*). In certain situations additional batches should be included in the ongoing stability programme. For example, an ongoing stability study should be conducted after any significant change or significant deviation to the synthetic route, process or container closure system which may have an impact upon the stability of the API (*13*).

Out-of-specification results or significant atypical trends should be investigated. Any confirmed significant change, out-of-specification result, or significant atypical trend should be reported immediately to the relevant finished product manufacturer. The possible impact on batches on the market should be considered in consultation with the relevant finished product manufacturers and the competent authorities.

A summary of all the data generated, including any interim conclusions on the programme, should be written and maintained. This summary should be subjected to periodic review.

2.2 Finished pharmaceutical product

2.2.1 *General*

The design of the stability studies for the FPP should be based on knowledge of the behaviour and properties of the API, information from stability studies on the API and on experience gained from preformulation studies and investigational FPPs.

2.2.2 *Selection of batches*

Data from stability studies should be provided on at least three primary batches of the FPP. The primary batches should be of the same formulation and packaged in the same container closure system as proposed for marketing. The manufacturing process used for primary batches should simulate that to be applied to production batches and should provide product of the same quality and meeting the same specification as that intended for marketing. In the case of conventional dosage forms with APIs that are known to be stable, data from at least two primary batches should be provided.

Two of the three batches should be at least pilot-scale batches and the third one can be smaller, if justified. 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.

2.2.3 *Container closure system*

Stability testing should be conducted on the dosage form packaged in the container closure system proposed for marketing. Any available studies carried out on the FPP outside its immediate container or in other packaging materials can form a useful part of the stress testing of the dosage form or can be considered as supporting information, respectively.

2.2.4 *Specification*

Stability studies should include testing of those attributes of the FPP that are susceptible to change during storage and are likely to influence quality, safety, and/or efficacy. The testing should cover, as appropriate, the physical, chemical, biological and microbiological attributes, preservative content (e.g. antioxidant or antimicrobial preservative) and functionality tests (e.g. for a dose delivery system). Examples of testing parameters in the stability studies are listed in Appendix 2. Analytical procedures should be fully validated and stability-indicating. Whether and to what extent replication should be performed will depend on the results of validation studies.

Shelf-life acceptance criteria should be derived from consideration of all available stability information. It may be appropriate to have justifiable differences between the shelf-life and release acceptance criteria based on the stability evaluation and the changes observed on storage. Any differences between the release and shelf-life acceptance criteria for antimicrobial preservative content should be supported by a validated correlation of chemical content and preservative effectiveness demonstrated during development of the pharmaceutical product with the product in its final formulation (except for preservative concentration) intended for marketing. 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.

2.2.5 *Testing frequency*

For long-term studies, frequency of testing should be sufficient to establish the stability profile of the FPP.

For products with a proposed shelf-life of at least 12 months, the frequency of testing at the long-term storage condition should normally be every three months over the first year, every six months over the second year and annually thereafter throughout the proposed shelf-life.

At the accelerated storage condition, a minimum of three time points, including the initial and final time points (e.g. 0, 3 and 6 months), from a six-month study is recommended. Where an expectation (based on

development experience) exists that results from accelerated testing are likely to approach significant change criteria, testing should be increased either by adding samples at the final time point or by including a fourth time point in the study design.

When testing at the intermediate storage condition is called for as a result of significant change at the accelerated storage condition, a minimum of four time points, including the initial and final time points (e.g. 0, 6, 9 and 12 months), from a 12-month study is recommended.

Reduced designs, i.e. matrixing or bracketing, where the testing frequency is reduced or certain factor combinations are not tested at all, can be applied if justified (*3*).

2.2.6 *Storage conditions*

In general an FPP should be evaluated under storage conditions with specified tolerances that test its thermal stability and, if applicable, its sensitivity to moisture or potential for solvent loss. The storage conditions and the lengths of studies chosen should be sufficient to cover storage, shipment and subsequent use with due regard to the climatic conditions in which the product is intended to be marketed.

Photostability testing, which is an integral part of stress testing, should be conducted on at least one primary batch of the FPP if appropriate. More details can be found in other guidelines (*3*).

The orientation of the product during storage, i.e. upright versus inverted, may need to be included in a protocol where contact of the product with the closure system may be expected to affect the stability of the products contained, or where there has been a change in the container closure system.

Storage condition tolerances are usually defined as the acceptable variations in temperature and relative humidity of storage facilities for stability studies. The equipment used should be capable of controlling the storage conditions within the ranges defined in these guidelines. The storage conditions should be monitored and recorded. Short-term environmental changes due to opening of the doors of the storage facility are accepted as unavoidable. The effect of excursions due to equipment failure should be assessed, addressed and reported if judged to affect stability results. Excursions that exceed the defined tolerances for more than 24 hours should be described in the study report and their effects assessed.

The long-term testing should cover a minimum of six or 12 months at the time of submission and should be continued for a period of time sufficient to cover the proposed shelf-life. For an FPP containing an API that is known to be stable and where no significant change is observed in the FPP stability

studies at accelerated and long-term conditions for at least 6 months data covering a minimum of six months should be submitted.

Additional data accumulated during the assessment period of the registration application should be submitted to the authorities if requested. Data from the accelerated storage condition and from the intermediate conditions, where appropriate, can be used to evaluate the effect of short-term excursions outside the label storage conditions (such as might occur during shipping).

Long-term, accelerated and, where appropriate, intermediate storage conditions for FPPs are detailed in the sections below. The general case applies if the FPP is not specifically covered by a subsequent section (2.1.7.1). Alternative storage conditions can be used if justified.

2.2.6.1 ***General case***

Study	Storage condition	Minimum time period covered by data at submission
Long-term[a]	25 °C ± 2 °C/60% RH ± 5% RH or 30 °C ± 2 °C/65% RH ± 5% RH or 30 °C ± 2 °C/75% RH ± 5% RH	12 months or 6 months as referred to in section 2.2.6
Intermediate[b]	30 °C ± 2 °C/65% RH ± 5% RH	6 months
Accelerated	40 °C ± 2 °C/75% RH ± 5% RH	6 months

[a] Whether long-term stability studies are performed at 25 °C ± 2 °C/60% RH ± 5% RH or 30 °C ± 2 °C/65% RH ± 5% RH or 30 °C ± 2 °C/75% RH ± 5% RH is determined by the climatic zone in which the FPP is intended to be marketed . Testing at a more severe long-term condition can be an alternative to storage at 25 °C/60% RH or 30 °C/65% RH.

[b] If 30 °C ± 2 °C/65% RH ± 5% RH or 30 °C ± 2 °C/75% RH ± 5% RH is the long-term condition, there is no intermediate condition.

If long-term studies are conducted at 25 °C ± 2 °C/60% RH ± 5% RH and "significant change" occurs at any time during six months' testing at the accelerated storage condition, additional testing at the intermediate storage condition should be conducted and evaluated against significant change criteria. In this case the initial application should include a minimum of six months' data from a 12-month study at the intermediate storage condition.

In general "significant change" for an FPP is defined as:

- A change from the initial content of API(s) of 5% or more detected by assay, or failure to meet the acceptance criteria for potency when using biological or immunological procedures. (*Note*: Other values may be applied, if justified, to certain products, such as multivitamins and herbal preparations.)
- Any degradation product exceeding its acceptance criterion.
- Failure to meet the acceptance criteria for appearance, physical attributes and functionality test (e.g. colour, phase separation, resuspendability,

caking, hardness, dose delivery per actuation). However, some changes in physical attributes (e.g. softening of suppositories, melting of creams, partial loss of adhesion for transdermal products) may be expected under accelerated conditions.

Also, as appropriate for the dosage form:

- failure to meet the acceptance criterion for pH;

or

- failure to meet the acceptance criteria for dissolution for 12 dosage units.

2.2.6.2 *FPPs packaged in impermeable containers*

Parameters required to classify the packaging materials as permeable or impermeable depend on the characteristics of the packaging material, such as thickness and permeability coefficient. The suitability of the packaging material used for a particular product is determined by its product characteristics. Containers generally considered to be moisture-impermeable include glass ampoules.

Sensitivity to moisture or potential for solvent loss is not a concern for FPPs packaged in impermeable containers that provide a permanent barrier to passage of moisture or solvent. Thus stability studies for products stored in impermeable containers can be conducted under any controlled or ambient relative humidity condition.

2.2.6.3 *FPPs packaged in semi-permeable containers*

Aqueous-based products packaged in semi-permeable containers should be evaluated for potential water loss in addition to physical, chemical, biological and microbiological stability. This evaluation can be carried out under conditions of low relative humidity, as discussed below. Ultimately it should be demonstrated that aqueous-based FPPs stored in semi-permeable containers could withstand environments with low relative humidity.

Other comparable approaches can be developed and reported for non-aqueous, solvent-based products.

Study	Storage condition	Minimum time period covered by data at submission
Long-term[a]	25 °C ± 2 °C/40% RH ± 5% RH or 30 °C ± 2 °C/35% RH ± 5% RH	12 months
Intermediate	30 °C ± 2 °C/65% RH ± 5% RH	6 months
Accelerated	40 °C ± 2 °C/not more than (NMT) 25% RH	6 months

[a] Whether long-term stability studies are performed at 25 °C ± 2 °C/40% RH ± 5% RH or 30 °C ± 2 °C/35% RH ± 5% RH is determined by the climatic condition under which the FPP is intended to be marketed. Testing at 30 °C/35% RH can be an alternative to the storage condition at 25 °C/40% RH.

Products meeting either of the long-term storage conditions and the accelerated conditions, as specified in the table above, have demonstrated the integrity of the packaging in semi-permeable containers. A significant change in water loss alone at the accelerated storage condition does not necessitate testing at the intermediate storage condition. However, data should be provided to demonstrate that the pharmaceutical product would not have significant water loss throughout the proposed shelf-life if stored at 25 °C/40% RH or 30 °C/35% RH.

For long-term studies conducted at 25 °C ± 2 °C/40% RH ± 5% RH, that fail the accelerated testing with regard to water loss and any other parameters, additional testing at the "intermediate" storage condition should be performed as described under the general case to evaluate the temperature effect at 30 °C.

A 5% loss in water from its initial value is considered a significant change for a product packaged in a semi-permeable container after an equivalent of three months' storage at 40 °C not more than (NMT) 25% RH. However, for small containers (1 ml or less) or unit-dose products, a water loss of 5% or more after an equivalent of three months' storage at 40 °C/NMT 25% RH may be appropriate, if justified.

An alternative approach to studies at the low relative humidity as recommended in the table above (for either long-term or accelerated testing) is to perform the stability studies under higher relative humidity and deriving the water loss at the low relative humidity through calculation. This can be achieved by experimentally determining the permeation coefficient for the container closure system or, as shown in the example below, using the calculated ratio of water loss rates between the two humidity conditions at the same temperature. The permeation coefficient for a container closure system can be experimentally determined by using the worst-case scenario (e.g. the most diluted of a series of concentrations) for the proposed FPP.

Example of an approach for determining water loss

For a product in a given container closure system, container size and fill, an appropriate approach for deriving the rate of water loss at the low relative humidity is to multiply the rate of water loss measured at an alternative relative humidity at the same temperature, by a water loss rate ratio shown in the table below. A linear water loss rate at the alternative relative humidity over the storage period should be demonstrated.

For example, at a given temperature, e.g. 40 °C, the calculated rate of water loss during storage at NMT 25% RH is the rate of water loss measured at 75% RH multiplied by 3.0, the corresponding water loss rate ratio.

Low-humidity testing conditions	Alternative testing condition	Ratio of water loss rates	Calculation
25 °C/40% RH	25 °C/60% RH	1.5	(100-40)/(100-60)
30 °C/35% RH	30 °C/65% RH	1.9	(100-35)/(100-65)
30 °C/35% RH	30 °C/75% RH	2.6	(100-35)/(100-75)
40 °C/NMT 25% RH	40 °C/75% RH	3.0	(100-25)/(100-75)

Valid water loss rate ratios at relative humidity conditions other than those shown in the table above can also be used.

2.2.6.4 ***FPPs intended for storage in a refrigerator***

Study	Storage condition	Minimum time period covered by data at submission
Long-term	5 °C ± 3 °C	12 months
Accelerated[a]	25 °C ± 2 °C/60% RH ± 5% RH or 30 °C ± 2 °C/65% RH ± 5% RH or 30 °C ± 2 °C/75% RH ± 5% RH	6 months

[a] Whether accelerated stability studies are performed at 25 ± 2 °C/60% RH ± 5% RH or 30 °C ± 2 °C/65% RH ± 5% RH or 30 °C ± 2 °C/75% RH ± 5% RH is based on a risk-based evaluation. Testing at a more severe accelerated condition can be an alternative to the storage condition at 25 °C/60% RH or 30 °C/65% RH.

If the FPP is packaged in a semi-permeable container, appropriate information should be provided to assess the extent of water loss.

Data from refrigerated storage should be assessed according to the evaluation section of these guidelines, except where explicitly noted below.

If significant change occurs between three and six months' testing at the accelerated storage condition, the proposed shelf-life should be based on the data available from the long-term storage condition.

If significant change occurs within the first three months' testing at the accelerated storage condition, a discussion should be provided to address the effect of short-term excursions outside the label storage condition, e.g. during shipment and handling. This discussion can be supported, if appropriate, by further testing on a single batch of the FPP for a period shorter than three months but with more frequent testing than usual. It is considered unnecessary to continue to test a product throughout six months when a significant change has occurred within the first three months of accelerated studies at the specific condition chosen in accordance with the risk analysis.

2.2.6.5 ***FPPs intended for storage in a freezer***

Study	Storage condition	Minimum time period covered by data at submission
Long-term	–20 °C ± 5 °C	12 months

For FPPs intended for storage in a freezer, the shelf-life should be based on the long-term data obtained at the long-term storage condition. In the absence of an accelerated storage condition for FPPs intended to be stored in a freezer, testing on a single batch at an elevated temperature (e.g. 5 °C ± 3 °C or 25 °C ± 2 °C or 30 °C ± 2 °C) for an appropriate time period should be conducted to address the effect of short-term excursions outside the proposed label storage condition.

2.2.6.6 ***FPPs intended for storage below -20 °C***

FPPs intended for storage at temperatures below -20 °C should be treated on a case-by-case basis.

2.2.7 *Stability commitment*

When the available long-term stability data on primary batches do not cover the proposed shelf-life granted at the time of approval, a commitment should be made to continue the stability studies post-approval to firmly establish the shelf-life.

Where the submission includes long-term stability data from the production batches as specified in section 2.2.2 covering the proposed shelf-life, a post-approval commitment is considered unnecessary. Otherwise, one of the following commitments should be made:

- If the submission includes data from stability studies on at least the number of production batches specified in section 2.2.2, a commitment should be made to continue the long-term studies throughout the proposed shelf-life and the accelerated studies for six months.
- If the submission includes data from stability studies on fewer than the number of production batches specified in section 2.2.2, a commitment should be made to continue the long-term studies throughout the proposed shelf-life and the accelerated studies for six months, and to place additional production batches, to a total of at least three, on long-term stability studies throughout the proposed shelf-life and on accelerated studies for six months.
- If the submission does not include stability data on production batches, a commitment should be made to place the first two or three production batches (see section 2.2.2) on long-term stability studies throughout the proposed shelf-life and on accelerated studies for six months.

The stability protocol used for studies on commitment batches should be the same as that for the primary batches, unless otherwise scientifically justified.

2.2.8 *Evaluation*

A systematic approach should be adopted to the presentation and evaluation of the stability information, which should include, as appropriate, results from the physical, chemical, biological and microbiological tests, including particular attributes of the dosage form (for example, dissolution rate for solid oral dosage forms).

The purpose of the stability study is to establish, based on testing a minimum number of batches of the FPP as specified in section 2.2.2, a shelf-life and label storage instructions applicable to all future batches of the FPP manufactured under similar circumstances. The degree of variability of individual batches affects the confidence that a future production batch will remain within specification throughout its shelf-life.

Where the data show so little degradation and so little variability that it is apparent from looking at the data that the requested shelf-life will be granted, it is normally unnecessary to go through the statistical analysis. However, a provisional shelf-life of 24 months may be established provided the following conditions are satisfied:

- The API is known to be stable (not easily degradable).
- Stability studies, as outlined above in section 2.1.11, have been performed and no significant changes have been observed.
- Supporting data indicate that similar formulations have been assigned a shelf-life of 24 months or more.
- The manufacturer will continue to conduct long-term studies until the proposed shelf-life has been covered, and the results obtained will be submitted to the national medicines regulatory authority.

An approach for analysing the data on a quantitative attribute that is expected to change with time is to determine the time at which the 95% one-sided confidence limit for the mean curve intersects the acceptance criterion. If analysis shows that the batch-to-batch variability is small, it is advantageous to combine the data into one overall estimate. This can be done by first applying appropriate statistical tests (e.g. p values for level of significance of rejection of more than 0.25) to the slopes of the regression lines and zero time intercepts for the individual batches. If it is inappropriate to combine data from several batches, the overall shelf-life should be based on the minimum time a batch can be expected to remain within acceptance criteria.

The nature of any degradation relationship will determine whether the data should be transformed for linear regression analysis. Usually the

relationship can be represented by a linear, quadratic or cubic function on an arithmetic or logarithmic scale. As far as possible, the choice of model should be justified by a physical and/or chemical rationale and should also take into account the amount of available data (parsimony principle to ensure a robust prediction).

Statistical methods should be employed to test the goodness of fit of the data on all batches and combined batches (where appropriate) to the assumed degradation line or curve.

Limited extrapolation of the long-term data from the long-term storage condition beyond the observed range to extend the shelf-life can be undertaken, if justified. This justification should be based on what is known about the mechanism of degradation, the results of testing under accelerated conditions, the goodness of fit of any mathematical model, batch size and the existence of supporting stability data. However, this extrapolation assumes that the same degradation relationship will continue to apply beyond the observed data.

Any evaluation should consider not only the assay but also the degradation products and other appropriate attributes. Where appropriate, attention should be paid to reviewing the adequacy of evaluation linked to FPP stability and degradation "behaviour" during the testing.

2.2.9 *Statements and labelling*

A storage statement should be established for the label based on the stability evaluation of the FPP. Where applicable, specific instructions should be provided, particularly for FPPs that cannot tolerate freezing. Terms such as "ambient conditions" or "room temperature" must be avoided.

There should be a direct link between the storage statement on the label and the demonstrated stability of the FPP. An expiry date should be displayed on the container label.

The recommended labelling statements for use, if supported by the stability studies, are provided in Appendix 3.

In principle, FPPs should be packed in containers that ensure stability and protect the FPP from deterioration. A storage statement should not be used to compensate for inadequate or inferior packaging. Additional labelling statements could be used in cases where the results of the stability testing demonstrate limiting factors (see also Appendix 3).

2.2.10 *In-use stability*

The purpose of in-use stability testing is to provide information for the labelling on the preparation, storage conditions and utilization period of

multidose products after opening, reconstitution or dilution of a solution, e.g. an antibiotic injection supplied as a powder for reconstitution.

As far as possible the test should be designed to simulate the use of the FPP in practice, taking into consideration the filling volume of the container and any dilution or reconstitution before use. At intervals comparable to those which occur in practice appropriate quantities should be removed by the withdrawal methods normally used and described in the product literature.

The physical, chemical and microbial properties of the FPP susceptible to change during storage should be determined over the period of the proposed in-use shelf-life. If possible, testing should be performed at intermediate time points and at the end of the proposed in-use shelf-life on the final amount of the FPP remaining in the container. Specific parameters, e.g. for liquids and semi-solids, preservatives, per content and effectiveness, need to be studied.

A minimum of two batches, at least pilot-scale batches, should be subjected to the test. At least one of these batches should be chosen towards the end of its shelf-life. If such results are not available, one batch should be tested at the final point of the submitted stability studies.

This testing should be performed on the reconstituted or diluted FPP throughout the proposed in-use period on primary batches as part of the stability studies at the initial and final time points and, if full shelf-life, long-term data are not available before submission, at 12 months or the last time point at which data will be available.

In general this testing need not be repeated on commitment batches (see 2.2.10).

2.2.11 *Variations*

Once the FPP has been registered, additional stability studies are required whenever variations that may affect the stability of the API or FPP are made, such as major variations (*13*).

The following are examples of such changes:

— change in the manufacturing process;
— change in the composition of the FPP;
— change of the immediate packaging;
— change in the manufacturing process of an API.

In all cases of variations, the applicant should investigate whether the intended change will or will not have an impact on the quality characteristics of APIs and/or FPPs and consequently on their stability.

The scope and design of the stability studies for variations and changes are based on the knowledge and experience acquired on APIs and FPPs.

The results of these stability studies should be communicated to the regulatory authorities concerned (*14*).

2.2.12 *Ongoing stability studies*

After a marketing authorization has been granted, the stability of the FPP should be monitored according to a continuous appropriate programme that will permit the detection of any stability issue (e.g. changes in levels of impurities or dissolution profile) associated with the formulation in the container closure system in which it is marketed. The purpose of the ongoing stability programme is to monitor the product over its shelf-life and to determine that the product remains, and can be expected to remain, within specifications under the storage conditions on the label.

This mainly applies to the FPP in the container closure system in which it is supplied, but consideration should also be given to inclusion in the programme of bulk products. For example, when the bulk product is stored for a long period before being packaged and/or shipped from a manufacturing site to a packaging site, the impact on the stability of the packaged product should be evaluated and studied. Generally this would form part of development studies, but where this need has not been foreseen, inclusion of a one-off study in the ongoing stability programme could provide the necessary data. Similar considerations could apply to intermediates that are stored and used over prolonged periods.

The ongoing stability programme should be described in a written protocol and results formalized as a report.

The protocol for an ongoing stability programme should extend to the end of the shelf-life period and should include, but not be limited to, the following parameters:

— number of batch(es) per strength and different batch sizes, if applicable. The batch size should be recorded, if different batch sizes are employed;
— 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 product labelling, should be used); and
— other applicable parameters specific to the FPP.

The protocol for the ongoing stability programme can be different from that of the initial long-term stability study as submitted in the marketing authorization dossier provided that this is justified and documented in the

protocol (for example, the frequency of testing, or when updating to meet revised recommendations).

The number of batches and frequency of testing should provide sufficient data to allow for trend analysis. Unless otherwise justified, at least one batch per year of product manufactured in every strength and every primary packaging type, if relevant, should be included in the stability programme (unless none is produced during that year). The principle of bracketing and matrixing designs may be applied if scientifically justified in the protocol (*15*).

In certain situations additional batches should be included in the ongoing stability programme. For example, an ongoing stability study should be conducted after any significant change or significant deviation to the process or container closure system. Any reworking, reprocessing or recovery operation should also be considered for inclusion (*13*).

Out-of-specification results or significant atypical trends should be investigated. Any confirmed significant change, out-of-specification result, or significant atypical trend should be reported immediately to the relevant competent authorities. The possible impact on batches on the market should be considered in consultation with the relevant competent authorities.

A summary of all the data generated, including any interim conclusions on the programme, should be written and maintained. This summary should be subjected to periodic review.

3. Glossary

The definitions provided below apply to the words and phrases used in these guidelines. Although an effort has been made to use standard definitions as far as possible, they may have different meanings in other contexts and documents. The following definitions are provided to facilitate interpretation of the guidelines. The definitions are consistent with those published in other WHO quality assurance guidelines. The Quality Assurance of Medicines Terminology Database was established in August 2005 and includes the definitions of terms related to quality assurance of medicines. This database is intended to help harmonize terminology and to avoid misunderstandings that may result from the different terms and their interpretations used in various WHO publications. The main publications used as a source of information to create the Quality Assurance of Medicines Terminology Database are the quality assurance guidelines included in the 36th–42nd reports of the WHO Expert Committee on Specifications for Pharmaceutical Preparations.

accelerated testing

Studies designed to increase the rate of chemical degradation and physical change of an API or FPP by using exaggerated storage conditions as part of

the stability testing programme. The data thus obtained, in addition to those derived from long-term stability studies, may be used to assess longer-term chemical effects under non-accelerated conditions and to evaluate the impact of short-term excursions outside the label storage conditions, as might occur during shipping. The results of accelerated testing studies are not always predictive of physical changes.

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.

batch

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

bracketing

The design of a stability schedule such that only samples at the extremes of certain design factors, e.g. strength and package size, are tested at all time points as in a full design. The design assumes that the stability of any intermediate levels is represented by the stability of the extremes tested. Where a range of strengths is to be tested, bracketing is applicable if the strengths are identical or very closely related in composition (e.g. for a tablet range made with different compression weights of a similar basic granulation, or a capsule range made by filling different plug fill weights of the same basic composition into different size capsule shells). Bracketing can be applied to different container sizes or different fills in the same container closure system.

climatic zone

The zones into which the world is divided based on the prevailing annual climatic conditions (see Appendix 1).

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.

container closure system

The sum of packaging components that together contains and protects the dosage form. This includes primary packaging components and secondary packaging components, if the latter are intended to provide additional protection to the FPP. A packaging system is equivalent to a container closure system.

dosage form

The form of the FPP, e.g. tablet, capsule, elixir or suppository.

excipient

A substance or compound, other than the API and packaging materials, that is intended or designated to be used in the manufacture of a FPP.

expiry date

The date given on the individual container (usually on the label) of a product up to and including which the API and FPP are expected to remain within specifications, if stored correctly. It is established for each batch by adding the shelf-life to the date of manufacture.

finished pharmaceutical product (FPP)

A product that has undergone all stages of production, including packaging in its final container and labelling. An FPP may contain one or more APIs.

impermeable containers

Containers that provide a permanent barrier to the passage of gases or solvents, e.g. sealed aluminium tubes for semisolids, sealed glass ampoules for solutions and aluminium/aluminium blisters for solid dosage forms.

in use

See Utilization period

long-term stability studies

Experiments on the physical, chemical, biological, biopharmaceutical and microbiological characteristics of an API or FPP, during and beyond the expected shelf-life and storage periods of samples under the storage conditions expected in the intended market. The results are used to establish the re-test period or the shelf-life, to confirm the projected re-test period and shelf-life, and to recommend storage conditions.

matrixing

The design of a stability schedule such that a selected subset of the total number of possible samples for all factor combinations is tested at a specified time point. At a subsequent time point, another subset of samples for all factor combinations is tested. The design assumes that the stability of each subset of samples tested represents the stability of all samples at a given time point. The differences in the samples for the same FPP should be identified as, for example, covering different batches, different strengths, different sizes of the same container closure system, and, possibly in some cases, different container closure systems.

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 re-test period (or shelf-life) of the API, or confirm or extend the shelf-life of the FPP.

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.

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 re-test period or shelf-life, as the case may be. A primary batch of an API should be at least a pilot-scale batch. For an FPP, two of the three batches should be at least pilot-scale batches, and the third batch can be smaller if it is representative with regard to the critical manufacturing steps. However, a primary batch may be a production batch.

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.

provisional shelf-life

A provisional expiry date which is based on acceptable accelerated and available long-term data for the FPP to be marketed in the proposed container closure system.

release specification

The combination of physical, chemical, biological, and microbiological tests and acceptance criteria that determine the suitability of an API or FPP at the time of its release.

re-test date

The date after which an active API should be re-examined to ensure that the material is still in compliance with the specification and thus is still suitable for use in the manufacture of an FPP.

re-test period

The period of time during which the API is expected to remain within its specification and, therefore, can be used in the manufacture of a given FPP, provided that the API has been stored under the defined conditions. After this period a batch of API destined for use in the manufacture of an FPP should be re-tested for compliance with the specification and then used immediately. A batch of API can be re-tested multiple times and a different portion of the batch used after each re-test, as long as it continues to comply with the specification. For most substances known to be labile, it is more appropriate to establish a shelf-life than a re-test period. The same may be true for certain antibiotics.

semi-permeable containers

Containers that allow the passage of solvent, usually water, while preventing solute loss. The mechanism for solvent transport occurs by adsorption into one container surface, diffusion through the bulk of the container material, and desorption from the other surface. Transport is driven by a partial-pressure gradient. Examples of semi-permeable containers include plastic bags and semi-rigid, low-density polyethylene (LDPE) pouches for large volume parenterals (LVPs), and LDPE ampoules, bottles and vials.

shelf-life

The period of time during which an API or FPP, if stored correctly, is expected to comply with the specification as determined by stability studies on a number of batches of the API or FPP. The shelf-life is used to establish the expiry date of each batch.

shelf-life specification

The combination of physical, chemical, biological, and microbiological tests and acceptance criteria that an FPP should meet throughout its shelf-life. In certain exceptional cases an unstable API might have a shelf-life specification (see section 1.3).

significant change

(See section 2.2.6.1.)

In general "significant change" for an FPP is defined as:

1. A 5% or more change in assay from its initial content of API(s), or failure to meet the acceptance criteria for potency when using biological or immunological procedures. (*Note*: other values may be applied,

if justified, to certain products, such as multivitamins and herbal preparations.)
2. Any degradation product exceeding its acceptance criterion.
3. Failure to meet the acceptance criteria for appearance, physical attributes and functionality test (e.g. colour, phase separation, resuspendability, caking, hardness, dose delivery per actuation). However, some changes in physical attributes (e.g. softening of suppositories, melting of creams or partial loss of adhesion for transdermal products) may be expected under accelerated conditions.

Also, as appropriate for the dosage form:

4. Failure to meet the acceptance criterion for pH.

Or

5. Failure to meet the acceptance criteria for dissolution for 12 dosage units.

specification

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.

stability indicating methods

Validated analytical procedures that can detect the changes with time in the chemical, physical or microbiological properties of the API or FPP, and that are specific so that the content of the API, degradation products, and other components of interest can be accurately measured without interference.

stability studies (stability testing)

Long-term and accelerated (and intermediate) studies undertaken on primary and/or commitment batches according to a prescribed stability protocol to establish or confirm the re-test period (or shelf-life) of an API or the shelf-life of an FPP.

stress testing (of the API)

Studies undertaken to elucidate the intrinsic stability of API. Such testing is part of the development strategy and is normally carried out under more severe conditions than those used for accelerated testing.

stress testing (of the FPP)

Studies undertaken to assess the effect of severe conditions on the FPP. Such studies include photostability testing and specific testing on certain products (e.g. metered dose inhalers, creams, emulsions, refrigerated aqueous liquid products).

supporting stability data

Supplementary data, such as stability data on small-scale batches, related formulations, and products presented in containers not necessarily the same as those proposed for marketing, and scientific rationales that support the analytical procedures, the proposed re-test period or the shelf-life and storage conditions.

utilization period

A period of time during which a reconstituted preparation of the finished dosage form in an unopened multidose container can be used.

References

1. Guidelines for stability testing of pharmaceutical products containing well established drug substances in conventional dosage forms. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-fourth report.* Geneva, World Health Organization, 1996, Annex 5 (WHO Technical Report Series, No. 863).

   These guidelines were revised at the thirty-seventh and fortieth meetings of the WHO Expert Committee on Specifications for Pharmaceutical Preparations. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-seventh report.* Geneva, World Health Organization, 2003 (WHO Technical Report Series, No. 908), p. 13 and *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fortieth report.* Geneva, World Health Organization, 2006 (WHO Technical Report Series, No. 937), p. 12.

2. *Regional Guidelines on stability testing of active substances and pharmaceutical products for the WHO Eastern Mediterranean Region*. August 2006 (http://www.emro.who.int/edb/media/pdf/EMRC5312En.pdf).

3. The following ICH Guidelines may be consulted in the context of stability testing:

   International Conference on Harmonisation. *ICH Q1A* (*R2*)*: Stability testing of new drug substances and products* (http://www.ich.org/LOB/media/MEDIA419.pdf).

   International Conference on Harmonisation. *ICH Q1B: Photostability testing of new drug substances and products* (http://www.ich.org/LOB/media/MEDIA412.pdf).

   International Conference on Harmonisation. *ICH Q1C: Stability testing of new dosage forms* (http://www.ich.org/LOB/media/MEDIA413.pdf).

   International Conference on Harmonisation. *ICH Q1D: Bracketing and matrixing designs for stability testing of new drug substances and products* (http://www.ich.org/LOB/media/MEDIA414.pdf).

   International Conference on Harmonisation. *ICH Q1E: Evaluation for stability data* (http://www.ich.org/LOB/media/MEDIA415.pdf).

   International Conference on Harmonisation. *ICH Q2R1*)*: Validation of analytical procedures: text and methodology* (http://www.ich.org/LOB/media/MEDIA417.pdf).

International Conference on Harmonisation. *ICH Q3A: Impurities in new drug substances* (http://www.ich.org/LOB/media/MEDIA422.pdf).

International Conference on Harmonisation. *ICH Q3B: Impurities in new drug products* (http://www.ich.org/LOB/media/MEDIA421.pdf).

International Conference on Harmonisation. *ICH Q5C: Stability testing of biotechnological/biological products* (http://www.ich.org/LOB/media/MEDIA427.pdf).

International Conference on Harmonisation. *ICH Q6A: Specifications: Test procedures and acceptance criteria for new drug substances and new drug products: Chemical substances* (http://www.ich.org/LOB/media/MEDIA430.pdf).

International Conference on Harmonisation. ICH Q6B: *Specifications: Test procedures and acceptance criteria for biotechnological/biological products* (http://www.ich.org/LOB/media/MEDIA432.pdf).

Further information can be found on the ICH homepage: http://www.ich.org/cache/compo/276-254-1.html.

4. Guidelines on active pharmaceutical ingredient master file procedure. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-second report*. Geneva, World Health Organization, 2008, Annex 4 (WHO Technical Report Series, No. 948).
5. WHO guidelines for stability evaluation of vaccines. In: *WHO Expert Committee on Biological Standardization. Fifty-seventh report.* Geneva, World Health Organization (WHO Technical Report Series, (in press)) (http://www.who.int/biologicals/publications/trs/areas/vaccines/stability/en/index.html).
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9. Zahn M. et al. 2006. A risk-based approach to establish stability testing conditions for tropical countries. *Journal of Pharmaceutical Sciences*, 95:946–965.

   Erratum: *Journal of Pharmaceutical Sciences*, 2007, 96:2177.
10. 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, Annex 5 (WHO Technical Report Series, No. 929).
11. Supplementary guidelines on good manufacturing practices: validation. 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, Chapter 1.

12. WHO good manufacturing practices: main principles for pharmaceutical products. 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, Chapter 1.
13. Guidance on variations to a prequalified product dossier. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-first report*. Geneva, World Health Organization, 2007, Annex 6 (WHO Technical Report Series, No. 943).
14. *Prequalification Programme – Priority Essential Medicines. A United Nations Programme managed by WHO. Information for applicants* (http://mednet3.who.int/prequal/).
15. *ASEAN Guideline on stability study of drug product*, 9th ACCSQ-PPWG Meeting, Philippines, 21–24 February 2005, version 22 February 2005.

Additional reading

Accelerated stability studies of widely used pharmaceutical substances under simulated tropical conditions. Geneva, World Health Organization, 1986 (WHO/PHARM/86.529).

Appendix 1

Long-term stability testing conditions as identified by WHO Member States[1]

In order to be able to reduce the amount of stability testing required, the number of different long-term testing conditions must be reduced to a sufficient extent. This approach was proposed by Paul Schumacher in 1972 (*1*) and by Wolfgang Grimm in 1986 (*2*), and in 1998 (*3*) when they defined four different long-term testing conditions, which match with the climatic conditions of the target markets categorized in just four different climatic zones. This concept is described in regulatory guidelines and pharmacopoeias and has become an established standard in developing finished pharmaceutical products (FPPs).

At the fortieth meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations held in Geneva in October 2005 (*4*), it was recommended to split the current Climatic Zone IV (hot and humid) into two zones: Climatic Zone IVA – for which 30 °C/65% RH will remain the standard long-term testing condition – and Climatic Zone IVB for which, if justified, 30 °C/75% RH will become the long-term testing condition. The criteria and long-term testing conditions proposed are listed in Table 1.

Table 1

Proposed criteria and long-term testing conditions

Climatic zone	**Definition**	**Criteria** Mean annual temperature measured in the open air/ mean annual partial water vapour pressure	**Long-term testing conditions**
I	Temperate climate	≤ 15 °C / ≤ 11 hPa	21 °C / 45% RH
II	Subtropical and Mediterranean climate	> 15 to 22 °C / > 11 to 18 hPa	25 °C / 60% RH
III	Hot and dry climate	> 22 °C / ≤ 15 hPa	30 °C / 35% RH
IVA	Hot and humid climate	> 22 °C / > 15 to 27 hPa	30 °C / 65% RH
IVB	Hot and very humid climate	> 22 °C / > 27 hPa	30 °C / 75% RH

[1] Any corrections or amendments should be addressed to the Medicines Quality Assurance Programme, Essential Medicines and Pharmaceutical Policies, World Health Organization, Avenue Appia, CH-1211 Geneva 27, Switzerland, for the attention of Dr S. Kopp.

Additional testing conditions, i.e. accelerated and – if applicable – intermediate conditions have to be used as described in these guidelines.

Selection of the conditions for stability testing is based on a risk analysis. Testing at a more severe long-term condition can be an alternative to storage testing at 25 °C/60% RH or 30 °C/65% RH.

The evaluation of the climatic conditions by each WHO Member State resulted in the recommended storage condition for long-term stability studies shown in Table 2 (in some of the countries listed, more extreme conditions are also accepted). The list is grouped by WHO regional offices.

Table 2
Stability conditions for WHO Member States by Region

Member State	**Stability conditions** Confirmed long-term testing condition
Regional Office for Africa (AFRO)	
Algeria	[*25 °C/60% RH*][3]
Angola	[*30 °C/65% RH*][3]
Benin	[*30 °C/65% RH*][3]
Botswana	[*25 °C/60% RH*][3]
Burkina Faso	30 °C/60% RH[2]
Burundi	[*30 °C/65% RH*][3]
Cameroon	30 °C/75% RH[2]
Cape Verde	[*30 °C/65% RH*][3]
Central African Republic	30 °C/75% RH[2]
Chad	[*30 °C/65% RH*][3]
Comoros	[*30 °C/65% RH*][3]
Congo	[*30 °C/65% RH*][3]
Côte d'Ivoire	[*30 °C/65% RH*][3]
Democratic Republic of the Congo	[*30 °C/65% RH*][3]
Equatorial Guinea	[*30 °C/65% RH*][3]
Eritrea	[*30 °C/65% RH*][3]
Ethiopia	[*30 °C/65% RH*][3]
Gabon	[*30 °C/65% RH*][3]
Gambia	**30 °C/65% RH**[1]
Ghana	30 °C/75% RH[2]
Guinea	[*30 °C/65% RH*][3]
Guinea-Bissau	[*30 °C/65% RH*][3]
Kenya	[*30 °C/65% RH*][3]
Lesotho	30 °C/75% RH[2]
Liberia	[*30 °C/65% RH*][3]
Madagascar	**30 °C/65% RH**[1]
Malawi	25 °C/60% RH[2]
Mali	[*30 °C/65% RH*][3]

Member State	**Stability conditions** Confirmed long-term testing condition
Mauritania	[*30 °C/65% RH*][3]
Mauritius	[*30 °C/65% RH*][3]
Mozambique	30 °C/75% RH[2]
Namibia	**30 °C/65% RH**[1]
Niger	[*30 °C/65% RH*][3]
Nigeria	30 °C/75% RH[2]
Rwanda	[*30 °C/65% RH*][3]
Sao Tome and Principe	30 °C/75% RH[2]
Senegal	[*30 °C/65% RH*][3]
Seychelles	[*30 °C/65% RH*][3]
Sierra Leone	30 °C/75% RH[2]
South Africa	**30 °C/65% RH**[1]
Swaziland	[*25 °C/60% RH*][3]
Togo	30 °C/75% RH[2]
Uganda	**30 °C/65% RH**[1]
United Republic of Tanzania	30 °C/75% RH[2]
Zambia	**25 °C/60% or 30 °C/65% RH**[1]
Zimbabwe	30 °C/75% RH[2]
Regional Office for the Americas (AMRO)	
Antigua and Barbuda	[*30 °C/75% RH*][3]
Argentina	*25* °C/60% RH[2]
Bahamas	[*30 °C/65% RH*][3]
Barbados	30 °C/75% RH[2]
Belize	[*30 °C/65% RH*][3]
Bolivia	[*30 °C/70% RH or 30 °C/75% RH*][3]
Brazil	**30 °C/75% RH**[1]
Canada	**30 °C/65% RH**[1]
Chile	30 °C/65% RH[2]
Colombia	[*30 °C/75% RH*][3]
Costa Rica	30 °C/65% RH[2]
Cuba	30 °C/75% RH[2]
Dominica	[*30 °C/65% RH*][3]
Dominican Republic	[*30 °C/65% RH*][3]
Ecuador	[*30 °C/65% RH*][3]
El Salvador	[*30 °C/65% RH*][3]
Grenada	[*30 °C/65% RH*][3]
Guatemala	[*30 °C/65% RH*][3]
Guyana	[*30 °C/70% RH or 30 °C/75% RH*][3]
Haiti	[*30 °C/65% RH*][3]
Honduras	[*30 °C/65% RH*][3]
Jamaica	[*30 °C/65% RH*][3]
Mexico	[*25 °C/60% RH*][3]

Member State	**Stability conditions** Confirmed long-term testing condition
Nicaragua	[*30 °C/65% RH*][3]
Panama	[*30 °C/75% RH*][3]
Paraguay	[*30 °C/65% RH*][3]
Peru	**30 °C/75% RH**[1]
Saint Kitts and Nevis	[*30 °C/65% RH*][3]
Saint Lucia	30 °C/75% RH[2]
Saint Vincent and the Grenadines	[*30 °C/75% RH*][3]
Suriname	[*30 °C/70% RH or 30 °C/75% RH*][3]
Trinidad and Tobago	[*30 °C/65% RH*][3]
United States of America	**25 °C/60% or 30 °C/65% RH**[1]
Uruguay	[*25 °C/60% RH*][3]
Venezuela (Bolivarian Republic of)	[*30 °C/70% RH or 30 °C/75% RH*][3]
Regional Office for the Eastern Mediterranean (EMRO)	
Afghanistan	**30 °C/65% RH**[1]
Bahrain	**30 °C/65% RH**[1]
Djibouti	**30 °C/65% RH**[1]
Egypt	**30 °C/65% RH**[1]
Iran (Islamic Republic of)	**30 °C/65% RH**[1]
Iraq	**30 °C/35% RH**[1]
Jordan	**30 °C/65% RH**[1]
Kuwait	**30 °C/65% RH**[1]
Lebanon	**25 °C/60% RH**[1]
Libyan Arab Jamahiriya	**25 °C/60% RH**[1]
Morocco	**25 °C/60% RH**[1]
Oman	**30 °C/65% RH**[1]
Pakistan	**30 °C/65% RH**[1]
Qatar	**30 °C/65% RH**[1]
Saudi Arabia	**30 °C/65% RH**[1]
Somalia	**30 °C/65% RH**[1]
Sudan	**30 °C/65% RH**[1]
Syrian Arab Republic	**25 °C/60% RH**[1]
Tunisia	**25 °C/60% RH**[1]
United Arab Emirates	**30 °C/65% RH**[1]
Yemen	**30 °C/65% RH**[1]
Regional Office for Europe (EURO)	
Albania	[*25 °C/60% RH*][3]
Andorra	[*25 °C/60% RH*][3]
Armenia	[*25 °C/60% RH*][3]
Austria	**25 °C/60% or 30 °C/65% RH**[1]
Azerbaijan	30 °C/65% RH[2]

Member State	**Stability conditions** Confirmed long-term testing condition
Belarus	[*25 °C/60% RH*][3]
Belgium	**25 °C/60% or 30 °C/65% RH**[1]
Bosnia and Herzegovina	[*25 °C/60% RH*][3]
Bulgaria	**25 °C/60% or 30 °C/65% RH**[1]
Croatia	[*25 °C/60% RH*][3]
Cyprus	**25 °C/60% or 30 °C/65% RH**[1]
Czech Republic	**25 °C/60% or 30 °C/65% RH**[1]
Denmark	**25 °C/60% or 30 °C/65% RH**[1]
Estonia	**25 °C/60% or 30 °C/65% RH**[1]
Finland	**25 °C/60% or 30 °C/65% RH**[1]
France	**25 °C/60% or 30 °C/65% RH**[1]
Georgia	[*25 °C/60% RH*][3]
Germany	**25 °C/60% or 30 °C/65% RH**[1]
Greece	**25 °C/60% or 30 °C/65% RH**[1]
Hungary	**25 °C/60% or 30 °C/65% RH**[1]
Iceland	[*25 °C/60% RH*][3]
Ireland	**25 °C/60% or 30 °C/65% RH**[1]
Israel	30 °C/70% or 30 °C/75% RH[2]
Italy	**25 °C/60% or 30 °C/65% RH**[1]
Kazakhstan	[*25 °C/60% RH*][3]
Kyrgyzstan	[*25 °C/60% RH*][3]
Latvia	**25 °C/60% or 30 °C/65% RH**[1]
Lithuania	**25 °C/60% or 30 °C/65% RH**[1]
Luxembourg	**25 °C/60% or 30 °C/65% RH**[1]
Malta	**25 °C/60% or 30 °C/65% RH**[1]
Monaco	25 °C/60% or 30 °C/65% RH[2]
Montenegro	[*25 °C/60% RH*][3]
Netherlands	**25 °C/60% or 30 °C/65% RH**[1]
Norway	[*25 °C/60% RH*][3]
Poland	**25 °C/60% or 30 °C/65% RH**[1]
Portugal	**25 °C/60% or 30 °C/65% RH**[1]
Republic of Moldova	[*25 °C/60% RH*][3]
Romania	**25 °C/60% or 30 °C/65% RH**[1]
Russian Federation	[*25 °C/60% RH*][3]
San Marino	[*25 °C/60% RH*][3]
Serbia	[*25 °C/60% RH*][3]
Slovakia	**25 °C/60% or 30 °C/65% RH**[1]
Slovenia	**25 °C/60% or 30 °C/65% RH**[1]
Spain	**25 °C/60% or 30 °C/65% RH**[1]
Sweden	**25 °C/60% or 30 °C/65% RH**[1]
Switzerland	**25 °C/60% or 30 °C/65% RH**[1]

Member State	Stability conditions Confirmed long-term testing condition
Tajikistan	[*25 °C/60% RH*][3]
The former Yugoslav Republic of Macedonia	25 °C/60% or 30 °C/65% RH[2]
Turkey	[*25 °C/60% RH*][3]
Turkmenistan	[*25 °C/60% RH*][3]
Ukraine	[*25 °C/60% RH*][3]
United Kingdom	**25 °C/60% or 30 °C/65% RH**[1]
Uzbekistan	[*25 °C/60% RH*][3]
Regional Office for South-East Asia (SEARO)	
Bangladesh	[*30 °C/65% RH*][3]
Bhutan	30 °C/65% RH[2]
Democratic People's Republic of Korea	[*25 °C/60% RH*][3]
India	**30 °C/70% RH**[1]
Indonesia	**30 °C/75% RH**[1]
Maldives	[*30 °C/65% RH*][3]
Myanmar	**30 °C/75% RH**[1]
Nepal	30 °C/75% RH[2]
Sri Lanka	[*30 °C/65% RH*][3]
Thailand	**30 °C/75% RH**[1]
Timor-Leste	[*30 °C/65% RH*][3]
Regional Office for the Western Pacific (WPRO)	
Australia	25 °C/60% or 30 °C/65% RH[2]
Brunei Darussalam	**30 °C/75% RH**[1]
Cambodia	**30 °C/75% RH**[1]
China	[*30 °C/65% RH*][3]
Cook Islands	[*30 °C/65% RH*][3]
Fiji	[*30 °C/65% RH*][3]
Japan	**25 °C/60% or 30 °C/65% RH**[1]
Kiribati	[*30 °C/65% RH*][3]
Lao People's Democratic Republic	**30 °C/75% RH**[1]
Malaysia	**30 °C/75% RH**[1]
Marshall Islands	[*30 °C/65% RH*][3]
Micronesia (Federated States of)	[*30 °C/65% RH*][3]
Mongolia	[*25 °C/60% RH*][3]
Nauru	[*30 °C/65% RH*][3]
New Zealand	25 °C/60% or 30 °C/65% RH[2]
Niue	[*30 °C/65% RH*][3]
Palau	[*30 °C/65% RH*][3]
Papua New Guinea	[*30 °C/65% RH*][3]
Philippines	**30 °C/75% RH**[1]
Republic of Korea	25 °C/60% or 30 °C/65% RH[2]

Member State	Stability conditions Confirmed long-term testing condition
Samoa	[*30 °C/65% RH*][3]
Singapore	**30 °C/75% RH**[1]
Solomon Islands	[*30 °C/65% RH*][3]
Tonga	[*30 °C/65% RH*][3]
Tuvalu	[*30 °C/65% RH*][3]
Vanuatu	[*30 °C/65% RH*][3]
Viet Nam	**30 °C/75% RH**[1]

[1] Information obtained through respective regional harmonization groups (e.g. ASEAN, ICH and GCC) and from official communications from national medicines regulatory authorities to WHO (entries in bold type).

[2] Information collated during the 13th International Conference of Drug Regulatory Authorities (ICDRA), 16–18 September 2008, held in Bern, Switzerland, from representatives of national medicines regulatory authorities (entries in normal type).

[3] Information provided by the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) [entries in italic type] based on the following references:
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Appendix 2
Examples of testing parameters

Section I for active pharmaceutical ingredients

In general, appearance, assay and degradation products should be evaluated for all active pharmaceutical ingredients (APIs). Other API parameters that may be susceptible to change should also be studied where applicable.

Section II for finished pharmaceutical products

The following list of parameters for each dosage form is presented as a guide to the types of tests to be included in a stability study. In general, appearance, assay and degradation products should be evaluated for all dosage forms, as well as the preservative and antioxidant content if applicable.

The microbial quality of multiple-dose sterile and non-sterile dosage forms should be controlled. Challenge tests should be carried out at least at the beginning and at the end of the shelf-life. Such tests would normally be performed as part of the development programme, for example, within primary stability studies. They need not be repeated for subsequent stability studies unless a change has been made which has a potential impact on microbiological status.

It is not expected that every test listed be performed at each time point. This applies in particular to sterility testing, which may be conducted for most sterile products at the beginning and at the end of the stability test period. Tests for pyrogens and bacterial endotoxins may be limited to the time of release. Sterile dosage forms containing dry materials (powder filled or lyophilized products) and solutions packaged in sealed glass ampoules may need no additional microbiological testing beyond the initial time point. The level of microbiological contamination in liquids packed in glass containers with flexible seals or in plastic containers should be tested no less than at the beginning and at the end of the stability test period; if the long-term data provided to the regulatory authorities for marketing authorization registration do not cover the full shelf-life period, the level of microbial contamination at the last time point should also be provided.

The list of tests presented for each dosage form is not intended to be exhaustive, nor is it expected that every test listed be included in the design of a stability protocol for a particular finished pharmaceutical product (FPP) (for example, a test for odour should be performed only when necessary and with consideration for the analyst's safety).

The storage orientation of the product, i.e. upright versus inverted, may need to be included in a protocol when contact of the product with the closure system may be expected to affect the stability of the products contained, or where there has been a change in the container closure system.

Tablets

Dissolution (or disintegration, if justified), water content and hardness/friability.

Capsules

- Hard gelatin capsules: brittleness, dissolution (or disintegration, if justified), water content and level of microbial contamination.
- Soft gelatin capsules: dissolution (or disintegration, if justified), level of microbial contamination, pH, leakage, and pellicle formation.

Oral solutions, suspensions and emulsions

Formation of precipitate, clarity (for solutions), pH, viscosity, extractables, level of microbial contamination.

Additionally for suspensions, dispersibility, rheological properties, mean size and distribution of particles should be considered. Also polymorphic conversion may be examined, if applicable.

Additionally for emulsions, phase separation, mean size and distribution of dispersed globules should be evaluated.

Powders and granules for oral solution or suspension

Water content and reconstitution time.

Reconstituted products (solutions and suspensions) should be evaluated as described above under "Oral solutions suspensions and emulsions", after preparation according to the recommended labelling, through the maximum intended use period.

Metered-dose inhalers and nasal aerosols

Dose content uniformity, labelled number of medication actuations per container meeting dose content uniformity, aerodynamic particle size distribution, microscopic evaluation, water content, leak rate, level of microbial contamination, valve delivery (shot weight), extractables/leachables from plastic and elastomeric components, weight loss, pump delivery, foreign particulate matter and extractables/leachables from plastic and elastomeric components of the container, closure and pump. Samples should be stored in upright and inverted/on-the-side orientations.

For suspension-type aerosols, microscopic examination of appearance of the valve components and container's contents for large particles, changes in morphology of the API particles, extent of agglomerates, crystal growth,

foreign particulate matter, corrosion of the inside of the container or deterioration of the gaskets.

Nasal sprays: solutions and suspensions

Clarity (for solution), level of microbial contamination, pH, particulate matter, unit spray medication content uniformity, number of actuations meeting unit spray content uniformity per container, droplet and/or particle size distribution, weight loss, pump delivery, microscopic evaluation (for suspensions), foreign particulate matter and extractables/leachables from plastic and elastomeric components of the container, closure and pump.

Topical, ophthalmic and otic preparations

Included in this broad category are ointments, creams, lotions, paste, gel, solutions, eye drops and cutaneous sprays.

- Topical preparations should be evaluated for clarity, homogeneity, pH, suspendability (for lotions), consistency, viscosity, particle size distribution (for suspensions, when feasible), level of microbial contamination/sterility and weight loss (when appropriate).
- Evaluation of ophthalmic or otic products (e.g. creams, ointments, solutions and suspensions) should include the following additional attributes: sterility, particulate matter and extractable volume.
- Evaluation of cutaneous sprays should include: pressure, weight loss, net weight dispensed, delivery rate, level of microbial contamination, spray pattern, water content and particle size distribution (for suspensions).

Suppositories

Softening range, disintegration and dissolution (at 37 °C).

Small volume parenterals (SVPs)

Colour, clarity (for solutions), particulate matter, pH, sterility, endotoxins.

Stability studies for powders for injection solution should include monitoring for colour, reconstitution time and water content. Specific parameters to be examined at appropriate intervals throughout the maximum intended use period of the reconstituted drug product, stored under condition(s) recommended on the label, should include clarity, colour, pH, sterility, pyrogen/endotoxin and particulate matter. It may be appropriate to consider monitoring of sterility after reconstitution into a product, e.g. dual-chamber syringe, where it is claimed that reconstitution can be performed without compromising sterility.

- The stability studies for Suspension for injection should include, in addition, particle size distribution, dispersibility and rheological properties.

- The stability studies for Emulsion for injection should include, in addition, phase separation, viscosity, mean size and distribution of dispersed phase globules.

Large volume parenterals (LVPs)

Colour, clarity, particulate matter, pH, sterility, pyrogen/endotoxin and volume.

Transdermal patches

In vitro release rates, leakage, level of microbial contamination/sterility, peel and adhesive forces.

Appendix 3
Recommended labelling statements

1. Active pharmaceutical ingredients

The statements that should be used if supported by the stability studies for active pharmaceutical ingredients (APIs) are listed in Table 1.

Table 1
Recommended labelling statements for active pharmaceutical ingredients (APIs)

Testing condition under which the stability of the API has been demonstrated	Recommended labelling statement[a]
25 °C/60% RH (long-term) 40 °C/75% RH (accelerated)	"Do not store above 25 °C"
25 °C/60% RH (long-term) 30 °C/65% RH (intermediate, failure of accelerated)	"Do not store above 25 °C"[b]
30 °C/65% RH (long-term) 40 °C/75% RH (accelerated)	"Do not store above 30 °C"[b]
30 °C/75% RH (long-term) 40 °C/75% RH (accelerated)	"Do not store above 30 °C"
5 °C ± 3 °C	"Store in a refrigerator (2 °C to 8 °C)"
-20 °C ± 5 °C	"Store in freezer"

[a] During storage, shipment and distribution of the API, the current *good trade and distribution practices (GTDP) for pharmaceutical starting materials* are to be observed (*1*). Details on storage and labelling requirements can be found in *WHO guide to good storage practices for pharmaceuticals* (*2*).

[b] "Protect from moisture" should be added as applicable.

2. Finished pharmaceutical products

The statements that should be used if supported by the stability studies for finished pharmaceutical products (FPPs) are listed in Table 2.

Table 2

Recommended labelling statements for finished pharmaceutical products (FPPs)

Testing condition under which the stability of the FPP has been demonstrated	Recommended labelling statement[a]
25 °C/60% RH (long-term) 40 °C/75% RH (accelerated)	"Do not store above 25 °C"
25 °C/60% RH (long-term) 30 °C/65% RH (intermediate, failure of accelerated)	"Do not store above 25 °C"[b]
30 °C/65% RH (long-term) 40 °C/75% RH (accelerated)	"Do not store above 30 °C" [b]
30 °C/75% RH (long-term) 40 °C/75% RH (accelerated)	"Do not store above 30 °C"
5 °C ± 3 °C	"Store in a refrigerator (2 °C to 8 °C)"
-20 °C ± 5 °C	"Store in freezer"

[a] During storage, shipment and distribution of the FPP, the current *good distribution practices (GDP) for pharmaceutical products* are to be observed (*3*). Details on storage and labelling requirements can be found in *WHO guide to* good storage practices *for pharmaceuticals* (*2*).

[b] "Protect from moisture" should be added as applicable.

In principle, FPPs should be packed in containers that ensure stability and protect the FPP from deterioration. A storage statement should not be used to compensate for inadequate or inferior packaging. Additional labelling statements that could be used in cases where the result of the stability testing demonstrates limiting factors are listed in Table 3.

Table 3

Additional labelling statements for use where the result of the stability testing demonstrates limiting factors

Limiting factors	Additional labelling statement, where relevant
FPPs that cannot tolerate refrigeration	"Do not refrigerate or freeze"[a]
FPPs that cannot tolerate freezing	"Do not freeze"[a]
Light-sensitive FPPs	"Protect from light"
FPPs that cannot tolerate excessive heat, e.g. suppositories	"Store and transport not above 30 °C"
Hygroscopic FPPs	"Store in dry condition"

[a] Depending on the pharmaceutical form and the properties of the FPP, there may be a risk of deterioration due to physical changes if subjected to low temperatures, e.g. liquids and semi-solids. Low temperatures may also have an effect on the packaging in certain cases. An additional statement may be necessary to take account of this possibility.

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2. Guide to good storage practices for pharmaceuticals. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-seventh report*. Geneva, World Health Organization, 2003, Annex 9 (WHO Technical Report Series, No. 908).
3. Good distribution practices for pharmaceutical products. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fortieth report*. Geneva, World Health Organization, 2006, Annex 5 (WHO Technical Report Series, No. 937). Currently under revision (working document QAS/08.252).

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Annex 3

Procedure for prequalification of pharmaceutical products

1. Introduction

The World Health Organization (WHO) provides United Nations agencies with advice on the acceptability in principle of pharmaceutical products for procurement by such agencies.

This activity of WHO aims to facilitate access to priority essential medicines that meet WHO-recommended norms and standards of acceptable quality.

WHO undertakes a comprehensive evaluation of the quality of pharmaceutical products, based on information submitted by the manufacturers of such products or other applicants, and on an inspection of the corresponding manufacturing facilities and clinical sites. This is done through a standardized procedure which is based on WHO-recommended quality standards. The quality of pharmaceutical products is obviously of crucial importance for the safety and efficacy of such products.

The pharmaceutical products found to meet the WHO-recommended quality standards are included in the list of medicines, as manufactured at the specified manufacturing sites, which are considered to be acceptable, in principle, for procurement by United Nations agencies. The list of prequalified pharmaceutical products is principally intended for use by United Nations agencies – including the Joint United Nations Programme on HIV/AIDS (UNAIDS), United Nations Children's Fund (UNICEF) and United Nations Population Fund (UNFPA) – to guide their procurement decisions. The growing list of pharmaceutical products that have been found to meet WHO-recommended standards may, however, also be of interest to other organizations and countries wishing to engage in the bulk procurement of pharmaceutical products.

Inclusion in the list does not imply any approval by WHO of the pharmaceutical products and manufacturing sites in question (which is the sole prerogative of national authorities). Moreover, inclusion in the list does not constitute an endorsement or warranty by WHO of the fitness of any product for a particular purpose, including its safety and/or efficacy in the treatment of specific diseases.

2. Glossary

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

active pharmaceutical ingredient (API)

Any substance or combination of substances used in a finished pharmaceutical product (FPP), intended to furnish pharmacological activity or to otherwise have direct effect in the diagnosis, cure, mitigation, treatment or prevention

of disease, or to have direct effect in restoring, correcting or modifying physiological functions in human beings.

applicant

The person or entity who, by the deadline mentioned in the invitation, submits an expression of interest (EOI) to participate in this procedure in respect of the product(s) listed in the invitation, together with the required documentation on such product(s).

contract research organization (CRO)

An organization (commercial, academic or other) to which an applicant may have transferred some of its tasks and obligations in relation to the conduct of clinical studies with the product submitted to WHO for assessment under the current procedure.

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.

invitation for expressions of interest or invitation

Invitation calling upon interested parties (e.g. manufacturers or other applicants) to submit an expression of interest (EOI) to WHO by a specified deadline for the purpose of participating in the WHO prequalification procedure in respect of the product(s) listed in the invitation. Such an EOI should be accompanied by the required documentation on the product(s) in question.

manufacturer

A company that produces, packages, repackages, labels and/or relabels pharmaceutical products.

pharmaceutical product

Any substance or combination of substances marketed or manufactured to be marketed for treating or preventing disease in human beings, or with a view to making a medical diagnosis in human beings, or to restoring, correcting or modifying physiological functions in human beings.

prequalification

Standardized quality assessment procedure of WHO to evaluate the acceptability, in principle, of pharmaceutical products for purchase by United Nations agencies. Agencies using information resulting from the prequalification procedure should perform additional steps of qualification prior to purchasing, such as ensuring financial stability and standing of the supplier, ability to supply the required quantities, security of the supply chain, preshipment quality control and other related aspects.

3. Purpose and principles

The purpose of this WHO procedure is to evaluate whether certain pharmaceutical products (considered by WHO to be vital for the prevention and treatment of HIV/AIDS, tuberculosis, malaria and other diseases, or for reproductive health) meet the requirements recommended by WHO and are manufactured in compliance with current good manufacturing practices (hereinafter referred to as GMP).

This procedure established by WHO is based on the following principles:[1]

- a general understanding of the production and quality control activities of the manufacturer;
- assessment of pharmaceutical product data and information on safety, efficacy and quality submitted by the manufacturer, including product formulation, manufacture and test data and results;
- inspection of the manufacturing site(s) for consistency in production and quality control of starting materials (with specific emphasis on APIs) and finished products through compliance with GMP;
- inspection of clinical testing units or CROs performing clinical trials for compliance with current good clinical practices (hereinafter referred to as GCP) and current good laboratory practices (hereinafter referred to as GLP);
- reliance on the information supplied by the national medicines regulatory authority;
- random sampling and testing of pharmaceutical products supplied;
- handling of complaints and recalls; and
- monitoring of complaints from agencies and countries.

WHO may also collaborate with national medicines regulatory authorities in the quality assessment. WHO recommends that applicants expressing interest in participation in the prequalification procedure inform the national medicines regulatory authorities in the country of manufacture of their intention and request them to collaborate with WHO in the quality assessment process. It is recommended that applicants provide the national medicines regulatory authorities with the necessary authorization to discuss the relevant product files with WHO representatives during dossier assessment and site inspections (subject to appropriate confidentiality provisions, if necessary).

[1] The prequalification procedure may also be based on approval by certain stringent regulatory agencies, such as, but not limited to, the United States Food and Drug Administration (USFDA) and the European Medicines Agency (EMEA), as described in section 4: Steps of the procedure.

4. Steps of the procedure

WHO undertakes a comprehensive evaluation of the quality of pharmaceutical products, based on information submitted by the applicants, and inspection[1] of the relevant manufacturing and clinical sites. (A flowchart showing the prequalification process is provided in Appendix 1.)

At regular intervals, and also taking into consideration pertinent input received from relevant United Nations agencies, WHO will publish an invitation to interested parties, requesting them to voluntarily participate in this procedure in respect of the products mentioned in the invitation. By submitting an expression of interest (EOI), the applicant undertakes to share information with WHO on all relevant aspects of manufacture and control of the specified products along with changes made and/or planned.

Interested applicants provide the necessary information to WHO by submitting a product dossier and other information as requested. The procedure will normally include:

- assessment of product dossiers, which must include product data and information as specified in the guidelines for submission, available on the WHO web site (www.who.int/prequal);
- inspection of manufacturing sites of finished pharmaceutical products (FPPs) and active pharmaceutical ingredients (APIs), which must adhere to GMP; and
- inspection of clinical sites (if applicable), which must adhere to GCP and GLP.

If the evaluation above demonstrates that a product and its corresponding manufacturing (and clinical) site(s) meet WHO-recommended standards, the product will be included in the list of pharmaceutical products that are considered to be acceptable, in principle, for procurement by United Nations agencies.

WHO reserves the right to terminate the evaluation of a specific product if the applicant is not able to provide the required information, and/or is unable to implement any corrective actions which WHO may require within a specified time period, or when the information supplied is inadequate to complete this procedure.

WHO recognizes the evaluation of relevant products by national medicines regulatory authorities which apply stringent standards for quality similar to those recommended by WHO, such as, for example, but not limited to the US Food and Drug Administration (USFDA) and the European Medicines Agency (EMEA).

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[1] No site inspection will occur when the product has been listed, based on the approval by stringent regulatory agencies, which are willing to share information with WHO.

Provided that the national medicines regulatory authority is willing to share certain information with WHO on the products in question, WHO will consider such products for inclusion in the list of WHO-prequalified products. It will do so as and when information about such products becomes available to WHO and when the holders of the regulatory approval of such products express their interest in having these products prequalified by WHO. These products will be added to the list of products prequalified by WHO, on the basis of the scientific assessment and inspections conducted by the regulatory authority concerned, and the exchange of relevant information between the regulatory authority and WHO.

5. Invitation for expressions of interest

The pharmaceutical products listed in an invitation for EOI are considered by WHO to be vital for the effective treatment and prevention of the specified diseases (including HIV/AIDS, malaria and tuberculosis) or for reproductive health. These products are normally included in either the WHO Model List of Essential Medicines or the relevant WHO treatment guidelines and recommendations (or both).

The products included in the WHO Model List of Essential Medicines are those that satisfy the priority health care needs of a population. They are selected, among other criteria, on the basis of disease prevalence, evidence on efficacy and safety and analysis of comparative cost-effectiveness.

Products included in WHO treatment guidelines are selected on the basis of an assessment of the evidence for benefits, risks, costs and appropriateness for use in a variety of situations, taking into account the needs of special populations and the values and preferences of the groups (professional and patient) using them.

Each invitation will be open and transparent, inviting all relevant parties to submit an EOI for the pharmaceutical products listed. Such an invitation will normally be published on the WHO web site and possibly also through other media, such as the international press.

In situations of high public health concern as determined by WHO, the Organization may also directly invite relevant parties to submit specified product dossiers for evaluation by WHO under this procedure without publication of an invitation for EOI.

6. Data and information to be submitted

Interested parties are expected to submit documentation on the pharmaceutical products as called for in the invitation for EOI. Applicants should submit their product dossiers with the required information to the

WHO focal point, before the deadline specified in the invitation. Guidance and instructions developed for the submission of the dossiers are made available on the WHO web site.

Normally the applicants who participate in the WHO prequalification scheme for pharmaceutical products are the manufacturers of the FPPs, as specified in the invitations for EOI. In the case that an applicant is not the manufacturer of the FPP, all relevant documentation, including (but not limited to) contract manufacturing documentation, should be submitted, demonstrating that the applicant is in full control of the manufacturing process for, and quality assurance of, the products submitted for prequalification.

In submitting an EOI for product evaluation, the applicant should send the following to the WHO focal point:

- a covering letter, expressing interest in participating in the WHO prequalification procedure and confirming that the information submitted in the product dossier is complete and correct;
- a product dossier, in the format specified in the WHO guidance documents on submitting product data and information;
- product samples, to enable visual examination and chemical and pharmaceutical analysis;
- a site master file for each manufacturing site listed in the product dossier, in the requisite format specified in the WHO guidance documents for submitting a site master file.

The documentation should be submitted in English in the format described below. Electronic submission of documentation (CD or DVD) is encouraged and should be in the WHO-recommended format together with a covering letter cross-referencing the information, as organized electronically.

For the product dossier, the structure and format of the common technical document (CTD), agreed in November 2000 within the framework of the International Conference on Harmonisation (ICH, see web site: www.ich.org) should be followed. Alternatively, a standard dossier in English, as prepared for the national medicines regulatory authorities, can be submitted, provided that it contains the information to the extent and detail required by the WHO guidance documents, and is cross-referenced. Data and information on APIs should be presented in the format described in the WHO guidance documents for submission of active pharmaceutical ingredient master files (APIMF).

For the purposes of this procedure, different requirements for documentation to be submitted apply to the following two categories of products:

- innovator products which are manufactured and marketed in the ICH region and/or associated countries, and are covered in these countries by patent protection;

- multisource generic products, as described in the WHO guidance document *Marketing authorization of pharmaceutical products with special reference to multisource (generic) products. A manual for a drug regulatory authority* (*1*).

For innovator products, the following aspects at least must be covered by appropriate documentation in the product dossier:

- a WHO-type certificate[1] of a pharmaceutical product, issued by one of the national medicines regulatory authorities of the ICH region and/or associated countries, together with the approved summary of product characteristics;
- assessment report(s) issued by the respective national medicines regulatory authorities;
- WHO-type batch certificate from the manufacturer.

For multisource generic products, the data and information to be submitted should be as described in *Marketing authorization of pharmaceutical products with special reference to multisource (generic) products. A manual for a drug regulatory authority* (*1*) and its revisions:

- details of the product;
- marketing authorization status;
- for the API(s):
  - properties of the API(s);
  - sites of manufacture;
  - route of synthesis;
  - specifications;
  - stability testing;
- for the FPP:
  - formulation;
  - sites of manufacture;
  - manufacturing procedure;
  - specifications for excipients;
  - specifications for the FPP;
  - container/closure system(s) and other packaging;
  - stability testing;
- product information:
  - summary of product characteristics;
  - package leaflet;
  - labelling;

[1] The WHO-type certificate refers to the certificate issued by national medicines regulatory authorities in accordance with the *WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce* as published in the WHO Technical Report Series, No. 863, 1996.

- summaries on:
  - — quality;
  - — biopharmaceutics (interchangeability).

The multisource generic products must be shown, either directly or indirectly, to be therapeutically equivalent to the comparator product if they are to be considered interchangeable. WHO will maintain and make public the list of comparator products for this purpose. The WHO web site provides guidance on the evidence needed for a product to be considered equivalent without the need for in vivo equivalence studies (i.e. application of biowaiver).

7. Screening of dossiers submitted

Each product dossier submitted by an applicant will be screened for completeness before being evaluated. Dossiers submitted for products which are not listed in an invitation for EOI or have not otherwise been invited by WHO will not be accepted for evaluation.

Similarly WHO will not consider dossiers that are incomplete. The applicant will be informed that an incomplete dossier has been received and will be requested to complete the dossier within a specified time period. In the event of non-compliance, the dossier may be rejected on grounds of incompleteness and returned to the applicant. Dossiers that are considered complete as the result of the screening will be retained by WHO for evaluation purposes.

8. Dossier assessment

The product information submitted in the dossiers will be assessed by teams of experts (assessors) appointed by WHO. The assessors involved in dossier assessment must have the relevant qualifications and experience in the fields of pharmaceutical development, quality assessment of pharmaceutical products, quality assurance, biopharmaceutics and other relevant fields.

The assessors will be appointed in accordance with a standard operating procedure (SOP) established by WHO. The assessors should preferably be from national medicines regulatory authorities and they will act as temporary advisers to WHO. The assessors must comply with the confidentiality and conflict of interest rules of WHO, as laid down in the relevant sections of this procedure.

The assessment of product dossiers will be done in accordance with SOPs established by WHO for that purpose so as to ensure uniformity in evaluation and timeliness of assessment activities. If needed, WHO may provide training to these experts.

Each applicant may request a hearing or meeting with the WHO experts involved in the assessment of this applicant's dossier to clarify issues identified by the WHO experts. In the case of multisource generic products, WHO may provide technical assistance to applicants regarding appropriate product information to be submitted as well as production and control requirements.

9. Site inspection

WHO will plan and coordinate the performance of inspections of the site(s) of manufacture of the API(s) and the FPP, and of the clinical testing units or CROs, as needed.

The inspections of the manufacturing site(s) are conducted to assess compliance with GMP as recommended by WHO (*2*,*3*) and include data verification. Site master files submitted by the applicant will be reviewed before an inspection is performed.

The inspections of clinical testing units or organizations are carried out to assess compliance with GCP and GLP (*4*–*6*), and to perform data verification.

The inspections will be performed by a team of inspectors consisting of experts appointed by WHO, preferably from national medicines regulatory authorities inspectorates, who will act as temporary advisers to WHO. The inspectors must have the relevant qualifications and experience to perform such inspections, be competent in areas such as production and quality control of pharmaceuticals, and have appropriate experience in GMP and GCP or GLP. The inspectors must comply with the confidentiality and conflict of interest rules of WHO, as laid down in the relevant sections of this procedure. If needed, WHO may provide training to these experts.

A WHO staff member will coordinate the team. Each team will perform the inspections and report on its findings to WHO in accordance with SOPs established by WHO for that purpose so as to ensure a standard harmonized approach. A representative of the national medicines regulatory authorities of the country of manufacture would normally be expected to accompany the team to the manufacturing and testing facilities to assess the compliance with GMP and GCP or GLP.

10. Reporting and communication of the results of the evaluation

Each assessment and inspection team will finalize its reports according to the established WHO SOP and format, describing the findings and including

recommendations to the applicant, manufacturer(s) and/or CROs where relevant.

The findings from the dossier assessment including, but not limited to, deficiencies of the documentation and data submitted, shall be communicated in writing to the applicant requesting submission of the missing data and information, as appropriate.

The inspection report will be communicated to the applicant, manufacturer(s) and/or CRO(s). If any additional information is required, or corrective action has to be taken by the manufacturer(s) or CROs, WHO will postpone its decision on the acceptability of the site(s) concerned until such information has been evaluated or the corrective action has been taken and found satisfactory in light of the specified standards.

WHO reserves the right to terminate this procedure for a specific product if the applicant is not able to provide the required information or implement the corrective actions within a specified time period, or if the information supplied is inadequate to complete this procedure.

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

As WHO is responsible for the prequalification procedure, the ownership of the reports lies with WHO. Thus, WHO shall be entitled to use and publish such reports subject always, however, to the protection of any commercially sensitive confidential information of the applicant, manufacturer(s) and/or testing organization(s). "Confidential information" in this context means:

— confidential intellectual property, "know-how" and trade secrets (including, e.g. formulas, programs, processes or information contained or embodied in a product, unpublished aspects of trade marks, patents, etc.); and
— commercial confidences (e.g. structures and development plans of a company).

Provisions of confidentiality will be contained in the exchange of letters, to be concluded before the assessment of the product dossier or inspection of the manufacturing and clinical sites, between WHO on the one hand and each applicant, manufacturer or CRO on the other hand.

Notwithstanding the foregoing, WHO reserves the right to share the full assessment and inspection reports with the relevant authorities of any interested Member State of the Organization and interested United Nations agencies.

11. Outcome of the prequalification procedure

Once WHO is satisfied that this procedure is complete for the relevant product, and that the WHO-recommended standards are met, the product, as manufactured at the specified manufacturing site(s), will be included in the list of prequalified pharmaceutical products. The list of prequalified pharmaceutical products will be compiled in accordance with an SOP established by WHO for final decision-making on inclusion in the list. The list will be published on the WHO web site and will specify the characteristics of the prequalified pharmaceutical products, as described in Appendix 2 to this procedure.

Each applicant will receive a letter from WHO informing it of the outcome of the quality assessment process in regard of the submitted product(s). Once the product(s) are included in the list of prequalified pharmaceutical products, the applicant shall be responsible for keeping WHO continuously updated on all relevant aspects of the manufacture and control of such product(s) and to meet any requirements, as agreed with WHO.

In accordance with World Health Assembly Resolution WHA57.14 of 22 May 2004, WHO will – subject to the protection of any commercially sensitive confidential information – publish WHO Public Assessment Reports (WHOPAR(s)) on the product dossier assessments and WHO Public Inspection Reports (WHOPIR(s)) on the manufacturers and CROs that were found to be in compliance with WHO-recommended guidelines and standards. These reports will be published on the WHO web site. Subject always to the protection of commercially sensitive confidential information, WHO shall also be entitled to publish negative evaluation outcomes.

The decision to list a pharmaceutical product is made based upon information available to WHO at that time, i.e. information in the submitted dossier and on the status of GMP, GLP and GCP at the facilities used in the manufacture and testing of the product at the time of the site inspection(s) conducted by WHO. This decision is subject to change on the basis of new information that may become available to WHO. If serious safety and/or quality concerns arise in relation to a prequalified product, WHO may delist the product after evaluation of the new evidence and a risk–benefit assessment, or may suspend the product until results of further investigations become available and are evaluated by WHO.

12. Maintenance of prequalification status

Applicants are required to communicate details to WHO of any changes (variations) in manufacture and control that may have an impact on the safety, efficacy and quality of the product, following the WHO *Guidance*

on variations to a prequalified product dossier, as adopted in 2006 (*7*) and its revisions.

It is the applicant's responsibility to provide WHO with the appropriate documentation (referring to relevant parts of the dossier) to prove that any intended or implemented variation will not have a negative impact on the quality of the product that has been prequalified. WHO will undertake an evaluation of variations according to the established WHO guidelines and SOPs and communicate the outcome to the applicant. Adherence to the reporting requirements will be addressed during the inspections carried out by WHO.

Random samples of prequalified products supplied by listed manufacturers or applicants will be taken for independent testing of final product characteristics. Certificates of analysis of final products released by the manufacturer and specifications for test methods should be provided by the manufacturer or applicant to WHO for review upon request. In the event of failure to meet the established criteria for testing, WHO will investigate the problem and communicate this to the manufacturer and applicant if other than the manufacturer.

Complaints concerning prequalified pharmaceutical products communicated to WHO will be investigated in accordance with an SOP established by WHO for that purpose. After investigation, WHO will provide a written report of the problem and include recommendations for action where relevant. WHO will make the report available to the applicant/manufacturer, and to the national medicines regulatory authority of the country where the manufacturing site is located. Subject always to the protection of commercially sensitive information as referred to above, WHO shall be entitled to make such reports public. In addition, WHO reserves the right to share the full report with the relevant authorities of interested Member States of the Organization and interested United Nations agencies.

WHO will furthermore arrange for the products and manufacturing sites included in the list to be re-evaluated at regular intervals. If, as a result of this re-evaluation, it is found that a product and/or specified manufacturing site no longer complies with the WHO-recommended standards, such products and manufacturing sites will be removed from the list. Failure of a manufacturer or applicant to participate in the re-evaluation procedure will also lead to removal from the list.

Re-evaluation, including re-inspections of manufacturing sites and CROs, will be done at regular intervals, based on risk assessment, but at least once every 5 years.

Re-evaluation, including re-inspections, shall also be performed:

- if any fraud or omissions by the applicant, manufacturer(s) of an FPP or API, or CROs in the initial assessment procedure or during the follow-up activities, becomes evident; and
- if WHO or any United Nations agency considers that a batch or batches of supplied prequalified pharmaceutical products are not in compliance with the specifications which were found to be applicable upon prequalification.

13. Cost recovery

WHO reserves the right to charge for this procedure on a cost recovery basis.

14. Confidentiality undertaking

The assessors and inspectors will treat all information to which they will gain access during the assessments and inspections, or otherwise in connection with the discharge of their responsibilities in regard to the above-mentioned project, as confidential and proprietary to WHO or parties collaborating with WHO in accordance with the terms set forth below.

Assessors and inspectors will take all reasonable measures to ensure that confidential information:

- is not used for any purpose other than the assessment/inspection activities described in this document; and
- is not disclosed or provided to any person who is not bound by similar obligations of confidentiality and non-use as contained herein.

Assessors 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.

15. Conflict of interest

Before undertaking the work, each assessor and inspector will also (in addition to the above-mentioned confidentiality undertaking) be required to sign a declaration of interest. If, based on this declaration of interest, it is felt that there is no risk of a real or perceived conflict of interest (or it is felt that there is only an insignificant and/or irrelevant conflict of interest),

and it is thus deemed appropriate for the assessor or inspector in question to undertake this work, he/she will discharge his/her functions exclusively as adviser to WHO. In this connection, each assessor and inspector is required to confirm that the information disclosed by him/her in the declaration of interest is correct and complete, and that he/she will immediately notify WHO of any change in this information.

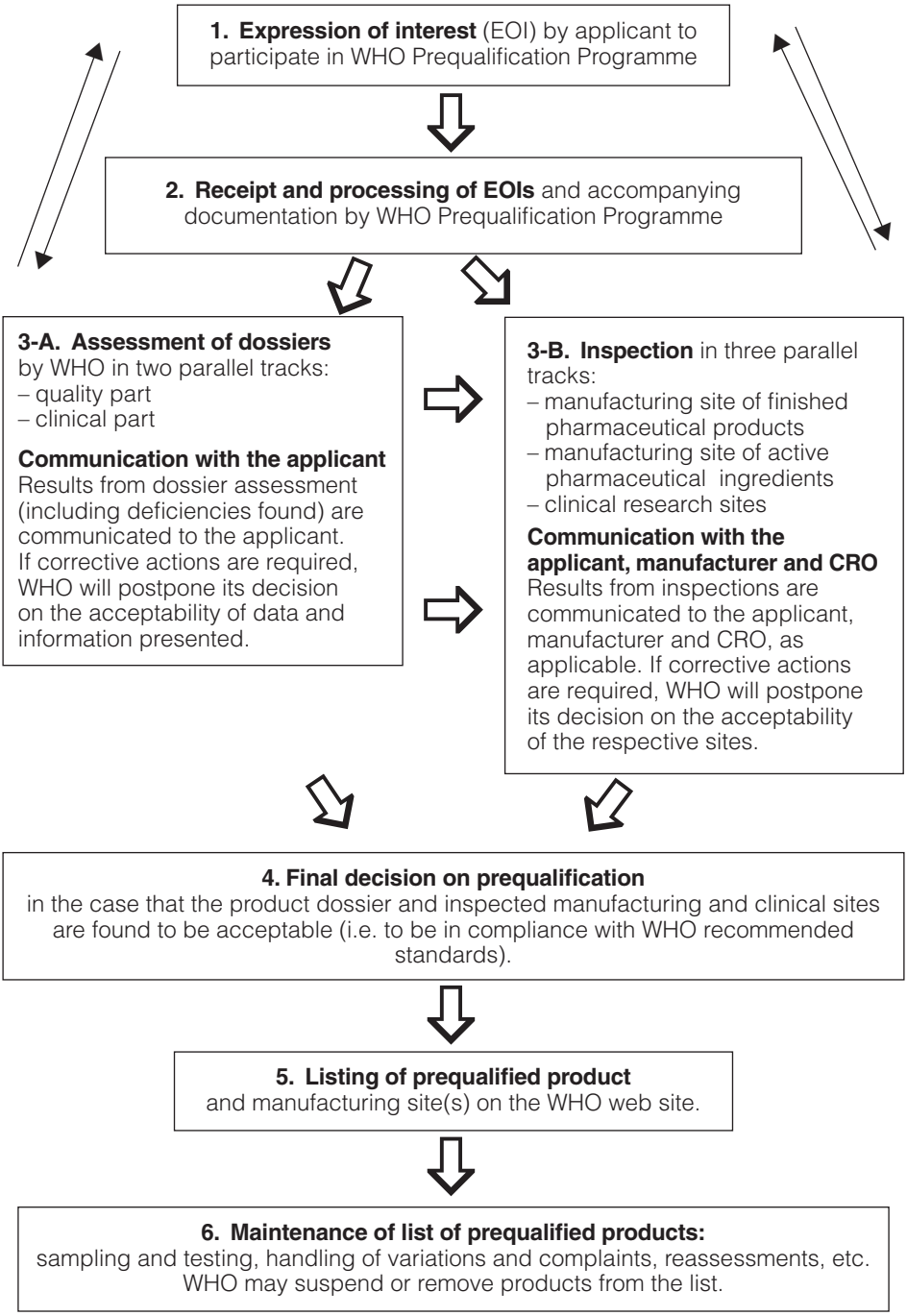
All inspectors furthermore agree that, at the manufacturer's or CRO's request, WHO will advise the manufacturer or CRO, in advance, of the identity of each inspector and the composition of the team performing the site inspection, and provide curricula vitae of the inspectors. The manufacturer or CRO then has the opportunity to express possible concerns regarding any of the inspectors to WHO before the visit. If such concerns cannot be resolved in consultation with WHO, the manufacturer or CRO may object to a team member's participation in the site visit. Such an objection must be made known to WHO by the manufacturer or CRO within 10 days of receipt of the proposed team composition. In the event of such an objection, WHO reserves the right to cancel all or part of its agreement with, and the activities to be undertaken by, that inspector.

References

1. *Marketing authorization of pharmaceutical products with special reference to multisource (generic) products. A Manual for a drug regulatory authority*. Geneva, World Health Organization, 1999. Regulatory Support Series, No. 5 (WHO/DMP/RGS/98.5).
2. *Quality assurance of pharmaceuticals. A compendium of guidelines and related materials. Volume 2,* Second updated edition. *Good manufacturing practices and inspection*. Geneva, World Health Organization, 2007.
3. *ICH Harmonised Tripartite Guideline Q7 – Good manufacturing practice guide for active pharmaceutical ingredients (Step 4 version)*. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, 2000 (http://www.ich.org/LOB/media/MEDIA433.pdf).
4. *Guidelines for good clinical practice (GCP) for trials on pharmaceutical products. Sixth report of the WHO Expert Committee on the Use of Essential Drugs*. Geneva, World Health Organization, 1995 (WHO Technical Report Series, No. 850), Annex 3.
5. *Good practices for national pharmaceutical control laboratories. Thirty-sixth report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations*. Geneva, World Health Organization, 2002 (WHO Technical Report Series, No. 902), Annex 3.
6. UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR). *Handbook of good laboratory practice (GLP)*. Geneva, World Health Organization, 2001.
7. *Guidance on variations to a prequalified product dossier. Forty-first report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations*. Geneva, World Health Organization, 2007 (WHO Technical Report Series, No. 943), Annex 6.

Appendix 1

Flowchart of WHO prequalification of pharmaceutical products



Appendix 2

Characteristics of the prequalified pharmaceutical product to be made available for public access on the WHO web site

— WHO product reference number
— International Nonproprietary Name (INN) of active pharmaceutical ingredient(s) (API(s))
— Dosage form and strength
— Trade name(s) of the product (if applicable)
— Name of applicant and official address
— Name of manufacturer of finished pharmaceutical product (FPP)
— Physical address of manufacturing site(s) (and unit, if applicable)
— Name of API manufacturer, physical address of manufacturing site(s) (and unit, if applicable)
— Product description (as in FPP specifications, i.e. coated, scored, etc.)
— Pack size(s), primary and secondary packaging material(s)
— Storage conditions
— Shelf-life (provisional, if applicable)
— Summary of product characteristics
— Package leaflet
— Labelling

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Annex 4

Procedure for assessing the acceptability, in principle, of active pharmaceutical ingredients for use in pharmaceutical products

1. Introduction

A significant part of the quality of a finished pharmaceutical product (FPP) is dependent on the quality of the active pharmaceutical ingredients (APIs) used for its production. Under the World Health Organization (WHO) guidelines on good manufacturing practices (GMP), it is the manufacturer of the FPP who is responsible for the overall quality of the product, i.e. including the choice of the suppliers and manufacturers of the ingredients.

However, in the context of globalization, APIs are sourced in a worldwide market and the risk of sourcing substandard or contaminated products is high. A proper system of qualification of suppliers can promote the constant sourcing of active ingredients of appropriate quality and thereby safeguard public health interests.

Full evaluation of suppliers of APIs, however, is a cost-intensive and resource-demanding activity, which only a few national medicines regulatory authorities (NMRAs) can afford. As a result, API assessment is not often part of granting marketing authorizations to FPPs, a situation which can undermine the quality and safety of marketed pharmaceutical products.

The need for quality assurance of APIs was noted in the resolutions of the 12th International Conference of Drug Regulatory Authorities in 2006. If adopted and implemented, this procedure would assist procurement agencies in validating the quality of the pharmaceutical products they are purchasing and facilitate product evaluation by NMRAs of WHO Member States as part of the marketing authorization procedures.

The purpose of this procedure is to provide relevant United Nations agencies and relevant authorities of WHO Member States, such as NMRAs, with advice on the acceptability, in principle, of APIs which are found to meet WHO-recommended quality standards.

Those APIs and their specified manufacturing sites which are found to meet the quality standards recommended by WHO are included in a list of APIs, as manufactured at the specified manufacturing sites, which have – at the time of their evaluation and inspection by WHO – been found to be acceptable, in

principle, for use in the production of pharmaceutical products. It remains the ultimate responsibility of the manufacturer of the FPP to ensure that the API, as accepted in principle, is suitable for the manufacture of the specific pharmaceutical product, for example in a sterile or a fixed-dose combination product.

Inclusion in the list does not imply any approval by WHO of the APIs and manufacturing sites in question. Moreover, inclusion in the list does not constitute a WHO endorsement or warranty of the fitness of any API for a particular purpose, including its use in a particular pharmaceutical product and the safety and/or efficacy of that pharmaceutical product in the treatment of specific diseases.

2. Glossary

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

active pharmaceutical ingredient (API)

Any substance or combination of substances used in a finished product, intended to furnish pharmacological activity or to otherwise have direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease, or to have direct effect in restoring, correcting or modifying physiological functions in human beings.

finished pharmaceutical product (FPP)

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

manufacture or production

All operations of purchase of materials and starting materials, preparation of the API and of the pharmaceutical product, including packaging and repackaging, labelling and re-labelling, quality control, release, storage and distribution and the related controls. The terms "manufacture" and "production" are used interchangeably in this document.

manufacturer of active pharmaceutical ingredient (API)

A company that produces, packages and labels active pharmaceutical ingredients (APIs).

3. Purpose and principles

The purpose of this quality assessment procedure is to evaluate whether the APIs meet the requirements recommended by WHO, including that they

are manufactured in compliance with WHO current good manufacturing practices (current good manufacturing practices being hereinafter referred to as GMP) (*1*, *2*). This will be done through standardized quality assessment and inspection procedures.

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

- a general understanding of the production and quality control activities of the manufacturer of the API;
- assessment of data and information on the API, submitted by the manufacturer, which includes the manufacturing process, material specifications, test data and results, including changes and variations;
- assessment of the API manufacturing site(s) for consistency in production and quality control of raw materials, with specific emphasis on key starting materials or intermediates and the final APIs during and after purification through compliance with WHO GMP;
- random sampling and testing of APIs;
- control of storage and distribution;
- handling of complaints and recalls; and
- monitoring of complaints from relevant United Nations agencies and national medicines regulatory authorities of WHO Member States.

WHO will collaborate with NMRAs and other organizations on quality assessment and site inspections. WHO recommends that manufacturers of APIs expressing interest in participating in the prequalification of APIs should inform and ask the relevant NMRA to collaborate with WHO in the quality assessment process. It is recommended that the manufacturers provide the national medicines regulatory authority with the necessary authorization to discuss the product files with WHO representatives during inspections where relevant or required (subject to appropriate confidentiality provisions, if necessary).

4. Steps of the procedure

WHO undertakes a comprehensive evaluation of the quality of APIs, based on information submitted by the applicants, and inspection of the relevant manufacturing site(s).

At regular intervals WHO will publish an invitation to interested parties, asking them to voluntarily participate in this procedure in respect of the substances mentioned in the invitation. By submitting an expression of interest (EOI), the applicant undertakes to share information with WHO on all relevant aspects of manufacture and control of the specified APIs together with any changes carried out and/or planned.

Interested applicants provide the necessary information to WHO by submitting an API dossier and other information as requested. Assessment will normally include evaluation of:

- API dossiers, which must include data and information as specified in the guidelines for submission (the guidelines are available on the WHO web site (www.who.int/prequal); and
- manufacturing sites of APIs, which must adhere to WHO GMP.

If evaluation demonstrates that an API and its corresponding manufacturing site(s) meet the standards recommended by WHO, it will be included in the list of APIs which have – at the time of their assessment and inspection – been found to be acceptable, in principle, for use in production of pharmaceutical products.

WHO reserves the right to terminate the procedure of quality assessment of a specific API if the applicant is not able to provide the required information, and/or the applicant is unable to implement any corrective actions, which WHO may require, within a specified time period, or when the information supplied is inadequate to complete the quality assessment process.

WHO recognizes the evaluation of relevant APIs by competent authorities which apply stringent standards for quality, similar to those recommended by WHO, such as, for example, but not limited to, the US Food and Drug Administration (USFDA), the European Medicines Agency (EMEA), and the European Directorate for the Quality of Medicines & HealthCare (EDQM).

Provided that the competent authority applying stringent standards is willing to share certain information with WHO on the API in question, WHO will consider this information for possible inclusion of the API in the list of WHO prequalified APIs. It will do so as and when information about such APIs becomes available to WHO. These products can be added to the list of APIs prequalified by WHO, on the basis of the scientific assessment and inspections conducted by the competent authority concerned, and the exchange of relevant information between the concerned authority and WHO.

5. Invitation for expression of interest

WHO will, at regular intervals, publish an invitation to manufacturers of specific APIs as identified in the invitation to submit an API dossier for evaluation in accordance with this procedure and the relevant guidelines.

The APIs listed in an invitation for expressions of interest (EOI) will generally be APIs for pharmaceutical products which:

— are considered by WHO to be vital for the effective treatment and prevention of the specified diseases, for example, but not limited to, the treatment of HIV/AIDS, malaria or tuberculosis; and which
— the WHO Expert Committee on Specifications for Pharmaceutical Preparations has identified as being of highest concern in relation to quality.

Each invitation will be open and transparent, inviting all relevant parties to submit an EOI for the APIs listed. Such an invitation will normally be published on the WHO web site and possibly also through other media, such as the international press.

Guidelines developed for the submission of the API dossier are available on the WHO web site at www.who.int/prequal and will be sent to interested manufacturers upon request.

6. Data and information to be submitted

Interested manufacturers are expected to submit documentation on the APIs as called for in the invitation for EOI. Applicants should submit their API dossiers, with the required information, to the WHO focal point, before the deadline specified in the invitation. Guidance and instructions developed for the submission of the dossiers shall be made available on the WHO web site. Data and information to be submitted in the API dossier should include the following:

General information

- nomenclature
- structure
- general properties

Manufacture

- site(s) of manufacture
- description of manufacturing process and process controls
- control of materials
- control of critical steps and intermediates
- process validation and/or evaluation
- manufacturing process development

Characterization

- elucidation of structure and other characteristics
- impurities

Control of the API

- specification

- analytical procedures
- validation of analytical procedures
- batch analysis
- justification of specification

Reference standards or materials

Container closure system

Stability

- stability summary and conclusion
- post-approval stability protocol and stability commitment
- stability data.

The above-listed content of the API dossier is the same as the common technical documentation (CTD) content for the API section and is in line with the content of the API master file (APIMF) dossier, open and restricted parts together, as established for the purposes of WHO prequalification of pharmaceutical products (*3*).

Holders of APIMFs whose dossiers as per the CTD have been assessed with a positive notified outcome by WHO as part of the prequalification procedure for a pharmaceutical product, and whose product has subsequently been included in the list of WHO prequalified pharmaceutical products can, in response to an invitation for EOI, apply in writing for evaluation under this API prequalification procedure without dossier assessment. WHO, however, reserves the right to assess those issues which are required to be evaluated under the present procedure, but which were not covered by the assessment of the APIMF dossier as part of the prequalification of a pharmaceutical product.

Alternatively, a drug master file, as prepared for or submitted to the NMRA of an ICH[1] region, can be submitted provided that it contains the information required. In such cases a covering letter cross-referencing the information should be provided by the manufacturer. In this regard, the WHO Pharmaceutical Starting Materials Certification Scheme (SMACS) can be used in support of the relevant data which are covered by the Scheme (*4*).

Changes in the manufacture of an API should be documented in the API dossier through appropriate change control procedures and communicated to WHO.

[1] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use.

7. Screening of dossiers submitted

Each API dossier submitted by an applicant will be screened for completeness prior to being evaluated. Dossiers submitted for APIs, which are not listed in an invitation for EOI or which have not otherwise been invited by WHO, will not be accepted for evaluation.

Similarly, WHO will not consider dossiers that are incomplete. The applicant will be informed that an incomplete dossier has been received and will be requested to complete the dossier within a specified time period. In the event of non-compliance the dossier may be rejected on grounds of incompleteness and returned to the applicant. Dossiers that are considered complete as the result of the administrative screening will be retained by WHO for evaluation purposes.

8. Assessment of API dossiers

The information on the API submitted in the dossier will be evaluated by teams of experts (assessors) appointed by WHO. The assessors involved in dossier assessment must have the relevant qualifications and experience in the fields of pharmacy, organic and analytical chemistry, quality assessment, quality assurance and other relevant fields.

The assessors will be appointed in accordance with a standard operating procedure (SOP) established by WHO. The assessors should preferably be from NMRAs and they will act as temporary advisers to WHO. The assessors must comply with the confidentiality and conflict of interest rules of WHO, as laid down in the relevant sections of this procedure.

The assessment of product dossiers will be done in accordance with SOPs established by WHO for that purpose so as to ensure uniformity in evaluation and timeliness of assessment activities. If needed, WHO may provide training to these experts.

9. Site inspection

Dependent on the outcome of the evaluation of the API dossier, the planning of inspections should take into account the types of API and the results and reports of inspections conducted by regulatory authorities or other competent organizations.

WHO will plan and coordinate the performance of inspections at the manufacturing site(s) of APIs and that of the key intermediate (if relevant) to assess compliance with the relevant sections of WHO GMP guidelines, and will compare the technical information on the manufacturing process

given in the API dossier submitted to WHO with the manufacturing process actually carried out on site.

The inspections will be performed by a team of inspectors consisting of experts appointed by WHO, preferably from NMRA inspectorates, who will act as temporary advisers to WHO. The inspectors must have the relevant qualifications and experience to perform such inspections, be competent in areas such as production and quality control of pharmaceuticals, and have appropriate experience in WHO GMP. The inspectors must comply with the confidentiality and conflict of interest rules of WHO, as laid down in the relevant sections of this procedure. If needed, WHO may provide training to these experts.

A WHO staff member will coordinate the team. Each team will perform the inspections and report on its findings to WHO in accordance with SOPs established by WHO for that purpose so as to ensure a standard harmonized approach. A representative of the NMRA of the country of manufacture would normally be expected to accompany the team to the manufacturing facilities to assess the compliance with GMP.

10. Reporting and communication of results of the evaluation

Each assessment and inspection team will finalize its reports according to the established WHO SOP and format, describing the findings and including recommendations to the applicant.

The findings from the dossier assessment, including, but not limited to, deficiencies of the documentation and data submitted, shall be communicated in writing to the applicant and will request submission of the missing data and information and for corrective actions, as appropriate.

The inspection report will be communicated to the applicant. If any additional information is required, or corrective action has to be taken by the manufacturer of the API and/or manufacturer of the key intermediate, WHO will postpone its decision of the acceptability of the respective site(s), until such information has been evaluated, or the corrective action has been taken and found satisfactory in light of the specified standards.

WHO reserves the right to terminate the procedure of quality assessment of a specific API if the applicant is not able to provide the required information or implement the corrective actions within a specified time period, or if the information supplied is inadequate to complete the quality assessment process.

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

As WHO is responsible for the quality assessment, the ownership of the reports lies with WHO. Thus, WHO shall be entitled to use and publish such reports, subject always, however, to the protection of any commercially sensitive confidential information of the manufacturer. "Confidential information" means:

- confidential intellectual property, "know-how" and trade secrets (including, e.g. programmes, manufacturing processes or information contained or embodied in an API dossier, unpublished aspects of trademarks, and patents); and
- commercial confidences (e.g. structures and development plans of a company).

Provisions of confidentiality will be contained in an exchange of letters between WHO and each applicant, to be concluded before the assessment of the API dossier or inspection of the manufacturing sites.

Notwithstanding the foregoing, WHO reserves the right to share the full evaluation and inspection reports with the relevant authorities of any interested Member State of the Organization and United Nations agencies.

11. Outcome of quality assessment procedure

Once WHO is satisfied that the quality assessment process is complete for the relevant API, and that the WHO-recommended standards are met, the API, as produced at the specified manufacturing site(s), will be included in the list of prequalified APIs. The list of prequalified APIs will be compiled in accordance with an SOP established by WHO for final decision-making on inclusion in the list. The list will be published on the WHO web site and will specify the characteristics of the prequalified APIs, as follows:

— API application WHO reference number;
— International Nonproprietary Name (INN) of active ingredient;
— name of API manufacturer, physical address of manufacturing site(s);
— applicant reference to pharmacopoeial or in-house standards;
— primary and secondary packaging material(s);
— retest period;
— storage conditions stated on labelling.

Each applicant will receive a letter from WHO informing it of the outcome of the quality assessment process regarding the submitted API applications. Once the APIs are included in the list of prequalified APIs, the applicant shall be held to keep WHO continuously updated on all relevant aspects of the manufacture and control of such APIs and to meet any requirements, as agreed with WHO.

In accordance with World Health Assembly Resolution WHA57.14 of 22 May 2004, WHO will, subject always to the protection of commercially sensitive confidential information, publish WHO Public Inspection Reports (WHOPIR(s)) on the manufacturers that were found to be in compliance with WHO-recommended guidelines and standards. These reports will be published on the WHO web site. WHO shall also be entitled to publish negative evaluation outcomes.

The decision to list an API is made based upon information available to WHO at that time, i.e. information in the submitted API dossier, and on the status of GMP at the facilities used in the manufacture and control of the API at the time of the site inspection(s) conducted by WHO.

This decision is subject to change on the basis of new information that may become available to WHO. If serious safety and/or quality concerns arise in relation to a prequalified API, WHO may delist the API or suspend the API until results of further investigations become available and are evaluated by WHO.

12. Procurement, sourcing and supply

All APIs included in the list should hold a certificate granted pursuant to the WHO SMACS prior to moving in international commerce (*4*).

Procuring United Nations agencies should be aware that manufacturers purchasing APIs from the sources included in the WHO list should still perform the relevant qualification of the manufacturer and quality control of the API with regard to the physicochemical characteristics and other aspects of the API that have an impact on the quality, safety and efficacy of the FPP (*5*).

Manufacturers of APIs, in turn, should be aware that inclusion in the list does not exclude their duties to communicate to buyers the necessary technical data.

13. Maintenance of prequalification status

Applicants are required to communicate details to WHO of any changes (variations) in manufacture and control that may have an impact on the safety, efficacy and quality of the API. It is the applicant's responsibility to provide WHO with the appropriate documentation (referring to relevant parts of the dossier) to prove that any intended or implemented variation will not have an impact on the quality of the API that has been prequalified. WHO will undertake an evaluation of variations according to the established WHO guidelines and SOPs and communicate the outcome to the applicant.

Adherence to the reporting requirements will be verified during the inspections carried out by WHO.

Random samples of APIs supplied to manufacturers of FPPs may be taken by WHO or by the NMRA of a Member State and submitted to WHO for independent testing. Certificates of analysis released by the manufacturer and specifications for test methods should be provided by the manufacturer to WHO for review upon request. In the event of failure to meet the established criteria for testing, WHO will investigate the problem and communicate this to the manufacturer concerned.

Complaints concerning prequalified APIs, communicated to WHO, will be investigated in accordance with an SOP established by WHO for that purpose. After investigation WHO will provide a written report of the problem and include recommendations for action where relevant. WHO will make the report available to the applicant, and to the NMRA of the country where the manufacturing site is located. Subject always to considerations of commercially sensitive information as referred to above, WHO also reserves the right to make such reports public if it considers this to be of public health concern. In addition, WHO reserves the right to share the full report with relevant authorities of interested Member States of the Organization and United Nations agencies.

WHO will at regular intervals arrange for the APIs and manufacturing sites included in the list to be re-evaluated. If, as a result of this re-evaluation, it is found that an API and/or specified manufacturing site no longer complies with the WHO-recommended standards, such APIs and manufacturing sites will be removed from the list. Failure of a manufacturer to participate in the reassessment procedure will also lead to removal from the list.

Re-evaluation, including reinspections of manufacturing sites, will be done at regular intervals based on risk assessment, but at least once every five years.

Re-evaluation, including reinspections, shall also be performed:

- if any fraud or omissions by the applicant/manufacturer of APIs in the initial assessment procedure or during the follow-up activities becomes evident; and
- if WHO or any of the relevant United Nations agencies or NMRAs of WHO Member States consider that a batch or batches of prequalified APIs supplied are not in compliance with the specifications which were found to be applicable upon prequalification.

14. Cost recovery

WHO reserves the right to charge for the quality assessment procedure on a cost recovery basis.

15. Confidentiality undertaking

The assessors and inspectors will treat all information to which they will gain access during the evaluations and inspections, or otherwise in connection with the discharge of their responsibilities in regard to the above-mentioned activities, as confidential and proprietary to WHO or parties collaborating with WHO in accordance with the terms set forth below.

Assessors and inspectors will take all reasonable measures to ensure:

- that confidential information is not used for any purpose other than the evaluation/inspection activities described in this document; and
- that it is not disclosed or provided to any person who is not bound by similar obligations of confidentiality and non-use as contained herein.

Assessors 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.

16. Conflict of interest

Before undertaking the work, each assessor and inspector will also (in addition to the above-mentioned confidentiality undertaking) be required to sign a declaration of interest. If, based on this declaration of interest, it is felt that there is no risk of a real or perceived conflict of interest (or it is felt that there is only an insignificant and/or irrelevant conflict of interest), and it is thus deemed appropriate for the evaluator or inspector in question to undertake this work, he/she will discharge his/her functions exclusively as adviser to WHO. In this connection, each assessor and inspector is required to confirm that the information disclosed by him/her in the declaration of interest is correct and complete, and that he/she will immediately notify WHO of any change in this information.

All inspectors furthermore agree, that at the manufacturer's request, WHO will advise the manufacturer in advance of the identity of each inspector and composition of the team performing the site inspection, and provide curricula vitae of the inspectors. The manufacturer then has the opportunity to express possible concerns regarding any of the inspectors to WHO prior to the visit. If such concerns cannot be resolved in consultation with WHO,

the manufacturer may object to a team member's participation in the site visit. Such an objection must be made known to WHO by the manufacturer within 10 days of receipt of the proposed team composition. In the event of such an objection, WHO reserves the right to cancel all or part of its agreement with, and the activities to be undertaken by, that inspector.

References

1. WHO good manufacturing practices: main principles for pharmaceutical products. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-seventh report*. Geneva, World Health Organization, 2003 (WHO Technical Report Series, No. 908), Annex 4; and related 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.
2. WHO good manufacturing practices: guidelines on active pharmaceutical ingredients. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-fifth report*. Geneva, World Health Organization, 1999 (WHO Technical Report Series, No. 885), Annex 5; and related 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.
3. Guidelines on Active Pharmaceutical Ingredient Master File Procedure. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-second report*. Geneva, World Health Organization, 2008 (WHO Technical Report Series, No. 948), Annex 4.
4. WHO Pharmaceutical Starting Materials Certification Scheme (SMACS): guidelines on implementation. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-eighth report*. Geneva, World Health Organization, 2004 (WHO Technical Report Series, No. 917), Annex 3.
5. Good trade and distribution practices for pharmaceutical active pharmaceutical ingredients. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-eighth report*. Geneva, World Health Organization, 2004 (WHO Technical Report Series, No. 917), Annex 2.