WHO Technical Report Series

992

WHO Expert Committee on Specifications for Pharmaceutical Preparations

Forty-ninth report

World Health Organization

The World Health Organization was established in 1948 as a specialized agency of the United Nations serving as the directing and coordinating authority for international health matters and public health. One of WHO's constitutional functions is to provide objective and reliable information and advice in the field of human health, a responsibility that it fulfils in part through its extensive programme of publications.

The Organization seeks through its publications to support national health strategies and address the most pressing public health concerns of populations around the world. To respond to the needs of Member States at all levels of development, WHO publishes practical manuals, handbooks and training material for specific categories of health workers; internationally applicable guidelines and standards; reviews and analyses of health policies, programmes and research; and state-of-the-art consensus reports that offer technical advice and recommendations for decision-makers. These books are closely tied to the Organization's priority activities, encompassing disease prevention and control, the development of equitable health systems based on primary health care, and health promotion for individuals and communities. Progress towards better health for all also demands the global dissemination and exchange of information that draws on the knowledge and experience of all WHO's Member countries and the collaboration of world leaders in public health and the biomedical sciences.

To ensure the widest possible availability of authoritative information and guidance on health matters, WHO secures the broad international distribution of its publications and encourages their translation and adaptation. By helping to promote and protect health and prevent and control disease throughout the world, WHO's books contribute to achieving the Organization's principal objective – the attainment by all people of the highest possible level of health.

The *WHO Technical Report Series* makes available the findings of various international groups of experts that provide WHO with the latest scientific and technical advice on a broad range of medical and public health subjects. Members of such expert groups serve without remuneration in their personal capacities rather than as representatives of governments or other bodies; their views do not necessarily reflect the decisions or the stated policy of WHO.

An annual subscription to this series, comprising about four to six such reports, costs CHF 150.00/US$ 180.00 (CHF 105.00/US$ 126.00 in developing countries). For further information, please contact: WHO Press, World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland (tel. +41 22 791 3264; fax: +41 22 791 4857; email: bookorders@who.int; order online: http://www.who.int/bookorders).

WHO Technical Report Series
992

WHO Expert Committee on Specifications for Pharmaceutical Preparations

Forty-ninth report

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

World Health Organization

WHO Library Cataloguing-in-Publication Data

Forty-ninth report of the WHO Expert Committee on specifications for pharmaceutical preparations.

(WHO technical report series ; no. 992)

1.Pharmaceutical Preparations - standards. 2.Technology, Pharmaceutical - standards. 3.Drug Industry - legislation. 4.Quality Control. I.World Health Organization. II.Series.

ISBN 978 92 4 120992 2 (NLM classification: QV 771)
ISBN 978 92 4 069396 8 (PDF)
ISSN 0512-3054

© World Health Organization 2015

All rights reserved. Publications of the World Health Organization are available on the WHO website (www.who.int) or can be purchased from WHO Press, World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland (tel.: +41 22 791 3264; fax: +41 22 791 4857; email: bookorders@who.int).

Requests for permission to reproduce or translate WHO publications – whether for sale or for non-commercial distribution – should be addressed to WHO Press through the WHO website (www.who.int/about/licensing/copyright_form/en/index.html).

The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by the World Health Organization in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.

All reasonable precautions have been taken by the World Health Organization to verify the information contained in this publication. However, the published material is being distributed without warranty of any kind, either expressed or implied. The responsibility for the interpretation and use of the material lies with the reader. In no event shall the World Health Organization be liable for damages arising from its use.

This publication contains the collective views of an international group of experts and does not necessarily represent the decisions or the policies of the World Health Organization.

Printed in Italy

Contents

WHO Expert Committee on Specifications for Pharmaceutical Preparations

Geneva, 13–17 October 2014

Members[1]

Professor S.A. Bawazir, Advisor to the Chief Executive Officer, Saudi Food and Drug Authority, Riyadh, Saudi Arabia (*Co-Chairperson*)

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

Ms M. Hirschhorn, Head, Quality and Chemistry Sector, Comisión para el Control de Calidad de Medicamentos, Montevideo, Uruguay

Professor J. Hoogmartens, Professor Emeritus, Laboratorium voor Farmaceutische Analyse, Leuven, Belgium

Professor S. Jin, Chief Expert for Pharmaceutical Products, National Institutes for Food and Drug Control, Beijing, People's Republic of China

Professor H.G. Kristensen, Vedbaek, Denmark

Ms G.N. Mahlangu, Director-General, Medicines Control Authority of Zimbabwe, Harare, Zimbabwe (*Chairperson*)

Dr L. Stoppa, Inspections and Certification Department, Manufacturing Authorisation Office, Italian Medicines Agency, Rome, Italy (*Co-Rapporteur*)

Dr A.J. van Zyl, Cape Town, South Africa (*Co-Rapporteur*)

Temporary advisers[2]

Dr P. Aprea, Head, Biological Products Department, National Administration of Drugs, Food and Medical Technology (ANMAT), Ministry of Health, Ciudad Autonoma de Buenos Aires, Argentina

Dr A.C. Moreira Marino Araujo, Brazilian Pharmacopeia Coordinator, Brazilian Health Surveillance Agency, Brasilia, Brazil

Dr G. Born, Scientist, Institute of Pharmaceutical Technology, Johann Wolfgang Goethe-University, Frankfurt, Germany

---

[1] Unable to attend: Ms L. Min Yong, Division Director, Pharmaceutical Division, Applied Sciences Group, Health Sciences Authority, Singapore; Mrs L. Paleshnuik, Arnprior, Ontario, Canada; Dr S. Parra, Manager, Generic Drug Quality Division 1, Bureau of Pharmaceutical Sciences, Therapeutic Products Directorate, Health Canada, Ontario, Canada; Dr G.N. Singh, Drugs Controller General, Ministry of Health and Family Welfare, Government of India, New Delhi, India.

[2] Unable to attend: Dr J.-L. Robert, Head of Unit, Service du Contrôle des Médicaments, Laboratoire National de Santé, Luxembourg.

Mr A. Garcia, Jefe de Servicio de Farmacocinética y Medicamentos Genéricos, División de Farmacología y Evaluación Clínica, Departamento de Medicamentos de Uso Humano, Agencia Española de Medicamentos y Productos Sanitarios, Madrid, Spain

Dr J. Gordon, Wolfville, Nova Scotia, Canada

Mr I. Jackson, Operations Manager, GMDP, Medicines and Healthcare products Regulatory Agency, London, England

Dr O. Le Blaye, Inspector, Trials and Vigilance Inspection Department, Agence nationale de sécurité du médicament et des produits de santé, Saint-Denis, France

Dr B. Li, Deputy Director General, National Institutes for Food and Drug Control, Beijing, People's Republic of China

Dr J.A. Molzon, Associate Director for International Programs, Center for Drug Evaluation and Research, United States of America Food and Drug Administration, Silver Spring, MD, USA

Dr G.L. Singal, Drugs Controller of Haryana, Food and Drugs Administration, Haryana, India

Dr D. Sun Cuilian, Senior Analytical Scientist, Pharmaceutical Laboratory, Pharmaceutical Division, Applied Sciences Group, Health Sciences Authority, Singapore

Dr J. Welink, Scientist, Medicines Evaluation Board, Utrecht, Netherlands

Representation from United Nations offices[3]

United Nations Children's Fund (UNICEF)

Dr P.S. Jakobsen, Quality Assurance Specialist, UNICEF Supply Division, Copenhagen, Denmark

Representation from specialized agencies and related organizations[4]

The Global Fund to Fight AIDS, Tuberculosis and Malaria

Ms S. Logez, Manager, Health Product Management Hub, Geneva, Switzerland

Representation from intergovernmental organizations[5]

Council of Europe

Dr A. Lodi, Head, Laboratory Department, European Directorate for the Quality of Medicines & HealthCare, Strasbourg, France

---

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

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

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

European Medicines Agency (EMA)
Dr R. Luigetti, Principal Administrator, International Affairs, London, England

Representation from nongovernmental organizations[6]

International Federation of Pharmaceutical Manufacturers and Associations (IFPMA)
Dr B. Fritschel, Director, Regulatory Quality & Compliance, Johnson & Johnson Regulatory Compliance, New Brunswick, NJ, USA

and

Ms V. Faillat-Proux, Senior Director, Regulatory Affairs, Access to Medicines, Sanofi, Gentilly, France

International Generic Pharmaceutical Alliance (IGPA)
Dr J. Maréchal-Jamil, Senior Manager, Quality & Regulatory Affairs, European Generic Medicines Association, Brussels, Belgium

World Self-Medication Industry (WSMI)
Dr R. Torano, Pharmacopoeial Technical Expert, GlaxoSmithKline, England

Observers[7]

Dr C.M. Limoli, Senior Program Manager, Center for Drug Evaluation and Research, United States of America Food and Drug Administration, Silver Spring, MD, USA

Professor B. Ning, Deputy Director, Division of Chemical Drugs, National Institutes for Food and Drug Control, Beijing, People's Republic of China

Dr T. Wang, Deputy Director, Shenzhen Municipal Institute for Drug Control, Shenzhen, People's Republic of China

Pharmacopoeias[8]

British Pharmacopoeia Commission
Mr A. Evans, Principal Pharmacopoeial Scientist, London, England

[6] Unable to attend: Commonwealth Pharmacists Association, London, England; European Chemical Industry Council/Active Pharmaceutical Ingredients Committee, Brussels, Belgium; International Pharmaceutical Excipients Council, Brussels, Belgium; International Pharmaceutical Federation, The Hague, Netherlands; International Society for Pharmaceutical Engineering, Tampa, FL, USA.

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

[8] Unable to attend: Farmacopea Argentina; Farmacopéia Brasileira, Pharmacopoeia of the People's Republic of China; Indian Pharmacopoeia Commission; Committee of the Japanese Pharmacopoeia; State Pharmacopoeia of the Russian Federation; Pharmacopoeia of Ukraine.

Indonesian Pharmacopoeia Commission
Dr A. Sulistiowati, Director, National Quality Control Laboratory of Drug and Food, Percetakan, Indonesia

and

Mrs T. Yulianti, Scientist, National Quality Control Laboratory of Drug and Food, Percetakan, Indonesia

Pharmacopoeia of the Republic of Korea
Dr H. Kim, Director, Pharmaceutical Standardization Research and Testing Division, Chungcheongbuk-do, Republic of Korea

and

Dr J. Lee, Scientist, Pharmaceutical Standardization Research and Testing Division, Chungcheongbuk-do, Republic of Korea

United States Pharmacopeia
Dr K. Moore, Manager, Pharmacopeial Harmonization, Rockville, MD, USA

and

Dr L.M. Santos, Senior Scientist, Monograph Modernization, Rockville, MD, USA

Representation from WHO regional offices[9]

WHO Secretariat

Health Systems and Innovation (HIS)
Dr M.-P. Kieny, Assistant Director-General

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

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

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

Dr D. Lei

Medicines Quality Assurance (EMP/TSN)
Dr S. Kopp, Group Lead (*Secretary*)

Dr H. Schmidt

[9] Unable to attend: Regional Office for Africa, Brazzaville, Congo; Regional Office for the Americas, Pan American Health Organization, Washington, DC, USA; Regional Office for the Eastern Mediterranean, Cairo, Egypt; Regional Office for Europe, Copenhagen, Denmark; Regional Office for South-East Asia, New Delhi, India; Regional Office for the Western Pacific, Manila, Philippines.

International Nonproprietary Names Programme (INN/TSN)
Dr R.G. Balocco Mattavelli, Group Lead

Prequalification Team (EMP/PQT)
Dr A. Fake

Dr D.G. Maire

Dr D. Mubangizi, Group Lead, Inspections

Dr U.A. Rosskopf

Ms J.K. Sawyer

Dr M. Stahl, Group Lead, Medicines Assessment

Dr I. Thrussell, Senior Inspector

Regulatory Systems Strengthening (RSS/RHT)
Dr S. Azatyan, Group Lead, Capacity Building and Harmonization Support

Dr L. Belgharbi

Safety and Vigilance Team (EMP/SAV)
Ms P. Bourdillon Esteve

Traditional and Complementary Medicine (HIS/Service Delivery and Safety (SDS)/TCM)
Dr Y. Maruyama

Mr David Bramley (report writer)

Declarations of interest

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

Dr P. Aprea, Professor S. Bawazir, Dr G. Born, Dr D. Sun Cullian, Dr T. Dekker, Dr A. Garcia Arieta, Dr J. Gordon, Mr I. Jackson, Ms M. Hirschhorn, Professor J. Hoogmartens, Professor S. Jin, Dr B. Li, Dr O. Le Blaye, Dr G.L. Singal, Dr L. Stoppa and Dr J. Welink reported no conflict of interest.

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

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

Dr J. Molzon reported that her employer, the United States Food and Drug Administration, was interested in good review and regulatory practices.

Dr A.C. Moreira Marino Araujo reported that she has worked at the regulatory health and surveillance agency in Brazil since 2007 and that her employer, ANVISA, has an interest related to the subject of the meeting.

Dr A.J. van Zyl reported that he has acted as a consultant, auditor and trainer for the pharmaceutical industry.

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

1. Introduction

The WHO Expert Committee on Specifications for Pharmaceutical Preparations met in Geneva from 13 to 17 October 2014. Mr C. de Joncheere, Director of the Department of Essential Medicines and Health Products (EMP) at the World Health Organization (WHO) welcomed participants on behalf of the Director-General.

Mr de Joncheere thanked the experts and advisers for their important contributions to the work of WHO in setting standards in the area of pharmaceuticals. He pointed out that the WHO Expert Committee on Biological Standardization was meeting at WHO headquarters during the same week and that the Chairpersons and Co-Chairpersons of both Expert Committees would have a briefing session with the Director-General. In addition, the Organization was hosting a consultation on International Nonproprietary Names (INN) for Pharmaceutical Substances. Other recent meetings with strong WHO involvement had included the fourth meeting of world pharmacopoeias and the recent International Conference of Drug Regulatory Authorities (ICDRA). Mr de Joncheere pointed out that such involvement is a key element in WHO's work.

Mr de Joncheere said that the restructuring of EMP had been completed in the past year and would enable WHO to face current and future challenges more effectively. In 2014 the World Health Assembly had adopted a large number of resolutions – on essential medicines, vaccines, medical products, regulatory activities and substandard/spurious/falsely-labelled/falsified/counterfeit (SSFFC) medical products – that directly related to EMP. Other World Health Assembly resolutions – such as those on traditional medicines and antimicrobial resistance – also impacted on EMP's work.

Participants were reminded that they participated in the meeting in their personal capacity as experts.

The meeting elected Ms G.N. Mahlangu as Chairperson, Professor S.A. Bawazir as Co-Chairperson, and Dr L. Stoppa and Dr A.J. van Zyl as Rapporteurs. Ms Mahlangu then took the chair.

Open session

The Chairperson welcomed the members, technical advisers and observers to the open session of the Expert Committee. The open session had been arranged in response to earlier expressions of interest by the diplomatic missions. It was noted that there were no representatives from the missions.

The Secretary of the Expert Committee explained the Committee's role and how the expert committee system of WHO worked. An expert committee is the highest advisory body to the Director-General and is established in the Constitution of the Organization. A set of specific rules and procedures govern

invitations to and participation in meetings of an expert committee. The WHO Expert Committee on Specifications for Pharmaceutical Preparations is one of WHO's oldest expert committees, dating from the time of the founding of the Organization. As a result of the work of this Expert Committee, there are 75 current WHO guidelines and good practice documents on the development, manufacture, inspection, distribution, quality control (QC) and related regulatory guidance for medicines, as well as some 50 training modules on good manufacturing practices (GMP), GMP inspection, laboratory practices and technology transfer.

Guidelines that are adopted by the Expert Committee are published as annexes to the meeting report, which is issued in the WHO Technical Report Series. Specifications adopted by the Committee are published in *The International Pharmacopoeia*.

2. General policy

2.1 International collaboration

2.1.1 Collaboration with international organizations and agencies

The Global Fund to Fight AIDS, Tuberculosis and Malaria

The activities and responsibilities of The Global Fund to Fight AIDS, Tuberculosis and Malaria were outlined for the Expert Committee. The Global Fund is an international funding institution for the three target diseases, providing 82% of all financing for tuberculosis medicines, 50% of all financing for malaria medicines and 21% of that for HIV medicines. During the period 2014 to 2016, the Global Fund will supply funding of approximately US$ 14 billion, of which an estimated US$ 6.3 billion will be spent on medicines and other health products.

The Global Fund focuses on the countries with the highest disease burden and the lowest ability to pay. Changes to its financing system have made the Fund more flexible in meeting countries' needs. Grants are made for three years of implementation, and an important element in ensuring that the programmes funded are successful is that the products to be procured are of the highest quality. The Global Fund is the funder and procurement is the responsibility of the grant recipient – a country, a United Nations agency or a nongovernmental organization. According to the Fund's principles, it funds the procurement only of quality-assured products that are in a form that supports adherence. All products must be assured by the United Nations Prequalification Team or by a stringent regulatory authority (SRA) and must be authorized for use in the recipient countries. The quality of products is monitored throughout the supply chain.

An expert review panel (ERP), hosted by WHO, was established in 2010 to review product dossiers and assess risks and benefits. For those products not yet approved by the Prequalification Team (PQT) – Medicines or by an SRA, the ERP gives a time-limited recommendation of not more than 12 months.

The Global Fund noted the importance of the critical normative guidance provided by WHO thanks to the Expert Committee system.

The Expert Committee noted the report and thanked the Global Fund for its strong commitment to quality assurance policies and acknowledged the close collaboration with WHO, especially Medicines Quality Assurance and PQT.

International Conference of Drug Regulatory Authorities (ICDRA)

Since 1980, ICDRA meetings have been held every two years to enable regulatory authorities to exchange information on medical products and to foster collaborative approaches to common issues. WHO provides the secretariat for ICDRA which is a self-supporting initiative. ICDRA's most recent meeting was

held in Rio de Janeiro, Brazil, in August 2014. The meeting was hosted by the Brazilian Health Surveillance Agency (ANVISA).

The biennial ICDRA meeting, which is organized specifically for regulators, also includes a two-day "pre-meeting" which is open to other interested parties. The 2014 pre-meeting focused on biosimilars, while the main meeting covered issues of common interest to regulators. The Rio meeting asserted that effective regulatory systems are an essential component of health-systems strengthening and called on countries to harmonize regulatory processes, to introduce fast-track processes for medical products that have already undergone rigorous evaluation in other countries and to share experiences of special procedures for registration of products in times of emergency. With regard to the Ebola epidemic, the regulators recommended that countries should ensure that emergency regulatory pathways are in place.

The Expert Committee noted the report.

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

The Co-chair of the ICH Global Cooperation Group reported that the Q3D Expert Working Group's guideline for elemental impurities was expected to reach Step 4 in late 2014. The final document will be placed on the ICH website.

The Q7 Implementation Working Group continues its work on developing questions and answers to address current issues raised by the use of the Q7 guideline, *Good manufacturing practice guide for active pharmaceutical ingredients*. The Implementation Working Group was endorsed by the ICH Steering Committee in October 2012. Experience gained with the implementation of the ICH Q7 Guideline since its finalization in 2000 had revealed uncertainties related to the interpretation of some sections. Technical issues with regard to GMP for active pharmaceutical ingredients (APIs) – also in the context of new ICH guidelines – would be addressed in the question-and-answer document in order to harmonize expectations during inspections, to remove ambiguities and uncertainties and to harmonize inspections of both small molecules and biotech APIs.

The development of a concept paper for a project on life-cycle management was also endorsed by the Steering Committee and a working group on this topic will be established. The aim is to provide guidance on a framework to facilitate the management of post-approval chemistry, manufacturing and control changes in a more predictable and efficient manner throughout the product life cycle. This new ICH guideline, which is intended to complement the existing ICH Q8 to Q11 guidelines, aims to promote innovation and continual improvement and to strengthen quality assurance and reliability of product supply, including through proactive planning of supply chain adjustments. The guidance will allow regulators to better understand a company's pharmaceutical

quality systems for management of post-approval chemistry, manufacturing and controls (CMC) changes.

The Expert Committee noted the report.

Pharmacopoeial Discussion Group (PDG)

The PDG consists of the European Pharmacopoeia, Japanese Pharmacopoeia and United States Pharmacopeia, with WHO as an observer. Its most recent meeting took place in Rockville, MD, USA, from 25 to 26 June 2014. The purpose of the PDG, which usually meets twice a year and holds monthly teleconferences, is to advance harmonization of pharmacopoeial standards. So far 29 of the 36 General chapters and 46 of the 62 excipient monographs on the current work programme have been harmonized. Approvals at the latest meeting included a new general chapter "Thermal analysis" and a revised general chapter "Polyacrylamide gel electrophoresis". The latter reflects recent developments and current practices and allows for greater flexibility in the use of ready-made gels. In addition, a new monograph for "Glucose monohydrate/anhydrous" was approved.

In light of the anticipated approval of the ICH Q3D guideline for elemental impurities, PDG members agreed to harmonize their general chapters on methods related to elemental impurities, with the United States Pharmacopeia serving as the coordinating pharmacopoeia. PDG members also agreed to add a general chapter on dynamic light scattering to its work programme, with the Japanese Pharmacopoeia as the coordinating pharmacopoeia.

The next PDG meeting, hosted by the European Pharmacopoeia in Strasbourg, was to be held in France from 12 to 13 November 2014.

The Expert Committee took note of the report.

WHO Member State mechanism on substandard/spurious/falsely-labelled/falsified/counterfeit (SSFFC) medical products

World Health Assembly resolution 65.19 established the WHO Member State mechanism on SSFFC medical products. Owing to the lack of funding there had been little opportunity to develop all aspects of the activities laid out in the workplan. Nevertheless the element of the workplan on collaboration on surveillance and monitoring had been successful. Two working groups had been established – one on recommendations to deal with SSFFC medical products and the other on determining what issues are outside the purview of the Member State mechanism. The Steering Committee of the mechanism met on 24 September 2014, and the third meeting of the mechanism was due to take place on 29–31 October 2014 to review the outcomes from the working groups. It was stressed that the mechanism is led by WHO Member States.

The Expert Committee noted the progress of the mechanism.

2.2 Cross-cutting pharmaceutical quality assurance issues

WHO Expert Committee on Biological Standardization

The WHO Expert Committee on Biological Standardization met in Geneva concurrently with the meeting of the Expert Committee on Specifications for Pharmaceutical Preparations. Attention was drawn to a major cross-cutting issue that concerns both of these expert committees: the need to respond to public health emergencies. The Ebola outbreak in West Africa had exemplified this need.

In August 2014, after declaring the Ebola outbreak a public health emergency, WHO released its Ebola response roadmap and created a number of cross-cutting teams of people with different knowledge, expertise and experience. The Emergency Committee that was convened issued temporary recommendations to reduce the risk of international spread. WHO was aware that some products were in the early stages of development. A meeting of ethicists was convened at which it was unanimously agreed that it was right to use these medicines in this situation. On 4 and 5 September 2014 a meeting on potential Ebola vaccines and therapies recommended that the use of whole-blood therapies and convalescent plasma be considered as a priority, together with safety studies of two candidate vaccines and the use of novel therapeutic products. Safety and efficacy data were needed but, if the current candidate vaccines were found to be safe, there was hope that an Ebola vaccine could be available by January 2015.

For the first time ever, the United Nations had established a mission for a public health emergency. The United Nations Mission for Ebola Emergency Response (UNMEER) is based in Accra, Ghana. In parallel with UNMEER, WHO had made the development, testing, licensing and use of new medicines a priority. Various experimental therapies were being worked on and WHO was working with regulators to have them studied in order to generate data. It was noted that regulators at the recent ICDRA meeting had emphasized the need for countries to have emergency regulatory pathways in place, to ensure rapid and proactive collaboration between regulators, and to drive innovative clinical trial design for situations where the use of traditional clinical trial designs might not be feasible. ICDRA's recommendations to WHO were:

- rapidly to provide scientific information on potential therapies and vaccines;
- to establish and lead a network of regulators; and
- to drive innovative clinical trial design for use in situations such as the Ebola emergency where traditional clinical trial designs may not be feasible.

Hence there was a clear need for guidance for regulators in emergency situations.

The attention of members of the Expert Committee was drawn to two WHO Internet links on Ebola: http://www.who.int/mediacentre/news/

ebola/01-october-2014/en/ (news and updates); and http://apps.who.int/iris/bitstream/10665/135591/1/WHO_HIS_SDS_2014.8_eng.pdf?ua=1 (WHO interim guidelines on use of convalescent whole blood and convalescent plasma).

Other cross-cutting issues between the two expert committees included the strengthening of national regulatory systems, assistance on capacity building for national blood safety systems, a global monitoring system for medicines shortages, transparency for clinical trial reviews, stronger platforms for capacity-building efforts, joint reviews of multicountry clinical trial approvals and guidelines on regulatory pathways for products to be used in public health emergencies.

Traditional and complementary medicine

Members of the Expert Committee were informed that WHO had already produced 11 major technical documents on herbal medicines under the guidance of the Expert Committee and that progress was being made in the development of several new guidelines in this area. These include guidelines on the conservation of medicinal plants, the selection of substances of herbal origin for QC of herbal medicines, good processing practices for herbal medicines, the safety management of toxic medicinal plants and a monograph on such plants.

The International Regulatory Cooperation on Herbal Medicines, established in 2006, currently has 30 members incorporating three regional bodies, including the European Union and the Association of Southeast Asian Nations. It is estimated that more than 120 WHO Member States now have regulation of herbal medicines in place and more than 70 WHO Member States monitor the safety of herbal medicines in pharmacovigilance systems. The second WHO global survey on traditional medicine had been conducted to assess the impact of earlier WHO strategies on traditional medicine. On this basis WHO had developed the new WHO traditional medicine strategy for the period 2014 to 2023 (launched in October 2013), and the Sixty-seventh World Health Assembly (May 2014) had adopted a resolution on traditional medicine, relating to its implementation. The three strategic objectives of the WHO traditional medicine strategy: 2014–2023 are: building the knowledge base for active management through appropriate national policies; strengthening quality assurance, safety and effectiveness by regulating products, practice and practitioners; and promoting universal health coverage by integrating services and self-health-care into national health systems.

The Expert Committee noted the report.

End of the open session and beginning of the private session

In accordance with WHO requirements, the declarations of interests of Expert Committee members and temporary advisers were presented to the meeting.

3. Quality control – specifications and tests

3.1 *The International Pharmacopoeia*

3.1.1 Workplan for *The International Pharmacopoeia*

Priorities for new monographs

The International Pharmacopoeia primarily specifies the quality of essential medicines that are listed on the WHO Model List of Essential Medicines (EML), in the invitations to manufacturers to submit an expression of interest (EOI) to the PQT – Medicines, or in other United Nations documents recommending the use of medicines for the treatment of specific diseases and/or for use by treatment programmes. The fourth edition of *The International Pharmacopoeia* had been published in October 2014 on CD-ROM and included the main volumes plus the First, Second, Third and Fourth Supplements.

To set priorities for future monographs, medicines had been selected for which public standards were not yet available, with the highest priority being assigned to medicines in the following groups:

- medicines for maternal, newborn, child and adolescent health;
- antimalarial medicines;
- antiviral medicines including antiretrovirals;
- antituberculosis medicines, specifically for the treatment of drug-resistant tuberculosis;
- medicines for neglected tropical diseases;
- medicines considered as life-saving commodities for women and children.

The Expert Committee received a list of 23 such monographs proposed for elaboration and eventual adoption by the Committee and subsequent publication in *The International Pharmacopoeia* (Table 1).

Table 1
Monographs proposed for elaboration and eventual inclusion in *The International Pharmacopoeia*

abacavir, efavirenz and lamivudine tablets
abacavir, lamivudine and nevirapine dispersible tablets
artemether and lumefantrine dispersible tablets
artesunate and amodiaquine tablets
artesunate and pyronaridine tablets
artesunate rectal capsules

Table 1 *continued*

atazanavir and ritonavir tablets
dolutegravir tablets
estradiol valerate and norethisterone enantate injection
etravirine tablets
ferrous fumarate tablets (co-blistered with ethinylestradiol and levonorgestrel)
lamivudine and tenofovir tablets
linezolid oral suspension
moxifloxacin tablets
norethisterone enantate injection
norethisterone tablets
p-aminosalicylic acid granules for oral solution
proteinamide tablets
pyrazinamide dispersible tablets
raltegravir tablets
terizidone capsules
terizidone tablets
zanamivir powder for inhalation

The Expert Committee expressed its appreciation for the work in identifying the highest priority medicines, but it was concerned that WHO could not include monographs on all medicines on the EML because of limited resources. It was noted that WHO was working on memoranda of understanding with national and regional pharmacopoeias to exchange information and to share monographs to help improve the situation in a way that would benefit both partners.

The Expert Committee endorsed the workplan as presented.

3.2 Specifications for medicines, including paediatric medicines and radiopharmaceuticals

3.2.1 Maternal, newborn, child and adolescent health medicines

Dexamethasone sodium phosphate

It was proposed to revise the monograph on dexamethasone sodium phosphate in *The International Pharmacopoeia*. The monograph was developed at the request of the United Nations (UN) Commission on Life-saving Commodities for Women and Children. A first draft was discussed at the consultation on specifications for medicines and quality control laboratory (QCL) issues in April 2014, following which a revised draft was circulated for comments. Following

further revision to take these comments into account, a copy of the current monograph with the proposed amendments indicated in the text was presented to Expert Committee members for consideration.

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

Dexamethasone phosphate injection

In view of the revision of the monograph on dexamethasone sodium phosphate, a revision of the monograph on dexamethasone phosphate injection had been prepared, at the request of the UN Commission on Life-saving Commodities for Women and Children. The first draft was discussed at the consultation in April 2014, following which a revised draft was sent out for comments. Following further revision to take these comments into account, a copy of the current monograph with proposed amendments indicated in the text was presented to Expert Committee members for consideration.

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

Levonorgestrel tablets

The monograph on levonorgestrel tablets was adopted at the meeting of the Expert Committee in 2011 and subsequently published on the website of *The International Pharmacopoeia*. The monograph contained a test for limiting the enantiomer dextronorgestrel. Subsequently, the monograph on levonorgestrel and ethinylestradiol tablets was developed and was adopted by the Expert Committee at its meeting in 2012. This monograph was adopted without the proposed test for dextronorgestrel as the Committee decided that the test for the enantiomer should be included in the Levonorgestrel API monograph.

While compiling the monographs for publication in the Fourth Supplement of *The International Pharmacopoeia* the Secretariat contacted selected experts to further discuss the test for dextronorgestrel in the monograph on levonorgestrel tablets. The experts recommended deletion of the test for the enantiomer from this monograph too. Consequently the monograph on levonorgestrel tablets was published in the Fourth Supplement without the test for the enantiomer.

As the monograph on levonorgestrel API was currently under revision, the Expert Committee was informed that it was intended to include the test for dextronorgestrel in the new draft proposal.

The Expert Committee noted the report.

Misoprostol, misoprostol 4% dispersion and misoprostol tablets

Draft monographs on misoprostol, misoprostol 4% dispersion and misoprostol tablets were reviewed by the Expert Committee. The drafts were completed

shortly before the meeting of the Expert Committee and had not yet been circulated for comment.

The Expert Committee noted the development of the monographs and suggested that, if possible, the dispersion monograph should cover different available misoprostol concentrations.

3.2.2 Antiviral medicines, including antiretrovirals

Atazanavir sulfate

Draft monographs on atazanavir sulfate and atazanavir capsules were submitted by a WHO collaborating laboratory in October 2013 and were circulated for comments before being discussed at the informal consultation in April 2014. Following the consultation, revised drafts of the two monographs were circulated and comments were collated before the submission of the monographs to the Expert Committee.

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

3.2.3 Antituberculosis medicines

Kanamycin for injection

In June 2014 a request was received from a user of *The International Pharmacopoeia* for a revision of the monograph on kanamycin for injection. It was proposed to align the sample concentration used in the identity tests B, C and D to those prescribed in the respective tests in the monographs on kanamycin monosulfate and kanamycin acid sulfate. The API monographs state that kanamycin monosulfate contains not less than 750 IU per mg (with reference to the dried substance) and kanamycin acid sulfate not less than 670 IU per mg (with reference to the dried substance). Members of the Expert Committee received the text of the current monograph with proposed corrections indicated in the text.

The Expert Committee adopted the monograph with the corrections agreed and requested that the monograph should be considered for further revision.

3.2.4 Medicines for tropical diseases

Albendazole chewable tablets

The draft proposal for a monograph on albendazole chewable tablets was discussed by the Expert Committee in 2011, after which it was further reviewed before being submitted to the Committee at its meeting in 2012. In April 2012 a second revision of the monograph was undertaken and was discussed by an informal consultation on new medicines, QC and laboratory standards before being circulated for further review. In 2013 the Expert Committee discussed

the monograph further and requested the inclusion of a dissolution test and an acceptance criterion.

The revision of the monograph on albendazole chewable tablets was discussed at the consultation in April 2014 and a first draft was received and sent out for comments in June 2014. The draft was duly revised taking into account the comments received and was submitted to the Expert Committee for discussion.

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

Levamisole hydrochloride

The first draft of the proposed monograph on levamisole hydrochloride was discussed at the consultation in April 2014, subsequent to which a draft was sent out for comments. Comments received were collated and the draft was submitted to the Expert Committee for consideration.

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

Pyrantel embonate

Following its receipt in early 2014, the first draft of the proposed revision of the monograph on pyrantel embonate was discussed at the consultation in April 2014. Following the consultation the draft was circulated for comments. Comments received were collated and the draft was submitted to the Expert Committee for consideration.

The Expert Committee adopted the monograph subject to the amendments agreed. Members noted that the pyrantel embonate monograph in *The European Pharmacopoeia* was being revised and proposed that the Secretariat ascertain whether a further revision of the WHO monograph would be necessary.

Pyrantel chewable tablets

It had been proposed to revise the monograph on pyrantel chewable tablets with a view to including a dissolution test. A draft of the proposed text was received in early 2014 and was discussed at the consultation in April 2014. The draft was subsequently circulated for comments. Comments received were collated and the draft was submitted to the Expert Committee for consideration, with amendments to the current monograph indicated in the text.

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

Pyrantel tablets

Following its receipt in early 2014, the first draft of the proposed revision of the monograph on pyrantel tablets was discussed at the consultation in April 2014.

Following the consultation the draft was circulated for comments. Comments received were collated and the draft was submitted to the Expert Committee for consideration.

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

3.2.5 Other anti-infective medicines

Fluconazole, fluconazole capsules and fluconazole for injection

In 2012 the Expert Committee reviewed the drafts of monographs on fluconazole, fluconazole capsules and fluconazole for injection, commenting on progress in developing the monographs and proposing further amendments. Following consideration by the informal consultation to discuss new medicines, QC and laboratory standards in June 2013, the revised drafts were circulated for comments. At its meeting in October 2013 the Expert Committee had adopted the monograph on fluconazole API subject to the amendments agreed, but had requested further revision of the monographs on fluconazole capsules and fluconazole injection. Comments on these two monographs were consolidated after the 2013 meeting and the monographs were discussed at the consultation on specifications for medicines and QCL issues in April 2014. The monographs underwent their second revision and were circulated for comments in May 2014. The draft monographs and the collated comments were submitted to the Expert Committee in October 2014 for discussion.

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

3.2.6 Medicines for anaesthesia, pain and palliative care

Dextromethorphan hydrobromide

Following consumption of dextromethorphan cough syrups contaminated with levomethorphan some 50 people had died in Pakistan in January 2013. A further incident of suspected intoxication involving 11 patients was reported in September 2013 in Paraguay. Investigations revealed that the medicines administered were manufactured using dextromethorphan hydrobromide which was contaminated with levomethorphan at levels of 9.5–22.6%. Following these incidents WHO issued Drug Alerts (Nos 126 and 129) and urged all Member States to ensure the quality of dextromethorphan/dextromethorphan hydrobromide API.

As a result of these events it was proposed to revise the monograph on dextromethorphan hydrobromide in *The International Pharmacopoeia* with a view to adding a statement under the section "Manufacture" requiring the production method to be validated to demonstrate that the substance, if

tested, would comply with a limit of not more than 0.1% for levomethorphan hydrobromide – a limit considered appropriate following a toxicological assessment. A chiral method, selective for levomethorphan, is currently being developed and should be included in the monograph at a later stage.

The draft monograph was circulated for comments in May 2014 and comments received were collated.

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

Levomethorphan limit tests for dextromethorphan containing finished products

Additional limit tests for levomethorphan in dextromethorphan dosage forms are to be set up to enable independent QCLs to establish whether or not APIs of pharmacopoeial quality have been used to manufacture dextromethorphan medicines. The resulting procedures are to be published in the "Supplementary information" section of *The International Pharmacopoeia*.

Expert Committee members received a laboratory report describing the elaboration of procedures to test for levomethorphan in dextromethorphan API and in finished products containing dextromethorphan.

The Expert Committee noted the progress made.

3.2.7 Radiopharmaceuticals

At the meeting of the Expert Committee in October 2013 the International Atomic Energy Agency (IAEA) provided members with an update on the development of radiopharmaceutical monographs. Consultants' meetings were organized by IAEA in December 2012 and May 2013 to discuss the update of the monographs of *The International Pharmacopoeia*. There was agreement that the radiopharmaceutical monographs should be updated as soon as possible, especially in view of new developments in radiopharmaceuticals and new documentation on them. It was also agreed that efforts should be made to ensure convergence of the radiopharmaceutical texts in different pharmacopoeias.

Draft monograph texts were circulated by WHO for comments as part of the updating process and a radiopharmaceutical pharmacopoeia update meeting was hosted in February 2014 by IAEA in collaboration with *The International Pharmacopoeia* and other pharmacopoeias. The participants at the meeting reviewed the comments received and adjusted the workplan in line with the progress made. Some 20 updated draft radiopharmaceutical monographs were discussed and were subsequently circulated to IAEA experts and other parties for comments. These comments are currently being evaluated by the IAEA experts.

The Expert Committee noted the report.

3.3 General monographs for dosage forms and associated method texts

3.3.1 General monographs

Rectal preparations

At its forty-second meeting in October 2007 the Expert Committee endorsed a review of general monographs. In the case of rectal preparations it was proposed to replace the current general monograph on suppositories with a general monograph that would include solid, liquid and semi-solid dosage forms intended for rectal application – including suppositories, rectal capsules, rectal solutions, emulsions and suspensions, powders and tablets for rectal solutions and suspensions and semi-solid rectal preparations. The draft monograph was circulated for comments in February 2014 and, following collation of the comments, was discussed at the informal consultation in April 2014.

The Expert Committee adopted the proposed monograph on rectal preparations.

Implementation of the revised general monograph on parenteral preparations in *The International Pharmacopoeia*: limits for the test for bacterial endotoxins

A revision of the general monograph on parenteral preparations was adopted by the Expert Committee at its meeting in October 2012. A major change to the monograph on parenteral preparations was the requirement for compliance of all such preparations with the test for bacterial endotoxins (or, where justified, pyrogens). In consequence, individual monographs on injectable dosage forms in *The International Pharmacopoeia* were investigated and proposals were made on limits of the bacterial endotoxins for those monographs on parenterals that currently do not have such a limit.

Endotoxin limits were proposed for the following monographs for inclusion in *The International Pharmacopoeia* (Table 2).

Table 2
Endotoxin limits to be used in *The International Pharmacopoeia* (Ph.Int.)

• artemether injection
• artemotil injection
• ephedrine sulfate injection
• ergometrine hydrogen maleate injection
• melarsoprol injection

Table 2 *continued*

• magnesium sulfate injection
• oxytocin injection
• pentamidine isetionate powder for injections[a]
• prednisolone sodium phosphate injection[b]
• quinine dihydrochloride injection
• zidovudine intravenous infusion

[a] Title of the monograph to be changed to: Pentamidine isetionate for injection.
[b] Title of the monograph to be changed to: Prednisolone phosphate injection.

The proposal was presented at the informal consultation to discuss new medicines, QC and laboratory standards in June 2013, subsequently revised and circulated for comments, then discussed by the Expert Committee in October 2013 and revised once more. Following a further round of comments in early 2014 the proposal was discussed at the informal consultation in April 2014.

The Expert Committee adopted the document as proposed.

3.3.2 General policy

Withdrawal of monographs

The Expert Committee discussed whether monographs that had been replaced should still be maintained in a "suppressed monographs" area within the "Supplementary information" section of *The International Pharmacopoeia*. The Secretariat proposed a text for indicating that monographs had been suppressed and would no longer be updated or revised and that International Chemical Reference Substances (ICRS) would no longer be monitored for the purposes mentioned in the monographs. Different pharmacopoeias appeared to have differing policies on monographs that were no longer used or had been replaced.

The Expert Committee agreed that suppressed monographs should continue to be accessible to users via the WHO website, but that they should be in a distinct section or archived so that they could not be mistaken for current monographs. The use of the proposed text would be appropriate for this purpose. However, only current monographs should be included on the CD-ROM. The Secretariat was requested to investigate options for archiving, including a time period(s), and policies for archiving and/or making available information on suppressed and revised monographs. The Secretariat was also asked to discuss the viability of this process with the technical staff and to report back to the Committee.

3.3.3 Analytical methods

Disintegration test for suppositories and rectal capsules

At its meeting in October 2012 the Expert Committee adopted a general method for determining the softening time of lipophilic suppositories for inclusion in the "Supplementary information" section of *The International Pharmacopoeia*. It was therefore proposed to revise chapter 5.4 "Disintegration test for suppositories" and to replace the current Method 2 with the method for determination of the softening time of lipophilic suppositories.

The draft monograph was received from a WHO expert in February 2014 and was subsequently circulated for comments before being discussed at the informal consultation in April 2014.

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

Disintegration test for tablets and capsules

It was proposed to include a disintegration test for large tablets in the test for disintegration of tablets and capsules. The draft monograph was received from a WHO expert in February 2014 and was subsequently circulated for comments before being discussed at the informal consultation in April 2014. The proposed method was reproduced with the permission of the *European Pharmacopoeia*, with amendments from the current monograph indicated in the text.

The Expert Committee adopted the monograph.

3.4 Update on the process for development of monographs

3.4.1 General

Revised procedure for the development of monographs and other texts for *The International Pharmacopoeia*

Monographs in *The International Pharmacopoeia* provide the quality dimension for the medicines (included on the basis of their efficacy and safety) in the EML and in WHO treatment guidelines. In the procedure it is foreseen that newly-approved monographs will be uploaded to the WHO website following their approval at each meeting of the Expert Committee. Users had reported that having monographs in different places was cumbersome. The Secretariat therefore proposed that, after each meeting of the Expert Committee, work would begin on producing a new electronic edition of *The International Pharmacopoeia* (on CD-ROM and online), which would make separate website publishing redundant. A document reflecting this new approach was considered by the Committee. Members of the Committee welcomed the intention to update the electronic version of *The International Pharmacopoeia* more frequently and expressed the wish that this update should be produced as soon as possible after the meeting.

The Expert Committee adopted the proposal to produce an annual update of *The International Pharmacopoeia* as soon as possible after each Expert Committee meeting and to discontinue the prepublication of the monographs on the website. The updated proposal is described in Annex 1 of the report.

3.4.2 Radiopharmaceuticals

Revised updating mechanism for the section on radiopharmaceuticals in *The International Pharmacopoeia*

In line with the proposal to revise the procedure for the development of monographs and other texts for *The International Pharmacopoeia*, similar amendments were proposed for the updating mechanism for the section on radiopharmaceuticals in *The International Pharmacopoeia*, which was published as Annex 1 of the forty-eighth report of the WHO Expert Committee.

The Expert Committee adopted the proposal. The updated proposal is contained in Annex 2 of this report.

4. Quality control – international reference materials (International Chemical Reference Substances and Infrared Reference Spectra)

4.1 Update on International Chemical Reference Substances

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

4.1.1 Report of the custodian centre

The Expert Committee received the annual report of the custodian centre, the European Directorate for the Quality of Medicines & HealthCare (EDQM), for 2013. The centre explained the workflow process for the establishment, storage, distribution and monitoring of ICRS for *The International Pharmacopoeia*. EDQM reported that 15 new ICRS were established in 2013.

The Committee discussed the proposal to avoid, where appropriate, using the physical standard (ICRS) and to replace it by using the ultraviolet (UV) absorptivity for assay. In addition, the Committee discussed this approach for other quantification purposes. There is also occasional inconsistency between the names of ICRS in *The International Pharmacopoeia* and the corresponding ICRS labelling, which is being brought into line. The custodian centre reported that two research projects on monitoring had been completed.

The Expert Committee thanked EDQM for the report, which was noted, and accepted the proposal to use the UV absorptivity for assay where appropriate. In addition, the Committee supported the adoption of this approach for other quantification purposes where appropriate.

4.1.2 Report of the dedicated subgroup

Twelve ICRS had been characterized by the custodian centre since the last meeting of the Expert Committee. The ICRS subgroup had extensively reviewed the related analytical reports and adopted the ICRS; the 12 ICRS were submitted to the Expert Committee for final endorsement.

The Expert Committee adopted the 12 ICRS and expressed its thanks to both EDQM and the members of the dedicated subgroup.

5. Quality control – national laboratories

5.1 External Quality Assurance Assessment Scheme

The External Quality Assurance Assessment Scheme (EQAAS) is a programme for the external evaluation of QC management systems in chemical control laboratories. Using interlaboratory comparisons, the programme determines the performance of participating laboratories in carrying out specific tests or measurements. The scheme supplements laboratories' internal quality assurance procedures by providing an external measure for their testing capabilities.

5.1.1 Summary report on External Quality Assurance Assessment Scheme Phase 5

The Expert Committee received a summary report from the Secretariat on EQAAS Phase 5 from January 2010 to December 2013. Laboratories in all six WHO regions had participated in the seven studies, although the number of laboratories participating varied from region to region. The seven studies were:

(i) assay by titration with a testing sample of metronidazole API;
(ii) water semi-micro determination with a testing sample of amodiaquine hydrochloride API;
(iii) dissolution test with a testing sample of artemether and lumefantrine tablets;
(iv) pH and weight per mL with a testing sample of abacavir oral solution;
(v) assay by liquid chromatography with a testing sample of artesunate and amodiaquine tablets;
(vi) dissolution test with a testing sample of rifampicin capsules;
(vii) assay by titration with a testing sample of chloroquine sulfate oral solution.

The results of the studies were varied and the Secretariat noted that there was still room for improvement regarding the performance of the laboratories, particularly for the dissolution test. Although the results between different phases were not strictly comparable because the participants were not always the same, the overall performance for the determination of the water content had improved in Phase 5 compared to previous phases. There was similar improvement regarding application of the liquid chromatography technique, where the percentage of satisfactory results had increased between Phase 3 and Phase 5. The Secretariat suggested that laboratory performance could be further improved with a continued programme of proficiency testing.

It was announced that WHO's letter to laboratories announcing the start of Phase 6 of EQAAS had been prepared and would be dispatched in the near future. A new fee system would be applicable for the future series. The Secretariat had been working to secure funding from donors to support national QCLs that may face challenges in paying the fee. It was recommended that national QCLs include financial support in the future to continue the EQAAS series with WHO in donor project submissions, e.g. with the Global Fund.

The Expert Committee noted the report from the Secretariat, including these new developments.

5.2 Training materials for quality control laboratories and microbiological laboratories

The Secretariat reported that five QC training modules had been made available on the CD-ROM entitled *Quality assurance of pharmaceuticals 2014* and on the website. The three new modules on QCLs cover: management and infrastructure; materials, equipment, instruments and other devices; and working procedures and safety; while two modules focus on good practices for pharmaceutical microbiology laboratories.

The Expert Committee welcomed this development and noted the report.

5.3 Report on implementation of WHO good practices for pharmaceutical control laboratories

The Secretariat provided an oral update on the implementation of *WHO good practices for pharmaceutical control laboratories*, in its report on a meeting with inspectors and experts providing technical assistance in the area of QC. The conclusion was that there was no need to revise the current good practices, but rather to complement them with questions and answers and training. The only topic that needed clarification in the form of guidelines was data integrity and this had already been identified as a possible topic for new GXP guidance by inspectors.

The Expert Committee noted the report.

6. Quality assurance – good manufacturing practices

6.1 Update of WHO good manufacturing practices for biologicals

A consultation on GMP for biological products was held in July 2014 with national regulatory authorities (NRAs), industry and GMP experts who reviewed the first draft of the new document on GMP for biological products. A second draft was in preparation and would be circulated and made available on the WHO website for public consultation by the end of 2014 and again in July 2015. If adopted by the Expert Committee on Biological Standardization in October 2015, the GMP for biologicals document would then be published and a number of companion documents would be required.

The Expert Committee noted the report.

6.2 Update of WHO good manufacturing practices: validation

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

The need for revision of the published guidelines on validation of GMP had been identified by PQT and a draft document was circulated for comment in early 2013. The focus of revision related to Appendix 7 (non-sterile process validation) of the Supplementary guidelines on good manufacturing practices: validation. In addition, comments were sought as to whether Appendix 3 (cleaning validation) should be revised in line with developments on setting health-based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities. At its meeting in October 2013 the Expert Committee had requested the Secretariat to process the comments and circulate the document accordingly. Consequently the revised working document was recirculated in March 2014 and feedback was discussed during an informal consultation on medicines quality: GXPs, inspection guides and risk management in April 2014. The document was circulated once more and comments collated and evaluated, before being submitted to the Expert Committee.

It was noted that the guidelines allowed for different approaches to process validation. The principles described are mainly applicable to non-sterile finished pharmaceutical dosage forms but it was felt that similar approaches might be applicable to APIs and sterile products. Thorough knowledge of product and process development studies, previous manufacturing experience and quality risk management principles would be essential in process validation since it focused on the life-cycle approach which links product and process development, and validation of the commercial manufacturing process, maintaining a state of control during routine commercial production. The guidelines recommend a risk-based approach to validation, as well as the use of in-line, online and/or

at-line controls and monitoring to ensure that a process is in a state of control during manufacture.

The Expert Committee reviewed the proposed changes and comments and adopted the revised text (Annex 3).

6.3 General guidance for inspectors on hold-time studies

In order to ensure the quality and stability of starting materials, intermediate products, bulk and finished products at all stages of manufacture, GMP procedures require that there should be a maximum allowable "hold time" so that in-process and bulk product can be held, pending the next processing step, without adverse effects on the quality of the material. As a result, a guidance document aimed at inspectors of hold-time studies was drafted at the end of 2012, circulated for comments in early 2013 and was reviewed by inspectors and PQT. Further review by expert inspectors led to a revised draft of the document being circulated and further feedback being received before submission to the Expert Committee in October 2013. Comments were subsequently reviewed by a subgroup of the Expert Committee and by the PQT – Inspections. Further review in early 2014 led to the document being discussed during an informal consultation on medicines quality: GXPs, inspection guides and risk management in April 2014. Another round of public review and comment was completed before the third revision of the document was submitted to the Expert Committee in 2014.

These guidelines focus primarily on issues that should be considered in the design of the hold-time studies during the manufacture of solid dosage forms. Many of the principles also apply to other dosage forms such as liquids, creams and ointments. The guidelines do not cover aspects of hold times in cleaning validation or the manufacture of APIs. It was noted that hold times should normally be determined prior to marketing of a product and following any significant changes in processes, equipment, starting and packaging materials. The Expert Committee reviewed the document and the comments received, proposing alternative text where appropriate.

The Expert Committee endorsed the guidance subject to the amendments proposed (Annex 4).

6.4 Update of model inspection report

An informal consultation on inspection, GMP and risk management guidance in medicine manufacturing was held in Geneva from 28 to 30 April 2014 with national inspectors and specialists, as well as staff of the PQT – Inspections. The participants at the meeting suggested updating the *Guidance on GMP: inspection report* (WHO Technical Report Series, No. 908, Annex 6), and the *Model certificate of GMP* (WHO Technical Report Series, No. 908, Annex 5). It was proposed to update the models taking into account the ones currently

used by the PQT – Inspections and the revision of the guidance related to the inspection report.

An outline of an update of the model inspection report prepared by PQT was submitted to the members of the Expert Committee who discussed the draft received and provided a number of comments.

The Expert Committee endorsed the proposals of the informal consultation, namely to update the current model formats taking into account the ones currently used by the PQT – Inspections, and to revise the guidance related to the inspection report.

6.5 Update of questions and answers for WHO good manufacturing practices for active pharmaceutical ingredients

Since the ICH Q7 guidance had been finalized, experience with implementing the guidance worldwide had led to requests for clarification of uncertainties related to the interpretation of certain sections. The questions and answers (Q&A) developed by the ICH Q7 Implementation Working Group are intended to respond to those requests. In WHO's GMP texts the answers to some of the questions were already addressed in an annex.

The ICH Q7 Implementation Working Group, Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients, met in November 2013 and May–June 2014 to continue the work on developing, reviewing and discussing the Q&As. Between these Working Group meetings, numerous regional meetings and telephone conferences took place. WHO contributed as an observer to the ICH Implementation Working Group, provided input gathered during the informal consultation of inspectors in April 2014 and contributed through the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S). When the Q&As have been finalized by the Implementation Working Group, the WHO Secretariat proposes that they be circulated to WHO experts and stakeholders to ask if these Q&As could serve as a replacement for Appendix 2 of *General notes: additional clarifications and explanations* published together with the *WHO good manufacturing practices for active pharmaceutical ingredients (bulk drug substances)* (i.e. WHO Technical Report Series, No. 957, 2010, Annex 2).

The Expert Committee endorsed the proposal.

6.6 Proposal for new guidance on good data management

The Expert Committee received feedback from an informal consultation on medicines quality: GXPs, inspection guides and risk management held in Geneva in April 2014. The participants included national inspectors and specialists in the various agenda topics, as well as staff of the PQT – Inspections.

The consultation recommended that a new guidance document should be prepared focusing on good data management.

The number of observations made regarding data management practices has been increasing. The quality of a study supporting a regulatory application cannot be assured unless data are true and fair. The regulatory system requires acceptable integrity of the data being considered. Failures in data integrity management can arise both because of poor systematic control of the systems for data management, owing to a lack of knowledge and human error, because data have been intentionally hidden or falsified, or selective data have been used to mislead. Many of the observations in routine inspections result from failures by organizations to apply robust systems that inhibit integrity failures, improve the detection of situations where integrity has been compromised, or to thoroughly investigate the root cause of the failures that are detected.

The Expert Committee discussed a concept paper received from the PQT – Inspections for the proposed structure of a new guidance document consolidating existing normative principles and in some cases giving illustrative examples on their implementation. The Committee endorsed the proposal.

6.7 Training materials

The Expert Committee noted that 41 GMP-related training modules were newly available on the CD-ROM entitled *Quality assurance of pharmaceuticals 2014*. The CD-ROM included 15 modules on basic GMP, seven on validation, five on the inspection process, four each on heating, ventilation and air conditioning (HVAC), and water, and three each on APIs and sterile products. A training video was also included.

The Expert Committee expressed its appreciation for the development of these training materials.

7. Quality assurance – new initiatives

7.1 International meetings of world pharmacopoeias

The third international meeting of world pharmacopoeias was held in London, England, from 10 to 11 April 2014. It was co-hosted by the Medicines and Healthcare products Regulatory Agency (MHRA), the British Pharmacopoeia Commission and WHO. During this meeting the third draft of the document on good pharmacopoeial practices (GPhP) was discussed in detail, with a review of more than 300 comments received from the world pharmacopoeias. The participants also discussed comments received during the public consultation on the concept paper phase. In view of the length of the GPhP text, it was decided to create a technical annex containing the technical details. A new drafting group (consisting of the Brazilian Pharmacopoeia, European Pharmacopoeia, Indian Pharmacopoeia, Japanese Pharmacopoeia, United States Pharmacopeia and the WHO Secretariat facilitating the process and representing *The International Pharmacopoeia*) was formed to further develop the technical annex.

Following the third meeting of world pharmacopoeias the GPhP text was reworked into a fourth draft which was circulated by the WHO Secretariat to all pharmacopoeias for comments. A preliminary version of the technical annex was drafted on the basis of parts of the previous GPhP text. The draft annex was reworked by the Japanese Pharmacopoeia, reviewed by the drafting group and further revised by the European Pharmacopoeia following the drafting group's suggestion to move more technical material into the annex, thus further consolidating the main text. This fourth draft was then circulated for comments.

The fourth international meeting of world pharmacopoeias was held in Strasbourg, France, from 8 to 10 October 2014. It was co-hosted by EDQM/the European Pharmacopoeia and WHO. The fourth draft of the document, which was discussed at this meeting, was close to finalization, with subgroups working further on two new sections. It was anticipated that the document would be circulated for public comments by the end of 2014.

It was noted that two further meetings were planned. The fifth international meeting of world pharmacopoeias was planned to be co-hosted by the United States Pharmacopeia in Rockville, MD, USA from 20 to 21 April 2015 and the sixth meeting was planned to be co-hosted by the Chinese Pharmacopoeia at a location in China in the second half of 2015.

The Expert Committee noted the report.

7.2 Good pharmacopoeial practices

The Expert Committee received a concept paper on the purpose and benefits of GPhP. The chief objective of the GPhP guidance was to harmonize approaches and policies on setting pharmacopoeial standards in order to support regulatory

authorities in controlling the quality of pharmaceutical ingredients, finished products and other materials, and to provide a tool that would enable the user or procurer to make an independent judgement on quality in order to safeguard the health of the public. The document describes a set of principles that provide guidance for national and regional pharmacopoeial authorities and facilitate the appropriate design, development, maintenance, publishing and distribution of pharmacopoeial standards.

The benefits of GPhP include facilitating collaboration among pharmacopoeias, leading to possibilities for work-sharing, prospective harmonization of standards and the acceptance of published standards between national and regional pharmacopoeial authorities, increasing access to and availability of quality medicines.

In addition, it is hoped that the establishment of GPhP may lead to the strengthening of global pharmacopoeial cooperation; providing stakeholders with a better understanding of how pharmacopoeial standards are developed and maintained; and improving cooperation between national and regional pharmacopoeia authorities and stakeholders, such as regulators and industry, in order to facilitate the global harmonization of standards and reduce duplication of work.

The Expert Committee was informed that the GPhP drafted over the past two years by the world pharmacopoeias would be circulated widely for public consultation by the end of 2014.

The Expert Committee noted the report.

7.3 Screening technologies for "suspect" spurious/ falsely-labelled/falsified/counterfeit medicines

In October 2013, members of the Committee expressed support for the development of a guidance document on rapid screening technologies that would provide an overview of the issues relating to "suspect" spurious/falsely-labelled/ falsified/counterfeit medicines (SFFC) and describe the different techniques available for use and their implementation. Rapid screening technologies were defined as the qualitative and/or quantitative technologies that could provide the preliminary data to spot suspicious samples in the field.

In October 2014, the Expert Committee received the draft of such a guidance document from the WHO Collaborating Centre in Beijing, People's Republic of China. The draft included: an introduction to the current situation of SFFC medical products and a brief history of rapid screening technologies; a list of currently available technologies outlining the advantages and disadvantages of each; and a section on the application and implementation of each screening technology in the future. It was noted that the screening technologies mentioned in these guidelines could be used either in the field or

in laboratories. The results of screening tests are preliminary ones but they can be used to identify suspicious medicines, triggering follow-up, such as further analysis for laboratory confirmation.

The Expert Committee agreed that the revised draft should be circulated for comments.

7.4 Laboratory functions survey regarding testing of spurious/falsely-labelled/falsified/counterfeit medical products[1]

At its forty-eighth meeting in October 2013, the Expert Committee noted the need for standard operating procedures (SOPs) for the testing of SFFC medical products and requested the Secretariat to prepare a draft of such SOPs. The WHO Collaborating Centre for the Quality Assurance of Medicines at North-West University, Potchefstroom, South Africa, had conducted a survey to assess the current practices used by pharmaceutical QCLs to evaluate SFFC products and an article had been prepared for publication in *WHO Drug Information* on the basis of the full report. Expert Committee members received copies of the article, as well as a draft outline for a possible guidance document for the testing of SFFCs by QCLs.

The outline proposed several sections, including but not limited to:

(i) introduction
(ii) scope
(iii) sources of samples to be analysed
(iv) sampling and documentation
(v) risk assessment and preliminary investigation
(vi) testing plan, specifications and test procedures
(vii) reporting of results obtained and dissemination of information
(viii) retention of samples and reports.

The authors of the survey report recommended establishing a multidisciplinary and collaborative task team to develop technical guidance, drafting a general procedure for the management and testing of SFFCs by QCLs on the basis of the properties identified, and drafting training manuals and presenting training sessions to QCLs. In addition an access-controlled Internet portal would facilitate collaboration and exchange of information.

[1] The survey focused on testing to detect SFFC products, beyond the routine QC testing for non-compliance with specifications.

The Expert Committee considered the draft outline for a guidance document for the testing of SFFCs by QCLs, made a number of proposals and suggested the continued development of this guidance.

7.5 FIP–WHO technical guidelines: points to consider in the provision by health-care professionals of children-specific preparations that are not available as authorized products

The draft of a guidance document on extemporaneous preparation of medicines for children, which had been commissioned by WHO, was considered in 2011 by the WHO Expert Committee on the Selection and Use of Essential Medicines, which has a subcommittee on paediatric medicines. That Expert Committee felt that extemporaneous preparation of medicines for children might be necessary in some situations but expressed concern about the risks of inappropriate preparations. Revised versions of the document were submitted to the forty-sixth, forty-seventh and forty-eighth meetings of the Expert Committee on Specifications for Pharmaceutical Preparations.

At its forty-eighth meeting in October 2013 the Expert Committee reviewed the draft document once more, proposing alternative text where appropriate, and concluded that the document was not yet ready for adoption. The Committee recommended some cautionary language and advised further consultation and review.

In response to the suggestions of the Expert Committee, a new draft was prepared, based on the working document discussed in 2013. The text had been reorganized and brought into line with the contents of the WHO document *Development of paediatric medicines: points to consider in formulation*. Parts of the original draft, such as an appendix on potential problems in compounding, had been reintroduced. Comments received on the working document were also taken into account. A new section on GMP aspects was proposed. It was pointed out that since the document is intended for a wide audience of practitioners, inclusion of a glossary would be advisable.

The Expert Committee reviewed the draft and comments received and decided that a meeting should be held between WHO, FIP and other interested parties in order to further discuss comments on the document.

7.6 Sampling procedures for market surveillance

Recommendations on the content of a protocol for surveys of the quality of medicines

As a result of recommendations made by the Expert Committee at its forty-sixth and forty-seventh meetings in 2011 and 2012, the Secretariat commissioned the development of guidance for sampling procedures based on examples obtained from many countries. Transparent and consistent reporting would provide robust evidence to assist in improving medicine quality by informing interventions.

A draft working document was discussed at the forty-eighth meeting of the Expert Committee in October 2013 when the Committee also noted the need for separate, specific guidance in relation to SFFC medical products. The document *Recommendations on the content of a survey protocol: surveys of the quality of essential medicines* was received from a group of experts in June 2014. The document was then circulated for comments and feedback was collated. This document was submitted to the Expert Committee as the first of two documents dealing with the monitoring and postmarketing surveillance of medicines and providing advice on survey protocols and sampling for medicines. A second specific guidance document was in preparation in relation to SFFC medical products (see section 7.6.1).

The document presents a summary of the steps necessary for conducting quality surveys, with discussion of different statistically valid sampling techniques for market surveillance. It discusses the advantages and disadvantages of such surveys and how they can be performed, and gives examples and SOPs that can be adapted to different situations.

The Expert Committee noted the comprehensive nature of the document and requested that a more practical guide be prepared while retaining the current version as a scientific background reference.

7.6.1 Sampling procedures for spurious/falsely-labelled/ falsified/counterfeit medical products

Following the recommendation made during the forty-eighth meeting of the Expert Committee in 2013 a working document on recommendations on the content of a survey protocol for surveys of the quality of medicines (see section 7.6) was prepared and circulated for comments. To comply with the second part of the Committee's recommendation the authors also drafted a specific text related to the sampling procedures for SFFC medical products.

The Expert Committee reviewed the document. In view of its overlap with the recommendations on the content of a survey protocol for surveys of the quality of medicines, and noting the proposed structure for a guidance document for the testing of SFFCs by QCLs (see section 7.4), the Committee requested the Secretariat to consider how the three documents could be merged or developed jointly.

8. Quality assurance – distribution and trade of pharmaceuticals

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

The WHO Certification Scheme for finished pharmaceutical products is an international voluntary agreement, originally endorsed by the World Health Assembly in 1969, which is designed to provide information about the quality of pharmaceutical products moving in international commerce to countries which participate in the scheme. The scheme includes 146 WHO Member States and the European Medicines Agency. The primary document of the scheme is the Model Certificate of Pharmaceutical Product, which is a national certificate for which WHO provides the template. Recent changes in the pharmaceutical industry and in the evolution of business models had made the application of the Certification Scheme more and more challenging. Yet, in spite of its limitations, some Member States appreciate its value. It was felt that, if used appropriately, the scheme could be a powerful instrument to assist NRAs in sharing information and avoiding duplication.

The Expert Committee agreed to the proposal that a circular letter be sent from WHO to the Organization's Member States regarding their use of and requirements for the Certificate of Pharmaceutical Product.

8.2 Monitoring and surveillance of the national supply chain

In 2012 the World Health Assembly Resolution WHA65.19 established the Member States mechanism on SSFFC medical products. The mechanism has established a workplan that includes surveillance and monitoring of SSFFC medical products. WHO's SSFFC medical products Global Monitoring and Surveillance Programme conducts this activity in order to assess the scale, scope and extent of harm from such products.

A rapid alert form that is used for reporting includes some 30 mandatory questions considered necessary to allow a preliminary analysis of the incident. The data on the completed form are electronically sent to WHO and uploaded to a dedicated database. Reports of incidents of suspected SSFFC medical products are received from trained focal points.

The WHO team first proceeds to conduct a risk assessment of the reported incident, with a special focus on the risk of harm to public health, and availability of the suspect product(s) to the public. A tailored software package is subsequently able to detect any duplications between the new incident and existing ones, such as product names, batch numbers, adverse reactions and various other elements. This enables the team to see if something similar has happened before, what was done about it and what the result was.

Full classification of a reported incident takes an average of three months and is done both at the product level in an empirical fashion (e.g. insufficient API or wrong packaging) and at the incident level to provide more contextual elements, e.g. intentional falsification.

Over 70% of reported SSFFC products have been found at patient level. Less than half the reported SSFFC medical products undergo laboratory testing, and a small proportion of products only undergo screening.

Detecting SSFFC medical products is a challenge for many different reasons. One reason is that most reported SSFFC medical products have not caused detectable adverse reactions. A proof of concept study by WHO and the Uppsala Pharmacovigilance Monitoring Centre was currently under way to explore how SSFFC medical products could be better detected through reports of lack of efficacy.

The programme had been operational since June 2013 and had carried out eight workshops worldwide since 2012 (pilot phase in September 2012), 80 WHO Member States were participating in the programme and more than 200 regulatory, laboratory and pharmacovigilance staff had been trained. As of mid-September 2014, some 500 SSFFC medical products had been reported to the database.

The programme offers a number of operational and strategic benefits, including: technical and operational support; interregional coordination support; early warnings/alerts; and validated evidence of the scope, scale and harm caused that can then be used to develop evidence-based policies and harness political willpower.

Vulnerabilities in the global supply chain are: unregulated supply chains (e.g. where pharmacists and hospitals obtain products from unlicensed sources, poor procurement practice); lack of access to safe products of adequate quality (e.g. because of stock shortages, price differentials, or lack of awareness of the danger of unlicensed products); and lack of effective law and criminal justice system (e.g. porous borders, corruption, and lack of deterrents).

Future activities would involve developing more tools and resources and strengthening regulatory systems. Further training material and targeted studies will be undertaken.

The Expert Committee noted the report.

8.3 Technical supplement materials to the WHO guidance for storage and transport of time- and temperature-sensitive pharmaceutical products

The document *WHO Model guidance for storage and transport of time- and temperature-sensitive pharmaceutical products* was published in 2011 as Annex 9 to the forty-fifth report of the Expert Committee (WHO Technical Report Series,

No. 961). Since then the Secretariat had worked with a number of experts to develop a set of technical supplements to amplify this guidance. The technical supplements had been reviewed by a group of external experts; public consultation drafts were posted on the WHO website in May–June 2014 and were distributed for comment at several international conferences on pharmaceutical cold chains. The technical supplements are intended to provide additional materials, with each one being linked back to a specific clause or clauses in the parent document. All 16 supplements are written in a standard format and each contains a reference section with hyperlinks to relevant supporting materials, most of them available free online. References to print publications have been minimized in order to avoid the difficulties associated with purchasing books and journals.

Table 3 lists the areas covered by the technical supplements.

Table 3
Areas covered by the technical supplements

Title
1. Selecting sites for storage facilities
2. Design of storage facilities
3. Estimating the capacity of storage facilities
4. Security and fire protection in storage facilities
5. Maintenance of storage facilities
6. Temperature and humidity monitoring systems for fixed storage areas
7. Qualification of temperature-controlled storage areas
8. Temperature mapping of storage areas
9. Maintenance of refrigeration equipment
10. Checking the accuracy of temperature control and monitoring devices
11. Qualification of refrigerated road vehicles
12. Temperature-controlled transport operations by road and by air
13. Qualification of shipping containers
14. Transport route profiling qualification
15. Temperature and humidity monitoring systems for transport operations
16. Environmental management of refrigeration equipment

The target readership for the model guidance and for the technical supplements includes regulators, logisticians and pharmaceutical professionals working in industry, government and international agencies.

The Expert Committee endorsed the documents and asked that they be published as appendices to the main guidance text, *WHO Model guidance for storage and transport of time- and temperature-sensitive pharmaceutical products* (Annex 5).

9. Prequalification of priority essential medicines

9.1 Update on the Prequalification Team managed by WHO

Medicines prequalification was initiated in 2001 as a service to UN procurement agencies. It entails comprehensive evaluation of the quality, safety and efficacy of a medicinal product, based on information submitted by the manufacturer and on inspection of the corresponding manufacturing and, if necessary, clinical site. WHO also prequalifies APIs and medicines QCLs and undertakes extensive capacity building for manufacturers, NRAs and QCLs.

Over time, the WHO List of Prequalified Medicinal Products has become a useful tool for any organization or agency undertaking or funding bulk purchasing of medicines. Similarly, the WHO List of Prequalified APIs is a valuable resource for manufacturers seeking to source quality APIs for use in the manufacture of finished pharmaceutical products (FPPs), while the WHO List of Prequalified Quality Control Laboratories is a useful reference for any organization charged with the responsibility of QC testing.

In 2013 WHO prequalified 62 FPPs (the highest annual number since the programme began), 23 APIs and three QCLs. Incremental improvements to prequalification processes continue to be made, as evidenced by the fact that the median time to prequalification of an FPP – whether that of WHO, the manufacturer, or the two combined – continues to decrease. This is attributable to the continuous improvements that WHO makes to its prequalification guidance, as well as to the efforts made by manufacturers who now have some familiarity with WHO prequalification processes.

Much of the value of prequalification by WHO lies in its consistency and replicability. But it is in monetary terms that its value becomes clear. For example, figures made available by the Global Fund in April 2014 showed expenditure of US$ 118 million on medicines that were prequalified alone (i.e. that had not been approved by an SRA), and that 90% of antimalarials procured with Global Fund funds had been prequalified. A recent (unpublished) estimate made by McKinsey & Company estimated savings for donors of US$ 1 billion in a single year due to the availability of prequalified medicines.

Significant donor funding was secured for medicines prequalification activities in late 2013. Earlier in 2013 fees had been introduced for some prequalification services as a means of ensuring some sustainability of income.

The pace of prequalification was maintained during January–October 2014: 38 FPPs were prequalified, new invitations to manufacturers to submit an EOI in product evaluation were posted on the WHO website (two for HIV/AIDS, one for reproductive health and two for APIs). The second invitation to suppliers and manufacturers of medical products for HIV/AIDS infection and related diseases invited them to submit an EOI for products used in the treatment of hepatitis B and C, for mono-infected or HIV co-infected patients.

More generally, reorganization of the Department of Essential Medicines and Health Products has resulted in closer alignment of the prequalification team with department teams working on development of norms and standards, pharmacovigilance and regulation.

The Expert Committee noted the report.

9.2 Revision of the collaborative registration procedure for prequalification of products

A proposal was received from PQT to revise the current collaborative procedure between PQT and national medicines regulatory authorities in the assessment and accelerated national registration of WHO-prequalified pharmaceutical products, as published in Annex 4 of the WHO Technical Report Series, No. 981 in 2013. The draft proposal for revision of the collaborative registration procedure had been sent out for comments to several stakeholders and, following feedback, a second draft was expected to be available in early 2015. Most of the changes reflect an extension to the vaccine area. Following a further round of comments, a legal review and another revision, it was anticipated that the revised procedure would be submitted to the Expert Committee in October 2015.

The Expert Committee endorsed the proposed revision of the collaborative procedure.

10. Prequalification of active pharmaceutical ingredients

10.1 Update on the prequalification of active pharmaceutical ingredients

PQT began the prequalification of APIs in 2010 to facilitate the identification of API sources by FPP manufacturers and to serve as a resource for resource-constrained NRAs. Prequalification involves both quality and GMP assessments. The team prequalified 23 APIs in 2013 and 17 between January and October 2014. It was reported that some countries now accepted WHO API prequalification, which makes procedures more efficient for regulators and increases the value to manufacturers. To streamline procedures, the team requires that submissions are made electronically and no longer on paper. In addition an amendment procedure has been introduced to facilitate changes to API master files.

The Expert Committee expressed its appreciation for the report.

11. Prequalification of quality control laboratories

11.1 Update on the prequalification of quality control laboratories

The prequalification procedure for QCLs was established in 2004 for Africa only and has since expanded worldwide. Participation is voluntary and both public and private QCLs may participate in the programme. As of September 2014 there were 35 prequalified laboratories and a further 39 interested ones. In each of the six WHO regions at least two national laboratories have been prequalified. Inspections and pre-audits are carried out within the quality control prequalification procedures.

The programme also includes capacity-building, with training and technical assistance, for national QCLs in developing countries. Since 2006 technical assistance has been provided to 46 national control laboratories. Seven training workshops took place in the period 2011–2013 and a further training seminar was held in South Africa in 2014 attended by 53 participants from 42 countries.

A large number of external experts are involved in this work, and a meeting for experts was held in May 2014 to clarify approaches. The major concern related to the integrity of data (see also section 6.6).

Prequalification enables QCLs to be considered for the provision of testing services to UN agencies and other organizations.

The Expert Committee expressed its appreciation for the report.

11.2 Update on WHO quality monitoring projects

A survey was conducted in connection with the UN Commission on Life-saving Commodities for Women and Children in order to identify products of good quality, and assess the quality of those currently available. Twelve products were selected for inclusion in the survey and 10 countries were identified for the sampling. Results showed 155 compliant products, 47 noncompliant ones and one that could not be evaluated. Oxytocin caused the most concern as it showed more noncompliant results than compliant ones. As a result of this survey, the national medicines regulatory authorities were able to take appropriate action.

The Expert Committee expressed its appreciation for the report.

12. Regulatory guidance

12.1 Recommendation for quality requirements – artemisinin starting materials

The specification for artemisinin used as a starting material is written in the style of *The International Pharmacopoeia* and refers to its general chapters and reference substances. It was thus decided to also publish the text in the "Supplementary information" section of *The International Pharmacopoeia*.

When publishing the text in *The International Pharmacopoeia* a number of editorial changes were made to the text published as: *Recommendations for quality requirements when plant-derived artemisinin is used as a starting material in the production of antimalarial active pharmaceutical ingredients*.

The Expert Committee therefore agreed that the amended text should be published as Annex 6 to the report.

12.2 Guidelines on variations for multisource products

In October 2013 the Expert Committee endorsed the development of a document on guidelines on variations for multisource products. The guidance document was developed between October 2013 and February 2014, followed by two rounds of circulation for comments and feedback.

This guidance document is intended to provide normative principles on the implementation of changes to a registered multisource medicinal product.

Technical requirements for the different types of variations are set out in other guidelines, including the *WHO guidelines on variations to a prequalified product* (WHO Technical Report Series, No. 981, 2013, Annex 3) in order to facilitate the submission of appropriate documentation by applicants and their assessment by national medicines regulatory authorities. A consultation to review the document and comments would be convened in the coming months.

The Expert Committee noted the update.

12.3 Guidelines on registration requirements to establish interchangeability (bioequivalence)

These guidelines are intended to provide recommendations to regulatory authorities when defining requirements for the approval of multisource (generic) pharmaceutical products. The guidelines provide appropriate in vivo and in vitro requirements to assure interchangeability of the multisource product without compromising the safety, quality and efficacy of the pharmaceutical product. At its forty-eighth meeting in October 2013, the Expert Committee discussed preliminary feedback on the proposed chapters of this document and noted that WHO guidance needed updating in view of recent new national and regional guidance in the area of interchangeability.

A revision of the guidelines was conducted by a group of experts. The revised document was then circulated for comments and, following collation of feedback, was discussed at an informal consultation held together with the PQT – Assessment. The guidelines were then widely recirculated in their revised form.

In connection with the revision of these guidelines the following related guidance texts are also under review and being updated:

- *Proposal to waive in vivo bioequivalence requirements for WHO Model List of essential medicines immediate-release, solid oral dosage forms* (WHO Technical Report Series, No. 937, 2006, Annex 8);
- *Additional guidance for organizations performing in vivo bioequivalence studies* (WHO Technical Report Series, No. 937, 2006, Annex 9);
- *Guidance on the selection of comparator pharmaceutical products for equivalence assessment of interchangeable multisource (generic) products* (WHO Technical Report Series, No. 902, 2002, Annex 11);
- *Guidance on the selection of pharmaceutical products for assessment of interchangeable multisource (generic) products* (working document QAS/14.594);
- *List of international comparator products* (working document QAS/14.595).

A number of points were discussed in detail together with the comments and feedback received during the consultation period.

The Expert Committee adopted the revised guidelines as Annex 7.

12.4 Guidance for organizations performing in vivo bioequivalence studies – revision

An informal consultation on inspection, GMP and risk management guidance in manufacturing of medicines was held in Geneva from 28 to 30 April 2014. The participants included national inspectors and specialists in the various agenda topics, as well as members of the PQT – Inspections.

The participants discussed the WHO *Additional guidance for organizations performing in vivo bioequivalence studies* (WHO Technical Report Series, No. 937, Annex 9) which was published in 1995, and pointed to a number of areas in which the document was more applicable to clinical trials in general and did not adequately address bioequivalence studies. For instance, the document included very little information on how bioanalysis should be conducted, made no mention of the need for incurred sample reanalysis and gave no explanations on how to perform line clearance.

It was proposed that this document should be updated to better address these and other areas and that the sections on bioanalysis should be consistent with current guidelines on bioanalytical method validation. There was a proposal to take into consideration the requirements for record retention/archiving, as included in WHO's *GMP for investigational medicines*, but it was noted that these guidelines would also require revision as they date back to 1996.

The Expert Committee supported the revision of the guidelines.

12.5 Update of Biowaiver list based on the WHO Model List of Essential Medicines

Following the forty-eighth meeting of the Expert Committee, the Secretariat had been in contact with the WHO Collaborating Centre, Frankfurt-am-Main, Germany to discuss the additional studies needed for the update of the proposal to waive in vivo bioequivalence requirements for the immediate-release, solid oral dosage forms on the EML (WHO Technical Report Series, No. 937, 2006, Annex 8). A list of all APIs for which additional studies are necessary, in view of the various updates of the EML, was collated and prioritized.

In addition, the WHO Collaborating Centre had participated actively in the process of revision of the general requirements for interchangeability and the Comparator Product List. On the basis of these discussions, the collaborating centre submitted a draft version of the revisions to the guidance. In this version it is proposed to separate the actual guidance text from the tables, including the entries for the various APIs included in the EML. This is analogous to the approach suggested for the update of the comparator guidance. The aim is to keep the tables separate as a "living" document in order to enable it to be updated in line with each new version of the EML. Efforts have been made to take into account WHO's guidance on comparator and multisource products.

The Expert Committee reviewed the outline of the draft document, including samples of the planned tables, and endorsed continued development of the document according to the proposal presented and taking into account the comments made.

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

A comparator product is a pharmaceutical product with which the multisource product is intended to be interchangeable in clinical practice. In 1999 the Expert Committee adopted a document containing a list of international comparator pharmaceutical products for equivalence testing and assessment of

interchangeable multisource (generic) products and included a decision-tree for use in identifying comparator pharmaceutical products.

In 2013 the Expert Committee reviewed two possible decision-trees – one for NRAs and one for PQT – and proposed dividing the list of comparator products into two distinct groups, namely oral products and other products. Following these recommendations work continued, with major research on the Internet, on updating of the entries and verification to ensure that the various EMLs were included. In addition an informal consultation was held in Copenhagen, Denmark, from 5 to 6 July 2014 attended by experts from NRAs, WHO Collaborating Centres and PQT.

During the informal consultation, in order to facilitate the updating and maintenance process, it was proposed to prepare two new, separate working documents – one on the selection of comparator products, including the general guidance on how to select comparator products, and another comprising the International Comparator Products List. Following the consultation in July 2014, the revised draft document (i.e. the general guidance) was circulated and comments were collated prior to the forty-ninth meeting of the Expert Committee.

After the consultation in Copenhagen in July 2014 a letter was sent to the International Generic Drug Regulators Pilot (IGDRP) requesting the assistance of its members in validating the entries in the International Comparator Products List. The IGDRP is a network of medicines regulatory authorities that was created to promote collaboration and convergence in generic drug regulatory programmes in order to address the challenges posed by increasing workloads, globalization and complexity of scientific issues. Members of the Expert Committee were also invited to review the current International Comparator Products List and submit comments and amendments to the Secretariat.

The Expert Committee endorsed the document on the selection of comparator products, including the general guidance on how to select such products, subject to the amendments agreed (Annex 8).

The Committee supported the move to request validation of the International Comparator Products List through the IGDRP and making it available on the website in order to receive feedback.

12.7 Good review practice

The good review practice working document presented was prepared under the leadership of the Asia-Pacific Economic Cooperation (APEC) Regulatory Harmonization Steering Committee (RHSC). The RHSC endorsed the attached revision of the good review practices (GRevP) document for submission to WHO. Based on outcomes and comments from the WHO consultation process, the document presented to the Expert Committee incorporated changes to the original GRevP document which was widely circulated for comments at the beginning of 2014.

The objective of the GRevP is to provide high-level guidance on GRevP principles and processes for use across a range of regulatory authority maturities. It is not intended to provide detailed instruction on how to conduct a scientific review. Rather it is envisioned as one building block in a set of tools, which is sufficiently expandable to accommodate additional annexes or ancillary documents in the future. With this in mind, the GRevP Working Group made significant efforts to carefully consider each of the consultation comments and act upon them where appropriate in the revised document. The working group also composed a written response to each consultation comment to explain whether, why and how a comment may or may not have been taken into account in the revised version. The revised version was then again circulated widely for comments.

The outcome of this revision process was presented to the Expert Committee together with the feedback received during the second consultation process.

The Expert Committee adopted the guidelines (Annex 9).

12.8 Good regulatory practices project

At its meeting in 2010, ICDRA requested WHO to collect best practices for collaboration and cooperation between NRAs, including exchange of information, joint assessments and inspections and activities aimed at reducing duplication. Subsequently WHO facilitated twinning between less developed agencies with well-established ones for training and capacity-building and a number of other inter-NRA activities. Feedback gathered from NRAs over more than a decade was reviewed to identify the authorities' main concerns.

A good regulatory practice workshop had been held in India from 10 to 12 July 2014 where it was agreed that the guidelines should be a high-level document that could apply to all regulatory areas and that it should target institutions regulating medicines, biologicals (including vaccines), medical devices, diagnostics, blood and blood components and traditional medicines. An international consultation was to be held in Geneva from 13 to 15 January 2015, further planning workshops were to take place in China and India in 2015 and a series of online meetings had been scheduled.

The objectives of the planning process are:

(i) to review the WHO NRA assessment process and indicators relevant to medicines and vaccines regulatory functions and issue recommendations to align, improve and/or update the current system; and

(ii) to develop a comprehensive policy on WHO roles and responsibilities in strengthening regulatory capacity globally.

The guidelines will include the five stages of preclinical, clinical, production and QC, marketing and sales, and postmarketing activities.

The Expert Committee discussed the planning process and welcomed the development of a comprehensive set of guidelines for all NRAs. The Committee requested to be kept informed of progress.

13. Nomenclature, terminology and databases

13.1 Quality assurance terminology

The WHO website provides access to a database of terms and definitions, which also indicates the respective WHO guidelines. The Secretariat reported that the database is being kept up to date.

13.2 International Nonproprietary Names for pharmaceutical substances

Almost 150 new international nonproprietary names for pharmaceutical substances (INNs) had been published during 2013. The INN database now contains more than 9000 names. During the fifty-seventh and fifty-eighth INN consultations a number of new stems were selected, as well as a list of pre-stems. As biosimilars are biologicals they should be named as such. However the INN expert group agreed that if biosimilars and innovator biologicals were given the same INN, a means to distinguish between them was required (e.g. a trade name). This is problematic since the same substance may be viewed as a biosimilar in some jurisdictions but not in others and there is as yet no INN-specific policy on biosimilars.

Some regulatory authorities had requested WHO to develop an identification system applicable to biosimilars and the INN expert group agreed that this needed to be addressed and that the aim should be global harmonization. A new biological qualifier scheme had been proposed to ensure that all biologicals (and not only biosimilars) that are given INNs should be clearly identified and should have the INN of the reference product as the first part of the name; there should be a parallel nomenclature scheme (the biological qualifier) that uniquely identifies the substance. The biological qualifier scheme would also be applicable to biologicals and not only to biosimilars.

The Expert Committee noted the report.

14. Miscellaneous

14.1 Strategy

EMP was currently in the process of writing its strategy and this would be communicated to the members of the Expert Committee once finalized.

14.2 Outreach

Members of the Expert Committee were also reminded that the quality assurance CD-ROM was available, as was the CD-ROM of *The International Pharmacopoeia* both having been updated in 2014.

Members were also encouraged to consult the WHO website for full information on the Expert Committee system within the work of WHO, and on the roles and responsibilities of Expert Committee members and advisers. Two brochures were recommended, one on the *WHO Expert Committee on Specifications for Pharmaceutical Preparations: How does it work?* and the other entitled *WHO Expert Committee on Specifications for Pharmaceutical Preparations: Meeting major public health challenges*.

Closing remarks

Dr L. Rago, Head of WHO's Medicines and other Health Technologies Team, thanked participants in the Expert Committee meeting for their contributions to the advancement of WHO's normative work. He noted that the chairpersons and co-chairpersons of the WHO Expert Committee on Specifications for Pharmaceutical Preparations and of the WHO Expert Committee on Biological Standardization would meet the Director-General of WHO for a discussion of technical issues raised in their Committee meetings.

The Chair closed the meeting, adding her own thanks to the members of the Expert Committee, the advisers and rapporteurs.

15. Summary and recommendations

The World Health Organization (WHO) Expert Committee on Specifications for Pharmaceutical Preparations advises the Director-General of WHO in the area of medicines quality assurance. It provides independent expert recommendations and guidance to ensure that medicines meet standards of quality, safety and efficacy in all WHO Member States. Its advice is developed through a broad consensus-building process and covers all areas of quality assurance of medicines, from their development to their distribution to patients.

At its forty-ninth meeting, held from 13 to 17 October 2014, the Expert Committee heard updates from the Global Fund to Fight AIDS, Tuberculosis and Malaria, the International Conference on Harmonisation and the Pharmacopoeial Discussion Group. Updates were also given on WHO's work on International Nonproprietary Names for pharmaceutical substances, on traditional and complementary medicines, on the WHO Member State Mechanism on substandard/spurious/falsely-labelled/falsified/counterfeit medicines, WHO's rapid alert system for monitoring and surveillance of national supply chains, and on the use of the WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce as endorsed by the World Health Assembly.

An overview was provided on cross-cutting issues concerning both this Committee and the WHO Expert Committee on Biological Standardization, which met concurrently in Geneva. The Committee heard an update on the Ebola outbreak and the ongoing efforts to expedite the development and provision of potential therapies and vaccines. Other cross-cutting issues included regulatory systems' strengthening, biotherapeutics, regulatory cooperation, for example, on clinical trials, and approaches to address shortages and emergencies. The Committee also heard a report from the biennial International Conference of Drug Regulatory Authorities, co-hosted in Brazil in August 2014 by WHO and the Brazilian regulatory authority ANVISA, which had produced recommendations on these and other regulatory topics.

In the area of QC, the Expert Committee reviewed new and revised specifications and general texts for inclusion in *The International Pharmacopoeia*, and received the annual report of the European Directorate for the Quality of Medicines & HealthCare, the custodian centre for ICRS. The Committee adopted a number of monographs, general texts and ICRS as listed below. It noted the report on Phase 5 of the External Quality Assurance Assessment Scheme and on new approaches to ensure sustainability of this scheme through user fees. The Committee received a concept paper on the benefits of good pharmacopoeial practices (GPhP), and was informed of progress achieved in developing a comprehensive document on GPhP through discussions at consecutive international meetings of world pharmacopoeias.

In the various quality assurance-related areas the Expert Committee was presented with a number of new and revised guidelines related to good manufacturing practices (GMP), distribution and trade of pharmaceuticals and regulatory practice. It adopted eight guidelines and 16 technical supplements as listed below, including a new guidance text on good review practice prepared under the leadership of the Asian-Pacific Economic Cooperation Regulatory Harmonization Steering Committee. The Committee took note of ongoing work to promote collaboration and information exchange through the good regulatory practice project and welcomed the development of a comprehensive set of guidelines for all national regulatory authorities through this project.

The Expert Committee received an update on WHO prequalification of medicines for procurement by international organizations, a programme whose impact had been described as a "quiet revolution in global public health" in a recent article published in the *Journal of Public Health Policy*.[2] Specific updates were also provided on prequalification of active pharmaceutical ingredients and of QCLs. A report was provided on the collaborative procedure for registration of prequalified medicines in WHO Member States; this procedure had been implemented successfully for medicines and was now to be extended to vaccines, and possibly to other product categories in the future.

At the organizational level, the Committee was informed that 2013 had seen the unification of the vaccines, medicines, diagnostics and medical devices prequalification work streams in the same WHO unit, a move which was expected to leverage best practice and promote synergies. A strategy for the WHO Essential Medicines and Health Products Department was in preparation. Updated training and outreach materials on WHO's activities on medicines had been made publicly available, including some 50 training modules on GMP, good laboratory practices and technology transfer, as well as information on the process and outcomes of the Expert Committee's work.

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

The following guidelines were adopted and recommended for use:

- Annex 1. Procedure for the development of monographs and other texts for *The International Pharmacopoeia* (revision)
- Annex 2. Updating mechanism for the section on radiopharmaceuticals in *The International Pharmacopoeia* (revision)

[2] t'Hoen, E, Hogerzeil, H, Quick, J, Sillo, H (2014) Journal of Public Health Policy. A quiet revolution in global public health. The World Health Organizations' Prequalification of Medicines Programme, pp 137-161.

- Annex 3. Guidelines on good manufacturing practices: validation, Appendix 7: non-sterile process validation (revision)
- Annex 4. General guidance for inspectors on hold-time studies (new)
- Annex 6. Recommendations for quality requirements when plant-derived artemisinin is used as a starting material in the production of antimalarial active pharmaceutical ingredients (revision)
- Annex 7. Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability (revision)
- Annex 8. Guidance on the selection of comparator pharmaceutical products for equivalence assessment of interchangeable multisource (generic) products (revision)
- Annex 9: Good review practices: guidelines for regulatory authorities (new)

In addition, 16 technical supplements to the WHO model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products were adopted for publication in a format which is appropriate to the large volume of this guidance (Annex 5).

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

For maternal, newborn, child and adolescent health medicines

dexamethasone sodium phosphate (revision)
dexamethasone phosphate injection

For antiviral medicines, including antiretrovirals

atazanavir sulfate
atazanavir capsules

For antituberculosis medicines

kanamycin for injection (revision)

For medicines to treat tropical diseases

albendazole chewable tablets (revision)
levamisole hydrochloride (revision)
pyrantel embonate (revision)
pyrantel chewable tablets (revision)
pyrantel tablets (revision)

For other anti-infective medicines

fluconazole capsules
fluconazole injection

For medicines for anaesthesia, pain and palliative care
dextromethorphan hydrobromide

General monographs for dosage forms
rectal preparations (revision of the General monograph on suppositories)

Analytical methods
disintegration test for suppositories and rectal capsules (revision of the chapter entitled Disintegration test for suppositories)
disintegration test for tablets and capsules (revision)

Following the implementation of the revised general monograph on Parenteral preparations the Committee adopted the proposed endotoxin limits for inclusion in 11 parenteral dosage form monographs lacking such specification, together with related updates to relevant monographs.

The Committee adopted 12 ICRS newly characterized by the custodian centre, EDQM.

The Committee further adopted the workplan for new monographs to be included in *The International Pharmacopoeia*.

Recommendations

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

The International Pharmacopoeia

The Committee recommended that the Secretariat, in collaboration with experts as appropriate, should:

- continue development of monographs, general methods and texts and general supplementary information, including radiopharmaceuticals monographs developed by the International Atomic Energy Agency, in accordance with the workplan and as decided at the meeting;
- ensure timely publication of annual updated versions of *The International Pharmacopoeia* as described in Annexes 1 and 2;
- investigate options and time period(s) for archiving suppressed or superseded monographs;
- where appropriate, replace the use of physical ICRS by ultraviolet absorptivity techniques for assay and for other quantification purposes.

Quality assurance – good manufacturing practices

- Update the model inspection report format and revise related guidance as proposed by the PQT – Inspections team.
- Consult with experts and stakeholders on replacing the *General notes: additional clarifications and explanations on GMP for active pharmaceutical ingredients* (WHO Technical Report Series, No. 957, 2010, Annex 2) with the questions and answers currently under development by the ICH Implementation Working Group.
- Develop a new guidance document on good data management along the lines of the concept paper proposed by the PQT – Inspections team.

Market surveillance and quality control testing

- Continue the development of a guidance document on rapid screening technologies for "suspect" spurious/falsely-labelled/falsified/counterfeit (SFFC) medicines.
- Continue the development of guidance on
  - QC testing of SFFC medicines,
  - sampling procedures, and
  - sampling procedures for SFFC medical products, considering possibilities to merge the three documents.

FIP–WHO technical guidelines

- Continue the development of a guidance document on extemporaneous preparation of medicines for children in collaboration with FIP and other interested parties.

Distribution and trade of pharmaceuticals

- Send a circular letter to WHO Member States to renew the request for information on their use of the WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce.

Regulation and regulatory collaboration

- Proceed with the revision of the collaborative registration procedure for prequalified products.

- Continue developing a high-level guidance text on variations to registered multisource medicinal products.
- Revise the guidance for organizations performing in vivo bioequivalence studies to reflect current related guidance and address persistent gaps.
- Continue revising the guidance on biowaivers in line with related technical guidelines, providing the medicines lists that are part of this guidance in a format that can be kept updated in line with the WHO Model List of Essential Medicines.
- Seek feedback on the proposed updated International Comparator Products List through the International Generic Drug Regulators Pilot and through the WHO website.
- Continue developing a comprehensive set of good regulatory practice guidelines for all national regulatory authorities and report back on progress to the Committee.

Nomenclature, terminology, databases and organizational systems

- Continue providing the database of terms and definitions covered by this Expert Committee on the WHO website.
- Consider developing a change-control procedure for revised guidelines.

Acknowledgements

Special acknowledgement was made by the Committee to:
Mrs W. Bonny, Ms M. Gaspard, Mr T. Human (intern), Dr S. Kopp, Dr H. Schmidt, Medicines Quality Assurance; Dr D.J. Wood, Coordinator, Technologies Standards and Norms; Dr L. Rägo, Head, Regulation of Medicines and other Health Technologies; Mr C. de Joncheere, Director, Department of Essential Medicines and Health Products, WHO, Geneva, Switzerland; and Mr D. Bramley, Prangins, Switzerland, who were instrumental in the preparation and proceedings of the meeting.

Technical guidance included in this report has been produced with the financial assistance of the European Union, the Bill & Melinda Gates Foundation and UNITAID.

The Committee also acknowledged with thanks the valuable contributions made to its work by the following agencies, institutions, organizations, pharmacopoeias, WHO Collaborating Centres, WHO programmes and persons: Active Pharmaceutical Ingredients Committee, European Chemical Industry Council, Brussels, Belgium; Belgian Association of the Pharmacists of the Pharmaceutical Industry, Meerbeke, Belgium; Asia-Pacific Economic Cooperation, Singapore; Brazilian Health Surveillance Agency, Brasilia, DF, Brazil; Commonwealth Pharmacists Association, London, England; European Commission, Brussels, Belgium; European Directorate for the Quality of Medicines & HealthCare, Council of Europe, Strasbourg, France; European Federation of Pharmaceutical Industries and Associations, Brussels, Belgium; European Generic Medicines Association, Brussels, Belgium; European Medicines Agency, London, England; The Global Fund to Fight AIDS, Tuberculosis and Malaria, Vernier, Switzerland; International Atomic Energy Agency, Vienna, Austria; International Federation of Pharmaceutical Manufacturers and Associations, Geneva, Switzerland; International Generic Pharmaceutical Alliance, Brussels, Belgium; International Pharmaceutical Excipients Council – Americas, Arlington, VA, USA; International Pharmaceutical Excipients Council Europe, Brussels, Belgium; International Pharmaceutical Federation, The Hague, Netherlands; International Society for Pharmaceutical Engineering, Tampa, Florida, USA; Latin American Association of Pharmaceutical Industries (ALIFAR), Buenos Aires, Argentina; Medicines and Healthcare products Regulatory Agency, Inspection, Enforcement and Standards Division, London, England; Swissmedic, Swiss Agency for Therapeutic Products, Berne, Switzerland; Therapeutic Goods Administration, Woden, ACT, Australia; United Nations Children's Fund, Supply Division, Copenhagen, Denmark; United Nations Children's Fund, New York, USA; United Nations Development Programme, New York, USA; United Nations Industrial Development Organization, Vienna, Austria; The World Bank, Washington, DC, USA; World Intellectual Property Organization, Geneva,

Switzerland; World Self-Medication Industry, Ferney-Voltaire, France; World Trade Organization, Geneva, Switzerland.

Laboratoire National de Contrôle des Produits Pharmaceutiques, Chéraga, Alger, Algeria; Instituto Nacional de Medicamentos, Buenos Aires, Argentina; Expert Analytic Laboratory, Centre of Drug and Medical Technology Expertise, Yerevan, Armenia; Laboratoire national de contrôle de qualité des médicaments et consommables médicaux, Cotonou, Benin; Agency for Medicinal Products and Medical Devices, Control Laboratory, Sarajevo, Bosnia and Herzegovina; Instituto Nacional de Controle de Qualidade em Saúde, Rio de Janeiro, Brazil; Laboratoire National de Santé Publique, Ouagadougou, Burkina Faso; National Product Quality Control Centre, Ministry of Health, Phnom Penh, Cambodia; Laboratoire National de Contrôle de Qualité des Médicaments et d'Expertise, Yaoundé, Cameroon; Departamento de Control Nacional, Unidad de Control de Calidad de Medicamentos comercializados, Institutu de Salud Pública, Santiago de Chile, Chile; National Institutes for Food and Drug Control, Beijing, People's Republic of China; Medicamentos y Productos Biológicos del INVIMA, Bogotá, Colombia; Laboratorio de Análisis y Asesoría Farmacéutica, Facultad de Farmacia, Universidad de Costa Rica, San José, Costa Rica; Laboratorio de Normas y Calidad de Medicamentos, Caja Costarricense de Seguro Social, Universidad de Costa Rica, Alajuela, Costa Rica; Laboratoire National de la Santé Publique, Abidjan, Côte d'Ivoire; Oficina Sanitaria Panamericana, OPS/OMS, Havana, Cuba; National Organization for Drug Control and Research, Cairo, Egypt; Drug Quality Control and Toxicology Laboratory, Drug Administration and Control Authority, Addis Ababa, Ethiopia; Centrale Humanitaire Médico-Pharmaceutique, Clermont-Ferrand, France; Food and Drugs Board, Quality Control Laboratory, Accra, Ghana; Laboratoire national de contrôle de qualité des medicaments, Conakry, Guinea; Laboratory for Quality Evaluation and Control, National Institute of Pharmacy, Budapest, Hungary; Central Drugs Laboratory, Kolkata, India; Provincial Drug and Food Quality Control Laboratory, Yogyakarta, Indonesia; Food and Drugs Control Laboratories, Ministry of Health and Medical Education, Tehran, Islamic Republic of Iran; Caribbean Regional Drug Testing Laboratory, Kingston, Jamaica; Mission for Essential Drugs and Supplies, Nairobi, Kenya; National Quality Control Laboratory for Drugs and Medical Devices, Nairobi, Kenya; Food and Drug Quality Control Center, Ministry of Health, Vientiane, Lao People's Democratic Republic; Laboratoire de Contrôle de Qualité des Médicaments, Agence du Médicament de Madagascar, Antananarivo, Madagascar; Centre for Quality Control, National Pharmaceutical Control Bureau, Petaling Jaya, Selangor, Malaysia; Laboratoire National de la Santé du Mali, Bamako, Mali; Laboratoire National de Contrôle des Médicaments, Rabat, Morocco; Quality Surveillance Laboratory, Windhoek, Namibia; National Medicines Laboratory, Department of Drug Administration, Kathmandu, Nepal; Laboratoire National de Santé Publique et d'Expertise, Niamey, Niger; Central

Quality Control Laboratory, Directorate General of Pharmaceutical Affairs and Drug Control, Ministry of Health, Muscat, Oman; Drug Control and Traditional Medicine Division, National Institute of Health, Islamabad, Pakistan; Instituto Especializado de Análisis, Universidad de Panamá, Panama; Centro Nacional de Control de Calidad, Instituto Nacional de Salud, Lima, Peru; Bureau of Food and Drugs, Department of Health, Muntinlupa City, Philippines; Laboratory for Quality Control of Medicines, Medicines Agency, Ministry of Health, Chisinau, Republic of Moldova; National Drug and Cosmetic Control Laboratories, Drug Sector, Saudi Food and Drug Authority, Riyadh, Saudi Arabia; Laboratoire National de Contrôle des Médicaments, Dakar Etoile, Senegal; Pharmaceutical Division, Applied Sciences Group, Health Sciences Authority, Singapore; Centre for Quality Assurance of Medicines, Faculty of Pharmacy, North-West University, Potchefstroom, South Africa; Research Institute for Industrial Pharmacy, North-West University, Potchefstroom, South Africa; National Drug Quality Assurance Laboratory, Ministry of Health, Colombo, Sri Lanka; National Drug Quality Control Laboratory, Directorate General of Pharmacy, Federal Ministry of Health, Khartoum, Sudan; Pharmaceutical Analysis Laboratory, R&D, The School of Pharmacy, Muhimbili University of Health and Allied Sciences, Dar-es-Salaam, United Republic of Tanzania; Tanzania Food and Drug Authority, Dar-es-Salaam, United Republic of Tanzania; Bureau of Drug and Narcotic, Department of Medical Sciences, Ministry of Public Health, Nonthaburi, Thailand; Laboratoire National de Contrôle des Médicaments, Tunis, Tunisia; National Drug Quality Control Laboratory, National Drug Authority, Kampala, Uganda; Central Laboratory for Quality Control of Medicines of the Ministry of Health of Ukraine, Kiev, Ukraine; Laboratory of Pharmaceutical Analysis, State Pharmacological Centre, Ministry of Health of Ukraine, Kiev, Ukraine; Laboratorio Control de Productos MSP, Comisión Para El Control de Calidad de Medicamentos, Montevideo, Uruguay; Instituto Nacional de Higiene "Rafael Rangel", Caracas, Venezuela; National Institute of Drug Quality Control, Hanoi, Viet Nam; Medicines Control Authority, Control Laboratory of Zimbabwe, Harare, Zimbabwe.

Farmacopea Argentina, Buenos Aires, Argentina; Farmacopeia Brasileira, Brasilia, DF, Brazil; British Pharmacopoeia Commission, Medicines and Healthcare products Regulatory Agency, London, England; Pharmacopoeia of the People's Republic of China, Beijing, People's Republic of China; Croatian Pharmacopoeia, Zagreb, Croatia; Czech Pharmacopoeia, Prague, Czech Republic; Danish Pharmacopoeia Commission, Copenhagen, Denmark; European Pharmacopoeia, European Directorate for the Quality of Medicines & HealthCare, Council of Europe, Strasbourg, France; Finnish Medicines Agency, Helsinki, Finland; Pharmacopée française, Agence nationale de sécurité sanitaire des produits de santé, Saint-Denis, France; German Pharmacopoeia Commission, Bonn, Germany; Indian Pharmacopoeia Commission, Raj Nagar, Ghaziabad,

India; Indonesian Pharmacopoeia Commission, Jakarta, Indonesia; Committee of the Japanese Pharmacopoeia, Tokyo, Japan; Kazakhstan Pharmacopoeia, Almaty, Kazakhstan; Pharmacopoeia of the Republic of Korea, Cheongwon-gun, Chungcheongbuk-do, Republic of Korea; Mexican Pharmacopoeia, México DF, Mexico; Polish Pharmacopoeia Commission, Warsaw, Poland, Portuguese Pharmacopoeia, Lisbon, Portugal; State Pharmacopoeia of the Russian Federation, Moscow, Russian Federation; Serbian Pharmacopoeia, Belgrade, Serbia; Slovakian Pharmacopoeia Commission, Bratislava, Slovakia; Spanish Pharmacopoeia, Royal, Madrid, Spain; Swedish Pharmacopoeia, Uppsala, Sweden; Swiss Pharmacopoeia, Berne, Switzerland; Pharmacopoeia of Ukraine, Kiev, Ukraine; United States Pharmacopeia, Rockville, MD, USA; Vietnamese Pharmacopoeia, Hanoi, Viet Nam.

WHO Centre Collaborateur pour la Conformité des Médicaments, Laboratoire national de Contrôle des Produits Pharmaceutiques, Alger, Algeria; WHO Collaborating Centre for Drug Quality Assurance, Therapeutic Goods Administration Laboratories, Woden, ACT, Australia; WHO Collaborating Centre for Drug Quality Assurance, National Institute for the Control of Pharmaceutical and Biological Products, Beijing, People's Republic of China; WHO Collaborating Centre for Research on Bioequivalence Testing of Medicines, Frankfurt am Main, Germany; WHO Collaborating Centre for Drug Information and Quality Assurance, National Institute of Pharmacy, Budapest, Hungary; WHO Collaborating Centre for Quality Assurance of Essential Drugs, Central Drugs Laboratory, Calcutta, India; WHO Collaborating Centre for Regulatory Control of Pharmaceuticals, National Pharmaceutical Control Bureau, Jalan University, Ministry of Health, Petaling Jaya, Malaysia; WHO Collaborating Centre for Drug Quality Assurance, Pharmaceutical Laboratory, Centre for Analytical Science, Health Sciences Authority, Singapore; WHO Collaborating Centre for Quality Assurance of Drugs, North-West University, Potchefstroom, South Africa; WHO Collaborating Centre for Quality Assurance of Essential Drugs, Bureau of Drug and Narcotic, Department of Medical Sciences, Ministry of Public Health, Nonthaburi, Thailand.

Health Systems and Innovation Cluster, WHO, Geneva, Switzerland; Department of Essential Medicines and Health Products, WHO, Geneva, Switzerland; Regulation of Medicines and other Health Technologies, WHO, Geneva, Switzerland; Prequalification Team, WHO, Geneva, Switzerland; International Nonproprietary Names, WHO, Geneva, Switzerland; Policy Access and Use, WHO, Geneva, Switzerland; Regulatory Systems Strengthening, WHO, Geneva, Switzerland; Safety and Vigilance, WHO, Geneva, Switzerland; Technologies, Standards and Norms, WHO, Geneva, Switzerland; Traditional and Complementary Medicine, WHO, Geneva, Switzerland; Office of the Legal Counsel, WHO, Geneva, Switzerland; Global Malaria Programme, WHO, Geneva, Switzerland; HIV/AIDS Programme, WHO, Geneva, Switzerland;

WHO Regional Office for Africa, Brazzaville, Congo; WHO Regional Office for the Americas/Pan American Health Organization, Washington, DC, USA; WHO Regional Office for the Eastern Mediterranean, Cairo, Egypt; WHO Regional Office for Europe, Copenhagen, Denmark; WHO Regional Office for South-East Asia, New Delhi, India; WHO Regional Office for the Western Pacific, Manila, Philippines.

Abbott, Allschwil, Switzerland; Abbott Laboratories, Abbott Quality & Regulatory, Dept. 03QY, Abbott Park, IL, USA; Dr F. Abiodun, Benin City, Nigeria; Dr E. Adams, Laboratorium voor Farmaceutische Chemie en Analyse van Geneesmiddelen, Leuven, Belgium; Dr M. Adarkwah-Yiadom, Standard Officer, Ghana Standards Board, Drugs, Cosmetics and Forensic Laboratory Testing Division, Accra, Ghana; Professor I. Addae-Mensah, Department of Chemistry, University of Ghana, Legon, Ghana; División de Química y Tecnología Farmacéutica, AEMPS. Madrid, Spain; Dr K. Agravat, Regulatory Affairs, Unimark Remedies Limited, Ahmedabad, India; Ms R. Ahmad, Centre for Product Registration, National Pharmaceutical Control Bureau, Ministry of Health, Petaling Jaya, Malaysia; Dr Sawsan Ahmed Jaffar, Director-General, Directorate General of Pharmaceutical Affairs and Drug Control, Ministry of Health, Muscat, Oman; Ajanta Pharma Ltd, Kandivli (West), Mumbai, India; Dr D. Alsmeyer, Apotex Inc., Toronto, Ontario, Canada; AMGEN Inc., Engineering, West Greenwich, RI, USA; Dr C. Anquez Traxler, European Self-Medication Industry, Brussels, Belgium; Dr P. Aprea, Director, Directorate of Evaluation and Control of Biologicals and Radiopharmaceuticals, National Administration of Medicines, Food and Medical Technology, Buenos Aires, Argentina; Dr N. Aquino, Inspector and Specialist in GMP and Risk Management, Brazilian Health Surveillance Agency, Brasilia, DF, Brazil; Dr A.C. Moreira Marino Araujo, Health Expert, Drugs Office, Post Approval Changes of Synthetic Drugs, Brazilian Health Surveillance Agency, Brasilia, DF, Brazil; Dr H. Arentsen, Regulatory Intelligence and Policy Specialist, Regulatory Development Strategy, H. Lundbeck A/S, Copenhagen-Valby, Denmark; Astellas Pharma Europe BV, Leiderdorp, Netherlands; Dr C. Athlan, Quality Reviewer, Swissmedic, Swiss Agency for Therapeutic Products, Berne, Switzerland; Dr R. Atkinson, Group Manager, BP & Laboratory Services and Secretary and Scientific Director, British Pharmacopoeia Commission, London, England; Dr A. Ba, Directeur, Qualité et Développement, Centrale Humanitaire Medico-Pharmaceutique, Clermont-Ferrand, France; Dr J.R. Ballinger, Guy's and St Thomas Hospital, London, England; Mr N. Banerjee, Cipla Limited, Goa, India; Dr H. Batista, US Food and Drug Administration, Silver Spring, MD, USA; Mr B. Baudrand, OTECI, Paris, France; Dr O.P. Baula, Deputy Director, State Pharmacological Center, Ministry of Health, Kiev, Ukraine; Professor S.A. Bawazir, Advisor to the Executive President, Saudi Food and Drug Authority, Riyadh, Saudi Arabia; Bayer Health Care Pharmaceuticals, Bayer Pharma AG, Berlin, Germany; Dr M.G. Beatrice, Vice

President, Corporate Regulatory and Quality Science, Abbott, Abbott Park, IL, USA; Dr T.L. Bedane, Drug Administration and Control, Addis Ababa, Ethiopia; Ms T.J. Bell, WHO Focal Point, US Food and Drug Administration, Silver Spring, MD, USA; Dr I.B.G. Bernstein, Director, Pharmacy Affairs, Office of the Commissioner/Office of Policy, US Food and Drug Administration, Silver Spring, MD, USA; Mr L. Besançon, General Secretary and CEO, International Pharmaceutical Federation, The Hague, Netherlands; Dr R.P. Best, President and CEO, International Society for Pharmaceutical Engineering, Tampa, FL, USA; Dr A. Bevilacqua, US Pharmacopeia, Bedford, MA, USA; Dr J. Bishop III, Review Management Staff, Office of the Director, Center for Biologics Evaluation and Research, United States Food and Drug Administration,, Silver Spring, MD, USA; Dr L. Bonthuys, Pretoria, South Africa; Mr M.H. Boon, Deputy Director, Overseas Audit Unit – Audit Branch, Audit & Licensing Division, Health Products Regulation Group, Singapore; Dr G. Born, Institute of Pharmaceutical Technology, Johann Wolfgang Goethe-University, Frankfurt, Germany; Professor R. Boudet-Dalbin, Paris, France; Dr B. Blum, Sandoz, France; Dr G. Bourdeau, Méréville, 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; Dr M. Brits, Director, WHO Collaborating Centre for the Quality Assurance of Medicines, North-West University, Potchefstroom Campus, Potchefstroom, South Africa; Mr C. Brown, Inspections Enforcement and Standards Division, Medicines and Healthcare Products Regulatory Agency, London, England; Dr W. Bukachi, Project Coordinator, International Affairs, US Pharmacopeia, Rockville, MD, USA; Ms A. Bukirwa, National (Food and) Drug Authority, Kampala, Uganda; Bureau of Drug and Narcotic, Department of Medical Sciences, Ministry of Public Health, Nonthaburi, Thailand; Dr F. Burnett, Managing Director, Pharmaceutical Procurement Service, Organization of Eastern Caribbean States, Casties, St Lucia; Dr W. Cabri, Research and Development, Director, Chemistry and Analytical Development, Sigma-tau Industrie Farmaceutiche Riunite SpA, Pomezia, Italy; Dr. D. Calam, Wiltshire, England; Dr N. Cappuccino, Lambertville, NJ, USA; Dr L. Cargill, Director, Caribbean Regional Drug Testing Laboratory, Kingston, Jamaica; Professor (Madame) R. Jiménez-Castellanos, Department of Pharmaceutics and Pharmaceutical Technology, Faculty of Pharmacy, Seville, Spain; Dr A. Castro, Regulatory Affairs Director and Senior Pharmacist, Roche Servicios SA, Heredia, Costa Rica; Dr D. Catsoulacos, Scientific Administrator, Manufacturing and Quality Compliance, Compliance and Inspection, European Medicines Agency, London, England; Mr J.-M. Caudron, Braine-le-Château, Belgium; Mr P. Cenizo, Southern African Pharmaceutical Regulatory Affairs Association (SAPRAA), Randburg, South Africa; Dr A.N.K. Chali, Chemical and Pharmaceutical Assessor, Uppsala, Sweden; Mr X. Chan, Project Manager, International Pharmaceutical Federation, The Hague, Netherlands; Dr B. Chapart,

Pharma Review Manager, Global Analytical Development, Sanofi-Aventis Pharma, Anthony, France; Ms Cheah Nuan Ping, Director, Cosmetics & Cigarette Testing Laboratory, Pharmaceutical Division, Applied Sciences Group, Health Sciences Authority, Singapore; Dr X. Chen, Director, Division of Drug Distribution Supervision, State Food and Drug Administration, Beijing, People's Republic of China; Professor Y. Cherrah, Faculté de Médecine et Pharmacie, Rabat, Morocco; Dr B.K. Choi, Director, Pharmaceutical Standardization, Osong Health Technology Administration Complex, Research and Testing Division of the Ministry of Food and Drug Safety, Cheongwon-gun, Chungbuk, Republic of Korea; Dr Y.H. Choi, Scientific Officer, Korea Food & Drug Administration, Cheongwon-gun, Chungbuk, Republic of Korea; Cipla Limited, Mumbai, India; 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, Macclesfield, Cheshire, England; Dr C. Craft, Member, United States Pharmacopeia International Health Expert Committee, Rockville, MD, USA; Dr R.L. Dana, Senior Vice President, Regulatory Affairs and Parenteral Drug Association Training and Research Institute, Parenteral Drug Association, Bethesda, MD, USA; Mr M.M. Das, Barisha, Kolkata, India; Dr V. Davoust, Quality & Regulatory Policy, Pharmaceutical Sciences, Pfizer Global Research & Development, Paris, France; 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; Directorate General of Pharmaceutical Affairs and Drug Control, Ministry of Health, Muscat, Oman; Professor J.B. Dressman, Director, Institut für Pharmazeutische Technologie, Biozentrum, Johann Wolfgang Goethe-Universität, Frankfurt am Main, Germany; Dr A.T. Ducca, Senior Director, Regulatory Affairs, Healthcare Distribution Management Association, Arlington, VA, USA; Dr T.D. Duffy, Lowden International, Tunstall, Richmond, N. Yorks, England; Dr S. Durand-Stamatiadis, Director, Information and Communication, World Self-Medication Industry, Ferney-Voltaire, France; Dr P. Ellis, Director, External Advocacy, Quality Centre of Excellence, GlaxoSmithKline, Brentford, Middlesex, England; European Compliance Academy Foundation, Heidelberg, Germany; European Medicines Agency, London, England; Fedefarma, Ciudad, Guatemala; F. Hoffman-La Roche Ltd, Basel, Switzerland; Dr A. Falodun, Department of Pharmaceutical Chemistry, Faculty of Pharmacy, University of Benin, Benin City, Nigeria; Federal Ministry of Health, Bonn, Germany; Dr E. Fefer, Member, United States Pharmacopeia International Health Expert Committee, Rockville, MD, USA; Dr R. Fendt, Head, Global Regulatory & GMP Compliance Pharma, Care Chemicals Division, BASF, Limburgerhof, Germany; Mr A. Ferreira do Nascimento, Agência Nacional de Vigilância, Brasília, Brazil; Mr M. FitzGerald, European Association of

Pharmaceutical Full-line Wholesalers, Brussels, Belgium; Dr A. Flueckiger, Head, Corporate Health Protection, Corporate Safety, Health & Environmental Protection, F. Hoffmann-La Roche, Basel, Switzerland; Dr G.L. France, Head, Q&A Compliance, EU Region, Novartis Consumer Health Services SA, Nyon, Switzerland; Mr T. Fujino, Director, International Affairs, Japan Generic Medicines Association, Tokyo, Japan; Mr A. García Arieta, Spanish Agency of Medicines and Medical Devices, Madrid, Spain; Miss Y. Gao, Project Manager, Chinese Pharmacopoeia Commission, Beijing, People's Republic of China; Dr M. Garvin, Senior Director, Scientific and Regulatory Affairs, Pharmaceutical Research and Manufacturers of America, Washington, DC, USA; Dr A. Gayot, Faculté de Pharmacie de Lille, Lille, France; Dr X. Ge, Senior Analytical Scientist, Pharmaceutical Laboratory, Pharmaceutical Division, Applied Sciences Group, Health Sciences Authority, Singapore; Dr L. Gibril, Compliance Coordinator, Novartis Pharma SAE, Amiria, Cairo, Egypt; Gilead Sciences International Ltd, Abington, Cambridge, England; Dr F. Giorgi, Research and Development, Analytical Development Manager, Sigma-tau Industrie Farmaceutiche Riunite SpA, Pomezia, Italy; Dr L. Girard, Head, Global Pharmacopoeial Affairs, Novartis Group Quality, Quality Systems and Standards, Basel, Switzerland; GlaxoSmithKline, Brentford, Middlesex, England; GlaxoSmithKline Biologicals SA, Wavre, Belgium; GlaxoSmithKline, Sales Training Centre, Research Triangle Park, NC, USA; Dr C. Sánchez González, Coordinator of Policies and Regulatory Affairs Centro para el Control de Medicamentos, Equipos y Dispositivos Médicos, La Habana, Cuba; Dr J. Gordon, Nova Scotia, Canada; Ms J. Gouws, Department of Health, Medicines Control Council, Pretoria, South Africa; Dr M. Goverde, QC Expert Microbiology, Novartis Pharma AG, Basel, Switzerland; Ms R. Govithavatangaphong, Director, Bureau of Drug and Narcotics, Department of Medical Sciences, Ministry of Public Health, Nonthaburi, Thailand; Dr J. Grande, Manager, Regulatory Affairs, McNeil Consumer Healthcare, Markham, England; Dr A. Gray, Senior Lecturer, Department of Therapeutics and Medicines Management and Consultant Pharmacist, Centre for the AIDS Programme of Research in South Africa (CAPRISA), Nelson R Mandela School of Medicine, University of KwaZulu-Natal, Congella, South Africa; Dr M. Guazzaroni Jacobs, Director, Quality and Regulatory Policy, Pfizer Inc., New York, NY, USA; Ms N.M. Guerrero Rivas, Radiofarmacia de Centroamérica, SA, Ciudad del Saber, Panamá, Panama; Guilin Pharmaceutical Company Ltd, Guilin, People's Republic of China; Dr R. Guinet, Agence nationale de sécurité du médicament et des produits de santé, Saint-Denis, France; Dr S. Gupta, Mankind Pharma Limited, Unit-II, Vill. Kishanpura, Paonta Sahib, Disst. Sirmour, India; Professor R. Guy, Professor of Pharmaceutical Sciences, Department of Pharmacy & Pharmacology, University of Bath, Bath, England; Dr N. Habib, Director General of Medical Supplies, Ministry of Health, Oman; Dr N. Hamilton, Industrial Quality and Compliance, Industrial Affairs, Sanofi Aventis, West Malling, Kent,

England; Ms J. Hantzinikolas, Therapeutic Goods Administration, Department of Health, Woden, ACT, Australia; Dr S. Harada, International Affairs Division, Minister's Secretariat, Ministry of Health, Labour and Welfare, Tokyo, Japan; Dr B. Hasselbalch, Acting Associate Director, Policy and Communications, and Director, Division of Policy, Collaboration & Data Operations, Office of Compliance, Center for Drug Evaluation and Research, United States Food and Drug Administration, Silver Spring, MD, USA; Dr A. Hawwa, Lecturer in Pharmacy (Medicines in Children), Medical Biology Centre, Queen's University Belfast, Belfast, Northern Ireland; Dr M. Hayes-Bachmeyer, Technical Regulatory Affairs, Pharmaceuticals Division, F. Hoffmann-la Roche, Basel, Switzerland; Mr Y. Hebron, Manager, Medicines and Cosmetics Analysis Department, Tanzania Food and Drugs Authority, Dar-es-Salaam, United Republic of Tanzania; Dr G.W. Heddell, Director, Inspection Enforcement & Standards Division, Medicines and Healthcare Products Regulatory Agency, London, England; Dr D. Hege-Voelksen, Swissmedic, Swiss Agency for Therapeutic Products, Berne, Switzerland; Ms J. Hiep, QA Pharmacist and Auditor, Adcock Ingram, Bryanston, South Africa; Ms M. Hirschhorn, Head, Quality and Chemistry Sector, Comisión para el Control de Calidad de Medicamentos (Drug and Control Commission), Montevideo, Uruguay; Dr K. Horn, Managing Director, Institute for Pharmaceutical and Applied Analytics, Official Medicines Control Laboratory, Bremen, Germany; F. Hoffmann-La Roche Ltd., Basel, Switzerland; Professor J. Hoogmartens, Leuven, Belgium; Dr K. Hoppu, Director, Poison Information Centre, Helsinki University Central Hospital, Helsinki, Finland; Dr H. Hoseh, Head of Registration Unit, Drug Directorate, Jordan Food and Drug Administration, Jordan; Dr X. Hou, Chemical & Materials, Singapore; Dr N. Ibrahim, National Pharmaceutical Control Bureau, Ministry of Health, Jalan University, Petaling Jaya, Indonesia; Indian Drug Manufacturers' Association, Mumbai, India; Infarmed, Lisbon, Portugal; Ipsen Pharma, Dreux, France; Dr J. Isasi Rocas, Pharmaceutical Chemist, Lima, Peru; Professor R. Jachowicz, Head, Department of Pharmaceutical Technology and Biopharmaceutics, Jagiellonian University Medical College, Faculty of Pharmacy, Kraków, Poland; Mr I. Jackson, Operations Manager, GMDP Inspections, Inspection, Enforcement & Standards Division, Medicines and Healthcare Products Regulatory Agency, London, England; Dr S.A. Jaffar, Director General, Pharmaceutical Affairs and Drug Control, Ministry of Health, Muscat, Oman; Johnson & Johnson, Latina, Italy; Ms M. Kira, Consultant, Non-Governmental Organizations and Industry Relations Section, Department of External Relations, World Intellectual Property Organization, Geneva, Switzerland; Dr R. Jähnke, Global Pharma Health Fund e.V., Frankfurt, Germany; Dr M. James, GlaxoSmithKline, Brentford, Middlesex, England; Dr A. Janssen, Manager, Regulatory Affairs, DMV Fonterra Excipients, FrieslandCampina Ingredients Innovation, Goch, Germany; Professor S. Jin, Chief Expert for Pharmaceutical

Products, National Institutes for Food and Drug Control, Beijing, People's Republic of China; Dr P. Jones, Director, Analytical Control, Pharmaceutical Sciences, Pfizer Global R&D, Sandwich, England; Dr Y. Juillet, Consultant, Paris, France; Mr D. Jünemann, Teaching Assistant; Institut für Pharmazeutische Technologie, Biozentrum, Johann Wolfgang Goethe-Universität, Frankfurt am Main, Germany; Ms A. Junttonen, Senior Pharmaceutical Inspector, National Agency for Medicines, Helsinki, Finland; Dr S. Kafkala, Analytical Development Director, Genepharm S.A., Pallini, Greece; Dr V. Kamde, Quality Management, Oman Pharmaceuticals, Oman; Dr M. Kaplan, Director, Institute for Standardization and Control of Pharmaceuticals, Jerusalem, Israel; Dr M. Karga-Hinds, Director, Barbados Drug Service, Christchurch, Barbados; Dr A.M. Kaukonen, National Agency for Medicines, Helsinki, Finland; Ms H. Kavale, Cipla, Mumbai, India; Dr T. Kawanishi, Deputy Director General, National Institute of Health Sciences, Tokyo, Japan; Dr S. Keitel, Director, European Directorate for the Quality of Medicines and Healthcare, Strasbourg, France; Dr K. Keller, Director and Professor, Federal Ministry of Health, Bonn, Germany; Dr M. Keller, Inspector, Division of Certificates and Licencing, Swissmedic, Swiss Agency for Therapeutic Products, Berne, Switzerland; Dr L. Kerr, Scientific Operations Adviser, Office of Laboratories and Scientific Services, Therapeutic Goods Administration, Woden, ACT, Australia; Dr M. Khan, Director, Federal Research Center Life Sciences, US Food and Drug Administration, Silver Spring, MD, USA; Dr S. Khoja, Vapi, Gujarat, India; Professor K. Kimura, Drug Management and Policy, Institute of Medical, Pharmaceutical and Health Sciences, Kanazawa University, Kanazawa-city, Japan; Dr H. Köszegi-Szalai, Head, Department for Quality Assessment and Control, National Institute of Pharmacy, Budapest, Hungary; Dr A. Kovacs, Secretariat, Pharmaceutical Inspection Co-operation Scheme, Geneva, Switzerland; Ms S. Kox, Senior Director Scientific Affairs, European Generic Medicines Association, Brussels, Belgium; Dr P. Kozarewicz, Scientific Administrator, Quality of Medicines Sector, Human Unit Pre-Authorization, European Medicines Agency, London, England; Dr A. Krauss, Principal Chemist, Office of Laboratories and Scientific Services, Therapeutic Goods Administration, Woden, ACT, Australia; Professor H.G. Kristensen, Vedbaek, Denmark; Dr J. Kumar, HLL Lifecare Ltd., Kanagala, Belgaum, India; Mr A. Kupferman, Bangkok, Thailand; Dr S. Kumar, Assistant Drugs Controller, Central Drugs Standard Control Organization, Food and Drug Administration Bhawan, New Delhi, India; Professor S. Läer, Institut für Klinische Pharmazie und Pharmakotherapie, Heinrich-Heine-Universität, Düsseldorf, Germany; Dr O. Le Blaye, Inspector, Trials and Vigilance Inspection Department, Agence nationale de sécurité du médicament et des produits de santé, Saint-Denis, France; Dr B. Li, Deputy Director General, National Institutes for Food and Drug Control, Ministry of Public Health, Beijing, People's Republic of China; Dr H. Li, Head, Chemical Products Division, Chinese Pharmacopoeia

Commission, Beijing, People's Republic of China; Dr C.M. Limoli, International Programs, Center for Drug Evaluation and Research, United States Food and Drug Administration, Silver Spring, MD, USA; Dr A. Lodi, Head, Laboratory Department, European Directorate for the Quality of Medicines and HealthCare, Strasbourg, France; Mr M. Lok, Head of Office, Office of Manufacturing Quality, Therapeutic Goods Administration, Woden, ACT, Australia; Ms M.Y. Low, Director, Pharmaceutical Division, Applied Sciences Group, Health Sciences Authority, Singapore; Lupin Ltd, Mumbai, Maharashtra, India; Dr J.C. Lyda, Senior Director, Regulatory Affairs, Parenteral Drug Association Europe, Glienicke/ Berlin, Germany; Mr D. Mader, Compliance Auditor, GlaxoSmithKline, Cape Town, South Africa; Dr C. Makokha, Kikuyu, Kenya; Ms G.N. Mahlangu, Director-General, Medicines Control Authority of Zimbabwe, Harare, Zimbabwe; Mangalam Drugs and Organics Limited, Mumbai, India; Dr M.A. Mantri, Bicholim, Goa, India; Martindale Pharma, Brentwood, Essex, England; Dr B. Matthews, Alcon, Hemel Hempstead, England; Dr Y. Matthews, Regulatory Operations Executive, GE Healthcare, Amersham, Bucks, England; Dr S.V.M. Mattos, Especialista em Regulação de Vigilância Sanitária, Coordenação da Farmacopeia Brasileira, Brazilian Health Surveillance Agency, Brasília, Brazil; Dr J.L. Mazert, France; Dr G. McGurk, Executive Inspector, Irish Medicines Board, Dublin, Ireland; Dr A. Mechkovski, Moscow, Russian Federation; Medicines and Healthcare Products Regulatory Agency, London, England; Medopharm, Chennai, Tamilnadu, India; Dr M. Mehmandoust, Agence nationale de sécurité du médicament et des produits de santé, Saint-Denis, France; Dr D. Mehta, Vigilance and Risk Management of Medicines, Medicines and Healthcare Products Regulatory Agency, London, England; Dr C. Mendy, Manager, Regulatory Policy, International Federation of Pharmaceutical Manufacturers and Associations, Geneva, Switzerland; Micro Labs Ltd, Kilpauk, Chennai, India; Dr M. Mikhail, Fresenius Kabi, Bad-Homburg, Germany; Dr J.H.McB. Miller, Ayr, Scotland; Dr O. Milling, Medicines Inspector, Medicines Control Division, Danish Medicines Agency, Copenhagen, Denmark; Dr S. Mills, Pharmaceutical Consultant, Ware, England; Ministry of Health, Government of Pakistan, Islamabad, Pakistan; Ministry of Health and Welfare, Tokyo, Japan; Dr J. Mitchell, GlaxoSmithKline, Belgium; Dr S. Moglate, United Nations Population Fund, UN City, Copenhagen, Denmark; Dr N.H. Mohd, Director General of Medical Supplies, Ministry of Health, Muscat, Oman; Ms N.H. Mohd Potri, Senior Assistant, Director, GMP and Licensing Division, Centre for Compliance and Licensing, National Pharmaceutical Control Bureau, Ministry of Health Malaysia, Petaling Jaya, Malaysia; Dr J.A. Molzon, Bethesda, MD, USA; Dr I. Moore, Product and Quality Assurance Manager, Croda Europe, Snaith, England; Dr J. Morénas, Assistant Director, Inspection and Companies Department, Agence nationale de sécurité du médicament et des produits de santé, Saint Denis, France; Dr K. Morimoto, Expert, Office of Review Management, Review Planning

Division, Pharmaceutical and Medical Devices Agency, Tokyo, Japan; Dr J.M. Morris, Irish Medicines Board, Dublin, Ireland; Mr T. Moser, Galenica, Berne, Switzerland; Dr A.E. Muhairwe, Executive Secretary and Registrar, National Drug Authority, Kampala, Uganda; Dr. S. Mülbach, Director, Senior Regulatory Counsellor, Vifor Pharma, Glattbrugg, Switzerland; Ms C. Munyimba-Yeta, Director, Inspectorate and Licensing, Pharmaceutical Regulatory Authority, Lusaka, Zambia; Mylan Laboratories Limited, Drug Regulatory Affairs, Jinnaram Mandal, Andhra Pradesh, India; Ms N. Nan, Chief Pharmacist, National Institutes for Food and Drug Control, Beijing, People's Republic of China; Miss X. Nan, Project Officer, China Center for Pharmaceutical International Exchange, Beijing, People's Republic of China; Dr E. Narciandi, Head, Technology Transfer Department, Center for Genetic Engineering & Biotechnology, Havana, Cuba; National Agency of Drug and Food Control, Jakarta Pusat, Indonesia; National Authority of Medicines and Health Products (INFARMED), Directorate for the Evaluation of Medicinal Products, Lisbon, Portugal; National Institute of Drug Quality Control of Vietnam, Hanoi, Viet Nam; NBCD Working Group, Leiden, Netherlands; Dr R. Neri, Sanofi, Antony, France; Dr E. Nickličková, Inspector, State Institute for Drug Control, Prague, Czech Republic; Professor A. Nicolas, Radiopharmacien, Expert analyse, Pharmacie, Hôpital Brabois Adultes, Vandoeuvre, France; Dr H.K. Nielsen, Technical Specialist, Essential Medicines, Medicines and Nutrition Centre, UNICEF Supply Division, Copenhagen, Denmark; Professor B. Ning, Deputy Director, Division of Chemical Drugs, National Institutes for Food and Drug Control, Beijing, People's Republic of China; Dr P. Njaria, Head, Quality Assurance Unit and Instrumentation, National Quality Control Laboratory, Nairobi, Kenya; Dr K. Nodop, Inspections, European Medicines Agency, London, England; Novartis Group Quality, Novartis Campus, Basel, Switzerland; Professor A. Nunn, Formby, Liverpool, England; Dr A. Ojoo, United Nations Children's Fund, Copenhagen, Denmark; Mr S. O'Neill, Managing Director, The Compliance Group, Dublin, Ireland; Dr L. Oresic, Head, Quality Assurance Department, Croatian Agency for Medicinal Products and Medical Devices, Zagreb, Croatia; Dr P.B. Orhii, Director-General, National Agency for Food and Drug Administration and Control, Abuja, Nigeria; Dr N. Orphanos, International Programs Division, Bureau of Policy, Science, and International Programs, Therapeutic Products Directorate, Health Products & Food Branch, Health Canada, Ottawa, Canada; Professor T.L. Paál, Director-General, National Institute of Pharmacy, Budapest, Hungary; Dr P.R. Pabrai, New Delhi, India; Dr R. Pai, Johannesburg, South Africa; Mrs L. Paleshnuik, Arnprior, Ontario, Canada; Dr S. Parra, Manager, Generic Drugs Quality Division 1, Bureau of Pharmaceutical Sciences, Therapeutic Products Directorate, Health Canada, Ottawa, Ontario, Canada; Dr D.B. Patel, Secretary-General, Indian Drug Manufacturers' Association, Mumbai, India; Dr P.S. Patil, Umedica Laboratories Pvt. Ltd, Vapi, Gujarat, India; Dr S.R. Srinivas Patnala, Grahamstown, South

Africa; Dr S. Patnala, Professor, Pharmaceutical Analysis and Coordinator, University Instrumentation Facility, KLE University, Belgaum, India; Dr A. Pazhayattil, Apotex Inc., Toronto, Ontario, Canada; Mr C. Perrin, Pharmacist, International Union Against Tuberculosis and Lung Disease, Paris, France; Dr M. Phadke, Senior Manager, Analytical Research, IPCA Laboratories, Mumbai, India; Pharmaceutical Inspection Co-operation Scheme, Geneva, Switzerland; Dr B. Phillips, Medicines and Healthcare Products Regulatory Agency, London, England; Dr R.D. Pickett, Supanet, Bucks, England; Dr B. Pimentel, European Chemical Industry Council, Brussels, Belgium; Polychromix, Inc., Wilmington, MA, USA; Dr A. Pontén-Engelhardt, Head of Stability Management, Global Quality, Operations, AstraZeneca, Södertälje, Sweden; Ms A. Poompanich, Bangkok, Thailand; Dr H. Potthast, Federal Institute for Drugs and Medical Devices, Berlin, Germany; Dr R. Prabhu, Regulatory Affairs Department, Cipla, Mumbai, India; Dr J. Prakash, Principal Scientific Officer, Indian Pharmacopoeia Commission, Raj Najar, Ghaziabad, India; Dr R.P. Prasad, Director, Department of Drug Administration, Kathmandu, Nepal; Ms S.J. Putter, Walmer, Port Elizabeth, South Africa; Quality Systems and Standards – Group Quality, Novartis Pharma AG, Basel, Switzerland; Ms M.-L. Rabouhans, Chiswick, London, England; Dr M. Rafi, Assistant Manager (Regulatory Affairs), HLL Lifecare Limited, Belgaum, Karnataka, India; Dr A. Rajan, Director, Celogen Lifescience & Technologies, Mumbai, India; Mr T.L. Rauber, Specialist in Health Surveillance, Agência Nacional de Vigilância Sanitária Agency, Brasilia, Brazil; Mr N. Raw, Inspection, Enforcement and Standards Division, Medicines and Healthcare Products Regulatory Agency, London, England; Mr N. Rech, Brazilian Pharmacopoeia, Brazilian Health Surveillance Agency, Brasilia, DF, Brazil; Dr J.-L. Robert, Service du Contrôle des Médicaments, Laboratoire National de Santé, Luxembourg; Dr S. Rönninger, Global Quality Manager, F. Hoffmann-La Roche, Basel, Switzerland; Dr J. Isasi Rosas, CNCC, Chorrillos, Lima, Peru; Dr N. Ruangrittinon, Bureau of Drug and Narcotic Department of Medical Sciences, Ministry of Public Health, Nonthaburi, Thailand; Dr L.A. Sotelo Ruiz, Comisión de Control Analítico y Ampliación de Cobertura, Tlalpan, Distrito Federal, Mexico; Rusan Pharma Ltd, Selaqui, Dehradun, India; Dr E.I. Sakanyan, Director, Centre of the Pharmacopoeia and International Collaboration, Federal State Budgetary Institution, Scientific Centre for Expert Evaluation of Medicinal Products, Moscow, Russian Federation; Dr A.P. Sam, Merck, Netherlands; Dr C. Sánchez González, Adviser, Centre para el Control de Medicamentos, Equipos y Dispositivos Médicos, Havana, Cuba; Dr E. Moya Sánchez, Radiofarmaceutica-Evaluadora de Calidad, División de Química y Tecnología Farmacéutica, Departamento de Medicamentos de Uso Umano, Agencia Española de Medicamentos y Productos Sanitarios, Madrid, Spain; Sanofi Aventis, Antony, France; Dr G. Mendes Lima Santos, Coordinator of Therapeutic Equivalence, Brazilian Health Surveillance Agency, Brasilia, DF, Brazil; Dr L.M. Santos,

Scientific Liaison – International Health, The United States Pharmacopeia, Rockville, MD, USA; Dr T. Sasaki, Pharmaceutical and Medical Devices Agency, Tokyo, Japan; Dr J. Satanarayana, Matrix Laboratories, Secunderabad, India; Dr B. Schmauser, Bundesinstitut für Arzneimittel und Medizinprodukte, Bonn, Germany; Dr A. Schuchmann, Brazil; Dr I. Seekkuarachchi, Project Manager, Takeda Pharmaceutical Co., Osaka, Japan; Dr A. Seiter, Member, United States Pharmacopeia International Health Expert Committee, Rockville, MD, USA; Ms K. Sempf, Teaching Assistant, Institut für Pharmazeutische Technologie, Biozentrum, Johann Wolfgang Goethe-Universität, Frankfurt am Main, Germany; 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 R. Shaikh, Pakistan; Shasun Research Centre, Chennai, Tamil Nadu, India; Dr P.D. Sheth, Vice-President, International Pharmaceutical Federation, New Delhi, India; Ms R. Shimonovitz, Head of Inspectorates, Institute for Standardization and Control of Pharmaceuticals, Ministry of Health, Israel; Shin Poong Pharmaceutical Co., Ltd, Seoul, Republic of Korea: Dr P.G. Shrotriya, Ambli, Ahmedabad, India; Dr M. Sigonda, Director-General, Tanzania Food and Drugs Authority, Dar-es-Salaam, United Republic of Tanzania; Dr G.L. Singal, Drugs Controller of Haryana, Department of Health Services, Civil Dispensary, Panchkula, Haryana, India; Dr A.K. Singh, Daman, India; Dr G.N. Singh, Secretary-cum-Scientific Director, Government of India, Central Indian Pharmacopoeia Laboratory, Ministry of Health and Family Welfare, Raj Nagar, Ghaziabad, India; Dr S. Singh, Professor and Head, Department of Pharmaceutical Analysis, National Institute of Pharmaceutical Education and Research, Nagar, Punjab, India; Ms K. Sinivuo, Senior Researcher and Secretary, National Agency for Medicines, Helsinki, Finland; Dr L. Slamet, Jakarta Selatan, Indonesia; Mr D. Smith, Principal Scientist, SSI, Guateng, South Africa; Dr R. Smith, Wolfson Brain Imaging Centre, University of Cambridge, Cambridge, England; Dr N. Kumar Soam, Mankind Pharma Limited, Unit-II, Vill. Kishanpura, Paonta Sahib, Disst. Sirmour, India; Dr M. Da Luz Carvalho Soares, Brazilian Pharmacopeia Coordinator, Brazilian Health Surveillance Agency, Brasilia, Brazil¸ Dr C. Sokhan, Deputy Director, Department of Drug and Food, Phnom Penh, Cambodia; Dr A. Spreitzhofer, AGES PharmMed, Vienna, Austria; Mr K. Srinivas, Group Legal Counsel, Trimulgherry, Secunderabad, Andhra Pradesh, India; State Regulatory Agency for Medical Activities, Ministry of Labour, Health and Social Affairs, Tbilisi, Georgia; Dr J.A. Steichen, Manager, Regulatory and Quality Compliance Services, Safis Solutions, LLC, Indianapolis, IN, USA; Dr Y. Stewart, Scientific, Technical and Regulatory Affairs, European Federation of Pharmaceutical Industries and Associations, Brussels, Belgium; Dr L. Stoppa, Inspections & Certifications Department, Manufacturing Authorisation Office, Italian Medicines Agency, Rome, Italy; Dr R.W. Stringham, Scientific Director, Drug Access Team, Clinton

Health Access Initiative, Boston, MA, USA; Dr N. Sullivan, Director, Sensapharm, Sunderland, England; Dr D. Sun Cuilian, Senior Analytical Scientist, Pharmaceutical Laboratory, Pharmaceutical Division, Applied Sciences Group, Health Sciences Authority, Singapore; Mr Philip Sumner, Pfizer Global Engineering, New York, NY, USA; Dr S. Sur, Kiev, Ukraine; Dr E. Swanepoel, Head, Operations, Research Institute for Industrial Pharmacy, North-West University, Potchefstroom, South Africa; Professor M. Sznitowska, Department of Pharmaceutical Technology, Medical University of Gdansk, Gdansk, Poland; Dr D. Teitz, Manager, Bristol-Myers Squibb Company, New Brunswick, NJ, USA; Teva API Division, Petah Tiqva, Israel; Dr N. Thao, National Institute of Drug Quality Control, Hanoi, Viet Nam; Dr B.B. Thapa, Chief Drug Administrator, Department of Drug Administration, Ministry of Health and Population, Kathmandu, Nepal; Dr R. Torano, Pharmacopoeial Technical Expert, GlaxoSmithKline, Co. Durham, England; Dr P. Travis, Team Leader – Compendial Affairs Group, Pfizer Inc., Parsippany, NJ, USA; 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, ACT, 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 Richard Turner, British Pharmacopoeia Commission, Medicines and Healthcare Products Regulatory Agency, London, England; United States of America Food and Drug Administration, Center for Drug Evaluation and Research, Silver Spring, MD, USA; United States of America Food and Drug Administration, Office of Pediatric Therapeutics, Office of the Commissioner, Rockville, MD, USA; Ms E. Uramis, GMP Advisor, Oficina Central Polo Científico, Havana, Cuba; Dr A.R.T. Utami, National Agency for Drugs and Food Control, Jakarta Pusat, Indonesia; Validation and Qualification Department, Pharmaceutical Laboratory, Esteve, Spain; Mrs M. Vallender, Editor-in-Chief, British Pharmacopoeia Commission Secretariat, London, England; Mr M. van Bruggen, EU Liaison – Regulatory Intelligence, F. Hoffmann-La Roche, Basel, Switzerland; Mr F. Vandendriessche, Merck, Sharp and Dohme Europe, Brussels, Belgium; Dr J.E. van Oudtshoorn, Pretoria, South Africa; Dr A.J. van Zyl, Sea Point, Cape Town, South Africa; Dr A. Kumar Velumury, Cipla Ltd, New Delhi, India; Mr A. Vezali Montai, Specialist in Regulation and GMP, Agência Nacional de Vigilância, Brasília, Brazil; Mrs L. Vignoli, Regulatory Affairs, Pharmaceuticals and Cosmetics, Roquette Cie, Lestren, France; Dr O. del Rosario Villalva Rojas, Executive Director, Quality Control Laboratories, National Quality Control Center, National Institute of Health, Lima, Peru; Mr L. Viornery, Agence nationale de sécurité du médicament et des produits de santé, Saint Denis, France; Dr L. Virgili, USA; Mr J. Wang, Deputy Commissioner, Dalian Food and Drug Administration, Dalian, Liaoning, People's Republic of China; Mr P. Wang, Deputy Secretary-General, Chinese

Pharmacopoeia Commission, Beijing, People's Republic of China; Mrs T. Wang, Deputy Director, Shenzhen Municipal Institute for Drug Control, Shenzhen, 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 D. Waters, Acting Scientific Operations Advisor, Office of Laboratories and Scientific Services, Therapeutic Goods Administration, Woden, ACT, Australia; Dr W. Watson, Associate Manager, CMC Regulatory Affairs, Gilead Sciences International, Cambridge, England; Professor W. Wieniawski, Polish Pharmaceutical Society, Warsaw, Poland; Dr J. Welink, Medicines Evaluation Board, Utrecht, Netherlands; Dr S. Wolfgang, US Food and Drug Administration, Silver Spring, MD, USA; Mr E. Wondemagegnehu Biwota, Addis Ababa, Ethiopia; World Self-Medication Industry, Ferney-Voltaire, France; Dr B. Wright, Group Manager, GMP/GDP, North East Region, Medicines Inspectorate, Medicines and Healthcare Products Regulatory Agency, York, England; Professor Z.-Y. Yang, Guangzhou Municipal Institute for Drug Control, Guangzhou, People's Republic of China; Professor Z.-Y. Yang, Member, United States Pharmacopeia International Health Expert Committee, Rockville, MD, USA; Dr D. Yi, Scientist, US Pharmacopeia, Rockville, MD, USA; Dr H. Yusufu, National Agency for Food and Drug Administration and Control, Abuja, Nigeria; Dr M. Zahn, Keltern, Germany; Dr H. Zhang, GMP Department Head, Center for Certification & Evaluation, Shanghai Food and Drug Administration, Shanghai, People's Republic of China; Dr T. Zimmer, CD Safety, Quality & Environmental Protection, Boehringer Ingelheim, Ingelheim, Germany; Dr N. Zvolinska, Deputy Director, Pharmaceutical Department, State Pharmacological Centre, Ministry of Health, Kiev, Ukraine; Mrs M. Zweygarth, Geneva, Switzerland.

Annex 1

Procedure for the development of monographs and other texts for *The International Pharmacopoeia*

Introduction

The process described below is designed to ensure wide consultation and transparency during monograph development and that the adopted texts are made available in a timely manner.

Subject to the availability of the necessary resources, the Secretariat aims to publish adopted monographs or general texts for inclusion in *The International Pharmacopoeia* after every meeting of the World Health Organization (WHO) Expert Committee on Specifications for Pharmaceutical Preparations. The proposed changes to the process for the development of monographs reflect this new approach.

Monographs in *The International Pharmacopoeia* provide an important element of the quality dimension for the medicines (included on the basis of their efficacy and safety) in the WHO model lists of essential medicines and in WHO treatment guidelines.

Major WHO programmes such as the Prequalification Team – Medicines (funded by the Bill & Melinda Gates Foundation and UNITAID) and others funded or managed by partner organizations such as the United Nations Children's Fund and the Global Fund to Fight AIDS, Tuberculosis and Malaria, rely heavily upon the quality specifications set out in *The International Pharmacopoeia*.

The procedure for the development of monographs and other texts for *The International Pharmacopoeia* is outlined in the *Note* "schedule for the adoption process" outlining the development history of a draft monograph, which is included in each working document that is circulated for comment. The phases of the development procedure are as follows.

- Phase 1: Identify specific pharmaceutical products for which quality control (QC) specifications need to be developed, following confirmation by all WHO parties concerned (including the Department of Essential Medicines and Health Products, specific disease programmes and the Prequalification Team – Medicines). Establish whether monographs also need to be developed for the active pharmaceutical ingredients (APIs) contained in the pharmaceutical products identified. Update the current workplan of *The International Pharmacopoeia*.

- Phase 2: Obtain the contact details for the manufacturers of the selected APIs and pharmaceutical products, as applicable, in collaboration with all parties concerned.
- Phase 3: Contact manufacturers to ask for QC specifications and samples to be provided.
- Phase 4: Identify and contact QC laboratories to collaborate in the project (the number of laboratories contacted will depend on how many APIs and pharmaceutical products have been identified in Phase 1).
- Phase 5: Make arrangements with the collaborating laboratories for drafting the specifications and undertaking the necessary laboratory work.
- Phase 6: Search for information on QC specifications available in the public domain.
- Phase 7: Perform laboratory testing, development and validation, if needed, of QC specifications.
- Phase 8: Follow the WHO Expert Committee consultative process: mail draft specifications to the WHO Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations and to specialists; provide drafts on the website.
- Phase 9: Contact collaborating manufacturers to ascertain the availability of the respective substances to establish International Chemical Reference Substances (ICRS), as necessary.
- Phase 10: Support the WHO host organization (European Directorate for the Quality of Medicines & HealthCare, Council of Europe) responsible for the establishment of ICRS.
- Phase 11: Collect and collate the comments received during the global consultative process.
- Phase 12: Discuss comments received during the consultation process with contract laboratories, WHO collaborating centres, and if relevant with the ICRS host organization; conduct additional laboratory testing to add, verify and/or validate specifications.
- Phase 13: Discuss the comments received during the consultation process and test results received as feedback from the collaborating laboratories in an informal consultation with experts and specialists.
- Phase 14: Recirculate draft monograph widely for comments.
- Phase 15: Repeat Phases 8–15, until the agreed draft is suitable for adoption.

- Phase 16: Present the drafts to the WHO Expert Committee on Specifications for Pharmaceutical Preparations for possible formal adoption. If not adopted, repeat Phases 8–14 as often as necessary. If the draft is adopted, proceed to Phase 17.
- Phase 17: Incorporate all changes agreed during the discussion leading to adoption together with any editorial corrections.
- Phase 18: Where necessary, also take into account any further comments that may be received after the consultation or meeting, owing to comment deadlines for recirculated texts (Phase 12 and subsequent phases) falling shortly after the relevant consultation or meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations.
- Phase 19: In all cases, confirm the amended text by correspondence with the relevant experts and/or contract laboratory before making it available on *The International Pharmacopoeia* website or publishing it in a new edition or supplement of *The International Pharmacopoeia*.
- Phase 20: Include adopted text in *The International Pharmacopoeia*.

Annex 2

Updating mechanism for the section on radiopharmaceuticals in *The International Pharmacopoeia*

Introduction

In line with the proposal to revise the procedure for the development of monographs and other texts for *The International Pharmacopoeia*, similar changes have been made to the Updating mechanism for the section on radiopharmaceuticals in *The International Pharmacopoeia* (published as Annex 1 of the forty-eighth report of the World Health Organization (WHO) Expert Committee on Specifications for Pharmaceutical Preparations, WHO Technical Report Series, No. 986, 2014).

Subject to the availability of the necessary resources, the Secretariat aims to publish adopted monographs or general texts for inclusion in *The International Pharmacopoeia* (Ph.Int.) after each meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations. The changes to the process for updating the section on radiopharmaceuticals reflect this new approach.

Updating mechanism for the section on radiopharmaceuticals

Based on the official process for developing monographs for inclusion in the Ph.Int. as outlined in WHO Technical Report Series, No. 992, 2015 (Annex 1), the following process was elaborated to fulfil the specific purpose of development and updating of radiopharmaceutical specifications, a joint project carried out by the International Atomic Energy Agency (IAEA) and WHO, in close collaboration with the Council of Europe (CoE) and other parties wishing to join.

- Phase 1: Identify a specific radiopharmaceutical specification that needs to be revised and/or developed in a joint meeting of IAEA, WHO and CoE experts, following confirmation by IAEA and WHO. Identify radiopharmacy experts to review the material and suggest additions, deletions or modifications as appropriate. Include and update the current workplan on the Ph.Int. website accordingly.
- Phase 2: Identify the information on specifications available in the *European Pharmacopoeia*, other pharmacopoeias and nuclear medicine resources. Arrange for draft monographs to be prepared.

This work, supported by IAEA, will be undertaken by individual experts and consultants through research contracts and/or supporting consultancy

meetings. IAEA should invite suitable experts with pharmacopoeia experience to strengthen the process.

- Phase 3: Mail draft specifications to the IAEA Technical Officers and to members of the WHO Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations and to specialists; provide drafts on the Ph.Int. website in accordance with the WHO Expert Committee on Specifications for Pharmaceutical Preparations and IAEA consultative processes.
- Phase 4: WHO forwards any feedback received to IAEA for review by IAEA experts.
- Phase 5: If applicable, discuss comments received during the consultation process with IAEA specialists, contract laboratories and, if relevant, with the International Chemical Reference Standards (ICRS) custodian centre (this arrangement to be confirmed by the European Directorate for the Quality of Medicines & HealthCare (EDQM)) and a specialized agency, as necessary (to be further reviewed with IAEA and EDQM).
- Phase 6: Communicate the outcome of the IAEA review to WHO
- Phase 7: Recirculate draft monograph for comments as in Phase 3.
- Phase 8: Repeat Phases 3–7 until the agreed draft is suitable for adoption.
- Phase 9: Present the drafts to the WHO Expert Committee on Specifications for Pharmaceutical Preparations for possible formal adoption. If not adopted, repeat Phases 3–7 as often as necessary. If the draft is adopted, proceed to Phase 10.
- Phase 10: Incorporate all changes agreed during the discussion leading to adoption together with any editorial corrections.
- Phase 11: In all cases, confirm the amended text by correspondence with the IAEA experts before making it available on the Ph.Int. website or publishing it in a new edition or supplement of *The International Pharmacopoeia*.
- Phase 12: Include adopted text in *The International Pharmacopoeia*.

Annex 3

Guidelines on good manufacturing practices: validation, Appendix 7: non-sterile process validation[1]

Background

The appendices of the *Supplementary guidelines on good manufacturing practices: validation* currently comprise the following:

Appendix 1. Validation of heating, ventilation and air-conditioning systems
Appendix 2. Validation of water systems for pharmaceutical use
Appendix 3. Cleaning validation
Appendix 4. Analytical method validation
Appendix 5. Validation of computerized systems
Appendix 6. Qualification of systems and equipment
Appendix 7. Non-sterile process validation – **revised text reproduced in this Annex**

[1] Supplementary guidelines on good manufacturing practices: validation. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fortieth report. Geneva: World Health Organization; 2006: Annex 4 (WHO Technical Report Series, No. 937).

1. Background and scope

Further to the *Supplementary guidelines on good manufacturing practices: validation*, as published in the World Health Organization (WHO) Technical Report Series, No. 937 (*1*), additional guidelines to support current approaches to good manufacturing practices (GMP) are published here. These guidelines are intended to further support the concept of process validation linked to quality risk management (QRM) and quality by design principles as described by WHO and the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

These guidelines allow for different approaches to process validation. The principles described are mainly applicable to non-sterile finished pharmaceutical dosage forms. Similar approaches may be applicable to active pharmaceutical ingredients (APIs) and sterile products. (See also recommendations in WHO Technical Report Series, No. 957, Annex 2 (*2*) and WHO Technical Report Series, No. 961, Annex 6 (*3*).)

A risk-based and life-cycle approach to validation is recommended.

Thorough knowledge of product and process development studies; previous manufacturing experience; and QRM principles are essential in all approaches to process validation, as the focus is now on the life-cycle approach. The life-cycle approach links product and process development, validation of the commercial manufacturing process and maintaining the process in a state of control during routine commercial production.

The use of process analytical technology (PAT), which may include in-line, online and/or at-line controls and monitoring, is recommended to ensure that a process is in a state of control during manufacture.

2. Glossary

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

at-line. Measurement where the sample is removed, isolated from, and analysed in close proximity to the process stream.

concurrent validation. Validation carried out during routine production of products intended for sale in exceptional circumstances when data from replicate production runs are unavailable because only a limited number of batches have been produced, batches are produced infrequently or batches are produced by a validated process that has been modified. Individual batches may be evaluated and released before completion of the validation exercise, based on thorough monitoring and testing of the batches.

control strategy. A planned set of controls, derived from current product and process understanding that assures process performance and product quality. The controls can include parameters and attributes related to API and finished pharmaceutical product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications and the associated methods and frequency of monitoring and control.

continued process verification. Documented scientific evidence that the process remains in a state of control during commercial manufacture.

critical process parameter. A process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored and/or controlled to ensure the process produces the desired quality.

critical quality attribute. A physical, chemical, biological or microbiological property or characteristic of materials or products that should be within an appropriate limit, range or distribution to ensure the desired product quality.

in-line. Measurement where the sample is not removed from the process stream: can be invasive or non-invasive.

life cycle. All phases in the life of a product from the initial development through marketing until the product's discontinuation (ICH Q8 (*4*)).

matrix approach or bracketing. Bracketing is the assessment of a single parameter or variable by identifying the edge(s) of the range of conditions for the parameter or variable and assessing these during validation to span the possible range of that parameter or variable. For example, bracketing can be applied to process parameters, multiple pieces of identical equipment and/or different size considerations for the same product. The rationale for using this strategy should be justified, documented and approved.

Matrixing involves the assessment of the effect of more than one parameter or variable by using a multidimensional matrix to identify the "worst-case" or "extreme" conditions for a combination of parameters or variables. These conditions are used during validation of the process, rather than validating all possible combinations. Matrixing is typically used when there are significant similarities between products in a product family (e.g. the same product with different strengths in the manufacturing stage or different products with a similar container-closure in the packaging stage). The rationale for using this strategy should be justified, documented and approved.

The use of a matrix approach or bracketing design would not be considered appropriate if it is not possible to demonstrate that the extremes are limited to the batches, products, strengths, container sizes or fills. For those excluded from the exercise there should be no risk to process capability.

online. Measurement where the sample is diverted from the manufacturing process, and may be returned to the process stream.

pharmaceutical quality system. Management system to direct and control a pharmaceutical company with regard to quality.

process qualification. Process qualification combines the actual facility, utilities, equipment (each now qualified) and the trained personnel with the commercial manufacturing process, control procedures and components to produce commercial batches; confirms the process design and demonstrates that the commercial manufacturing process performs as expected.

process validation. The collection and evaluation of data, from the process design stage through to commercial production, which establishes scientific evidence that a process is capable of continuously delivering the finished pharmaceutical product meeting its predetermined specifications and quality attributes.

quality target product profile (QTPP). A prospectively documented summary of the quality characteristics of a finished pharmaceutical product (FPP) that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the FPP. The QTPP forms the basis of design for the development of the product and typically would include:

- intended use in clinical setting, route of administration, dosage form, delivery systems;
- dosage strength(s);
- container-closure system;
- therapeutic moiety release or delivery and attributes affecting pharmacokinetic characteristics (e.g. dissolution, aerodynamic performance) appropriate to the FPP dosage form being developed;
- FPP quality criteria (e.g. sterility, purity, stability and drug release) appropriate for the intended marketed product.

real-time release testing. The ability to evaluate and ensure the quality of in-process and/or final product based on process data, which typically include a valid combination of measured material attributes and process controls.

state of control. A condition in which the set of controls consistently provides assurance of continued process performance and product quality.

3. Introduction

Process validation data should be generated for all products to demonstrate the adequacy of the manufacturing process. The validation should be carried out in accordance with GMP and data should be held at the manufacturing location whenever possible and should be available for inspection.

Process validation is associated with the collection and evaluation of data throughout the life cycle of a product – from the process design stage through

to commercial production – and provides scientific evidence that a process is capable of consistently delivering a quality product.

A risk assessment approach should be followed to determine the scope and extent to which process(es) and starting material variability may affect product quality. The critical steps and critical process parameters should be identified, justified and documented and based on relevant studies carried out during the design stage and on process knowledge, according to the stages of the product life cycle. During process validation and qualification, the critical process parameters should be monitored.

It may be helpful to use a flow diagram depicting all the operations and controls in the process to be validated. When applying QRM to a given operation, the steps preceding and following that operation should also be considered. Amendments to the flow diagram may be made where appropriate, and should be recorded as part of the validation documentation.

Manufacturers should ensure that the principles of process validation described in these guidelines are implemented. These cover the phases of validation during process design, scale-up, qualification of premises, utilities and equipment and process performance qualification, and continuous process verification to ensure that the process remains in a state of control.

The objectives of process validation include ensuring that:

- the process design is evaluated to show that the process is reproducible, reliable and robust;
- the commercial manufacturing process is defined, monitored and controlled;
- assurance is gained on a continuous basis to show that the process remains in a state of control.

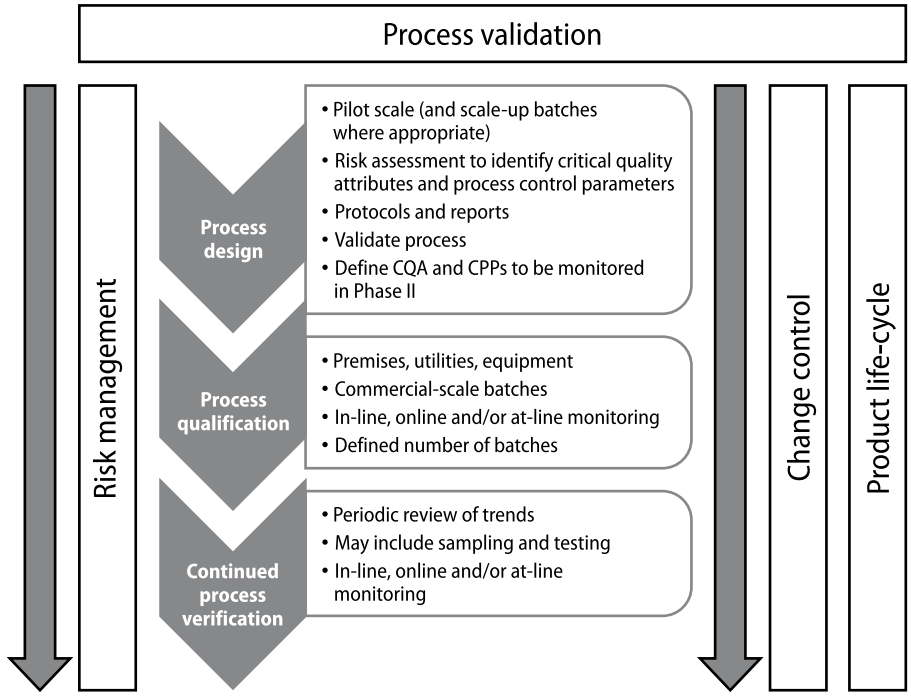
The validation should cover all manufactured strengths of a product and the extent of validation at each manufacturing site should be based on risk assessment. A matrix approach or bracketing may be acceptable and should also be based on appropriate risk assessment.

There are various approaches to process validation which include: traditional process validation (consisting of prospective and concurrent validation); process design followed by process qualification and continued process verification; or a combination of traditional process validation and the new approach described in these guidelines. Historical data should be evaluated in cases where there have been changes to the process.

Manufacturers should plan to implement the new approach to process validation, which covers process design, process qualification and continued process verification throughout the product life cycle.

Figure A3.1 shows the phases in the new approach to process validation.

Figure A3.1
Phases of process validation



CQA, critical quality attribute; CPPs, critical process parameters.

4. Process design

Under the life-cycle approach, the focus of validation is shifted from commercial-scale batches to development. Product development activities provide key inputs to the process design stage, such as the intended dosage form, the quality attributes and a general manufacturing pathway. Laboratory or pilot-scale models designed to be representative of the commercial process can be used to estimate variability.

Process design should normally cover design of experiments, process development, the manufacture of products for use in clinical trials, pilot-scale batches and technology transfer. Process design should be verified during product development.

Process design should cover aspects for the selection of materials, expected production variation, selection of production technology/process and qualification of the unitary processes that form the manufacturing process as a whole, selection of in-process controls, tests, inspection and its suitability for the control strategy.

As part of the process validation life cycle some process validation studies may be conducted on pilot-scale batches (corresponding to at least 10% or 100 000 units, whichever is the greater) of the production scale. Where the batch size is smaller and/or where the process is tailored to the geometry and capacity of specific equipment, it may be necessary to provide production-scale validation data.

Process qualification and continued process verification should always be linked to process design and be referenced to those specific batches used in studies critical to the development of the product, for example, the batch(es) used for pivotal clinical assessments (biobatch(es)), e.g. bioequivalence testing in the case of multisource products) and toxicological studies. The number of batches included in the process design stage of validation should be appropriate and sufficient to include (but not be limited to) the expected variations in starting materials, and confirm the suitability of the equipment and manufacturing technology. A statistically-based design of experiment approach can be helpful during this stage. Processes and results should be appropriately documented.

A development report and/or a technology transfer document, formally reviewed and approved by research and development personnel, and formally accepted by manufacturing, engineering and quality personnel, should be prepared. Such a document may include information such as QTPP, desired clinical performance, bills of materials, approved suppliers, finished product specifications and test methods, in-process testing specifications, equipment recommendations, master batch production records, master batch packaging records, stability reports, critical quality attributes, critical process parameters, batch comparisons, data on formulation batches, stability batches, clinical/biobatches and scale-up batches. These documents should be readily available to the manufacturing site.

The goal is to design a suitable process for routine commercial manufacturing that can consistently deliver a product that meets its required quality attributes.

5. Process qualification

Personnel, premises, utilities, support systems and equipment should be appropriately qualified before manufacturing processes are validated. Materials, environmental controls, measuring systems, apparatus and methods should be considered during validation. The stages of qualification of equipment may include design, installation, operation and performance of equipment (for more details see (WHO Technical Report Series, No. 937, Annex 4 (*1*)).

Traditionally, three batches have been considered the normal and acceptable number for process validation; however, the number of batches should

be justified and based on a risk assessment that includes, for example, variability of results from the process design stage, variability of materials, product history, where the product is being transferred from and where it will be produced. Manufacturers should define the stage at which the process is considered to be validated and the basis on which that decision was made. The decision should include a justification for the number of batches used based on the complexity and expected variability of the process and critical quality attributes (CQAs). Successful completion of process performance qualification stage of the life cycle is required for commercial distribution.

A risk assessment should be performed for the change from scale-up to commercial batch size. Process qualification should confirm that scale-up in batch size did not adversely affect the characteristics of the product and that a process that operates within the predefined specified parameters consistently produces a product which meets all its CQAs and control strategy requirements.

The process should be verified on commercial-scale batches prior to marketing of the product.

Extensive in-line and/or online and/or at-line controls may be used to monitor process performance and product quality in a timely manner. Results on relevant quality attributes of incoming materials or components, in-process material and finished products should be collected. This should include the verification of attributes, parameters and end-points and assessment of CQA and critical process parameter (CPP) trends. Process analytical technology applications and multivariate statistical process control can be used.

Manufacturers are encouraged to implement the new validation approach to ensure that processes are of known and acceptable capability. As full implementation of this approach may take time, the traditional approach of prospective validation and concurrent validation (used infrequently and restricted to the scenarios described in section 2) may be acceptable in the interim. A combination of elements of the traditional process validation approach and the new continuous process verification approach may be considered appropriate, subject to appropriate controls being in place, based on scientific justification and risk management principles.

Validation should be done in accordance with process validation protocols. A written protocol is essential for this stage of process validation. The protocol should include or reference at least the following elements:

- the manufacturing conditions including operating parameters, processing limits and component (raw material) inputs;
- the data to be collected and when and how they will be evaluated;
- the type of testing or monitoring to be performed (in-process, release, characterization) and acceptance criteria for each significant processing step;

- the scientifically justified sampling plan, including sampling points, number of samples and the frequency of sampling for each unit operation and attribute;
- the number of batches for which additional monitoring is proposed;
- status of the validation of analytical methods used in measuring the process, in-process materials and the product;
- a description of the statistical models or tools used;
- review and approval of the protocol by appropriate departments and the quality unit;
- a description of the process;
- details of the equipment and/or facilities to be used (including measuring or recording equipment) together with its calibration status;
- the variables to be monitored with appropriate justification;
- the samples to be taken – who, where, when, how, how many and how much (sample size);
- the product performance characteristics or attributes to be monitored, together with the test methods;
- the acceptable limits;
- personnel responsibilities;
- details of methods for recording and evaluating results, including statistical analysis.

Data should be collected and reviewed against predetermined acceptance criteria and fully documented in process validation reports. The report should reflect the validation protocol. A dual protocol report can be used; however, such reports must be designed to ensure clarity and sufficient space for recording of results. The outcome should confirm that the acceptance criteria have been met. Any deviations (including abandoned studies) should be explained and justified.

The planned commercial production and control records, which contain the operational limits and overall strategy for process control, should be carried forward to the next phase for confirmation.

6. Continued process verification

Manufacturers should monitor product quality of commercial batches after completion of process design and process qualification. This will provide evidence that a state of control is maintained throughout the product life cycle.

The scope and extent of process verification will be influenced by a number of factors including:

- prior development and knowledge of the manufacturing of similar products and/or processes;
- the extent of process understanding gained from development studies and commercial manufacturing experience;
- the complexity of the product and/or manufacturing process;
- the level of process automation and analytical technologies used;
- for legacy products, with reference to the product life-cycle process robustness and manufacturing history since the point of commercialization, as appropriate.

Manufacturers should describe the appropriateness and feasibility of the verification strategy (in the protocol) including the process parameters and material attributes that will be monitored as well as the validated analytical methods that will be employed.

Manufacturers should define:

- the type of testing or monitoring to be performed;
- the acceptance criteria to be applied;
- how the data will be evaluated and the actions to be taken.

Any statistical models or tools used should be described. If continuous processing is employed, the stage at which the commercial process is considered to be validated should be stated based on the complexity of the process, expected variability and manufacturing experience of the company.

Periods of enhanced sampling and monitoring may help to increase process understanding as part of continuous improvement. Information on process trends, such as the quality of incoming materials or components, in-process and finished product results and non-conformances should be collected and assessed to verify the validity of the original process validation or to identify changes required to the control strategy.

The scope of continued process verification should be reviewed periodically and modified if appropriate throughout the product life cycle.

7. Change management

Manufacturers should follow change control procedures when changes are planned to existing systems or processes.

The change control procedure and records should ensure that all aspects are thoroughly documented and approved, including regulatory approval where appropriate (variation).

Sufficient data should be generated to demonstrate that the revised process will result in a product of the desired quality, consistent with approved specifications.

Validation should be considered when changes to production and/or control procedures are planned. Based on risk assessment, changes that may require revalidation could include (but are not limited to):

- changes in the master formula, methods, starting material manufacturer, starting material manufacturing process, excipient manufacturer, excipient manufacturing process;
- changes in the equipment or instruments (e.g. addition of automatic detection systems);
- changes associated with equipment calibrations and the preventive maintenance carried out, which may impact the process;
- production area and support system changes (e.g. rearrangement of areas or a new water-treatment method);
- changes in the manufacturing process (e.g. mixing times, drying temperatures);
- transfer of processes to another site;
- unexpected changes (e.g. those observed during self-inspection or during routine analysis of process trend data);
- changes to standard operating procedures;
- changes to cleaning and hygiene programmes.

Depending upon the nature of the change being proposed the change control process should consider whether existing approved specifications will be adequate to control the product subsequent to the implementation of the change.

References

1. Supplementary guidelines on good manufacturing practices: validation. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fortieth report. Geneva: World Health Organization; 2006: Annex 4 (WHO Technical Report Series, No. 937).
2. WHO good manufacturing practices for active pharmaceutical ingredients. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-fourth report. Geneva: World Health Organization; 2010: Annex 2 (WHO Technical Report Series, No. 957).
3. WHO good manufacturing practices for sterile pharmaceutical products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-fifth report. Geneva: World Health Organization; 2011: Annex 6 (WHO Technical Report Series, No. 961).
4. ICH harmonised tripartite guideline, pharmaceutical development Q8(R2), Current Step 4 version, dated August 2009 (http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q8_R1/Step4/Q8_R2_Guideline.pdf, accessed 15 January 2014).

Further reading

Guideline on process validation. London: Committee for Medicinal Products for Human Use (CHMP), Committee for Medicinal Products for Veterinary Use (CVMP); 2012 (EMA/CHMP/CVMP/QWP/70278/2012-Rev1) (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/04/WC500125399.pdf, accessed 15 January 2015).

Guidance for industry. Process validation: general principles and practices. Silver Spring (MD): US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), Center for Veterinary Medicine (CVM); 2011 (Current Good Manufacturing Practices (CGMP) Revision 1).

ICH harmonised tripartite guideline, quality risk management, Q9, Current Step 4 version, dated 9 November 2005.

ICH harmonised tripartite guideline, pharmaceutical quality system, Q10, Current Step 4 version, dated 4 June 2008 (http://www.ich.org/products/guidelines/quality/article/quality-guidelines.html, accessed 15 January 2014).

Quality assurance of pharmaceuticals. WHO guidelines, related guidance and GXP training materials. Geneva: World Health Organization; 2014 (CD-ROM).

WHO good manufacturing practices: main principles for pharmaceutical products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-eighth report. Geneva: World Health Organization; 2014: Annex 2 (WHO Technical Report Series, No. 986 (http://www.who.int/medicines/areas/quality_safety/quality_assurance/GMPPharmaceuticalProductsMainPrinciplesTRS961Annex3.pdf, accessed 15 January 2015).

WHO guidelines on quality risk management. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-seventh report. Geneva: World Health Organization; 2013: Annex 2 (WHO Technical Report Series, No. 981).

Annex 4

General guidance on hold-time studies

1. Introduction and background

Manufacturers should ensure that the products that they manufacture are safe, effective and of the quality required for their intended use. Systems should be in place to ensure that pharmaceutical products are produced according to validated processes and to defined procedures. Manufacturing processes should be shown to be capable of consistently manufacturing pharmaceutical products that are of the required quality and that comply with their specifications.

Good manufacturing practices (GMP) require that arrangements should be made to ensure that the dispensed raw materials and packaging materials, intermediate products, bulk and finished products are stored under appropriate conditions. Storage arrangements should not have deleterious effects on the subsequent processing, stability, safety, efficacy or quality of starting materials, intermediate products and bulk products prior to final packing. Maximum acceptable holding periods should therefore be established to ensure that intermediates and bulk product can be held, pending the next processing step, without producing results outside the acceptance criteria for the quality of the material. Normally, intermediate and bulk products should not be stored beyond the established hold time.

The choice of maximum holding period should be supported by relevant data. Studies may extend beyond the chosen maximum but it is not necessary to extend testing to determine the extreme limits at which failure occurs.

2. Glossary

Some important terms used in these guidelines are defined below. They may have different meanings in other contexts.

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

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

3. Scope

These guidelines focus primarily on aspects that should be considered in the design of the hold-time studies during the manufacture of non-sterile solid dosage forms. Many of the principles described here also apply to other dosage forms such as liquids, creams and ointments. These guidelines do not cover aspects for hold times in cleaning validation, or the manufacturing of active pharmaceutical ingredients (APIs) or biologicals.

These guidelines are intended as a basic guide for use by manufacturers of pharmaceuticals and by GMP inspectors. This document is not intended to

prescribe a process for establishing hold times, but reflects aspects that should be considered in the design of the hold-time study.

Manufacturers should gather scientific and justifiable data to demonstrate that the dispensed raw materials and packaging materials, intermediate and bulk products:

- remain of appropriate quality before processing to the next stage;
- meet the acceptance criteria.

The finished product should meet the release specifications.

4. Aspects to be considered

Hold time can be considered as the established time period for which materials (dispensed raw materials, intermediates and bulk dosage form awaiting final packaging) may be held under specified conditions and will remain within the defined specifications.

Hold-time studies establish the time limits for holding the materials at different stages of production to ensure that the quality of the product does not produce results outside the acceptance criteria during the hold time. The design of the study should reflect the holding time at each stage.

Hold times should normally be determined prior to marketing of a product. The risk assessment of changes in processes, equipment, storage conditions, starting or packaging materials should include an assessment of whether further hold-time studies should be performed. Hold-time studies may be included during development on pilot-scale batches or during scale-up, and should be confirmed during process validation of commercial-scale processing (*1*). Further data can also be collected as part of an investigation of a deviation that occurred during manufacture.

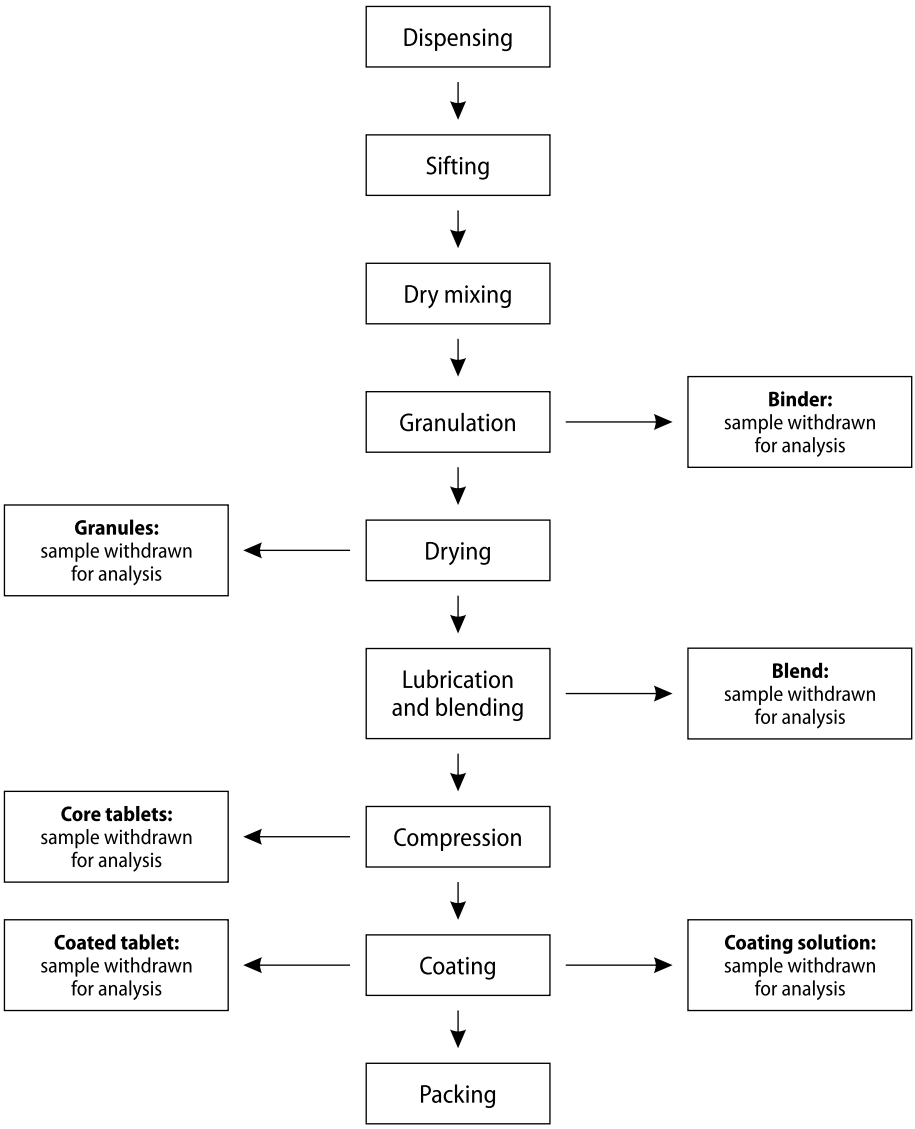
Manufacturers may use a flow chart to review the manufacturing procedure for a product and then break up the critical stages of the manufacturing process on the basis of the time period required for the particular storage and processing stages, typical pauses in the manufacturing campaign, and the potential impact of storage with reference to environmental and storage conditions. An example of a flow chart is given in Figure A4.1.

As an example, for oral tablets that are coated, the following stages may be considered:

- binder preparation to granulation – consider the granulate;
- wet granulation to drying – consider the dried granulate;
- dried granules to lubrication/blending – consider the lubricated blend;
- blend to compression;
- compression to coating – consider the tablet cores;

- coating solution to preparation – consider the coating solution;
- coating to packing – consider the bulk coated tablets;
- coating to packing in bulk;
- packing of bulk to finished packed dosage form.

Figure A4.1
Example of a flow chart for reviewing the manufacturing procedure



A written protocol, procedure or programme should be followed, which includes, for example, the activities to be performed, test parameters and acceptance criteria appropriate to the material or product under test. The protocol and report should generally include the following: a title; reference number; version; date; objective; scope; responsibility; procedure; description of the material or product; sample quantities; sampling method and criteria; acceptance limits; frequency of sampling; sampling locations; pooling of samples; storage conditions; type of container; methods of analysis; results; conclusion; recommendation; signatures; and dates. Acceptance criteria are typically more stringent than registered specifications, to provide assurance that the material is well within control. When setting the specifications, any known stability trends will need to be taken into account.

For certain products, microbiological aspects should also be considered and included where appropriate.

All testing of bulk intermediates and product should be performed using validated stability-indicating methods.

Typically one or more batches of a material, intermediate or product can be used for determining hold times. A risk-based approach can be used to determine the appropriate number of batches, considering the characteristics of the materials and other relevant aspects. A representative sample of the batch of material or product subjected to the hold-time study should be held for the defined hold period. The hold period for each category of material should be established on the basis of the study by keeping the material in either the original or simulated container used in production. The containers in which hold-time samples are stored should be the same pack as is used in production unless the pack is exceptionally large, in which case one that is equivalent (constructed of the same material and using the same closure system as the production packaging system) may be used. Reducing the size of container, when this is necessary for testing holding time, should be justified.

Where the headspace of containers used for bulk storage in manufacturing and/or quarantine is important, for example, because of a risk of potential degradation as a result of oxidation, then the hold-time studies should represent worst-case conditions. In such cases, the ratio of headspace to contents in the test containers should be at least as great as the maximum that is possible in routine production (especially taking into account part-filled containers). The environmental conditions for sample storage should be the same as those of the quarantine area/manufacture stage. A sampling plan should be established and followed for taking samples for testing at the different intervals. The amount of sample required should be calculated based on the batch size, the intervals, and the tests to be performed. Results should be compared with the initial baseline data on the control sample. Samples may be pooled for analysis where appropriate,

e.g. when the analysis of a composite sample will not lead to issues that would be detectable in single samples being missed when the samples are pooled.

Where appropriate, statistical analysis of the data generated should be performed to identify trends and to justify the limits and hold time set.

Batches of finished products made from intermediates or bulk products and subjected to a hold-time study should be considered for long-term stability testing if data show adverse trending or shifting patterns during the intermediate time points up to the end of the shelf-life. The shelf-life of the product – irrespective of hold times – should be measured from the time the active ingredients are mixed with other ingredients. Normally, intermediate and bulk products should not be stored beyond the established hold time.

Table A4.1 provides examples of stages, study times and tests that may be considered for a coated tablet.

Table A4.1
Examples of stages, study times and tests that may be considered, based on risk assessment and specific product needs

Stage	Test to be carried out as per specification	Study time
Binder preparation	Microbial test, appearance, viscosity, if applicable	Initial, 2, 5, 8 hours. In case of starch: initial, 2, 5 hours
Dispersions prepared (including granulation pastes, coating solution and coating suspension	Physical appearance, specific gravity, viscosity, sedimentation, pH, microbial test	Initial, 12, 24, 36, 48, 60, 72 hours
Granule	Description, assay, related substances, loss on drying, water content, particle size distribution, bulk density, tap density, angle of repose	Initial, 15th day, 30th day, 45th day
Blend	Microbial test, loss on drying, blend uniformity, particle size, bulk/tapped density	Initial, 15th day, 30th day, 45th day
Core tablets – uncoated (in bulk container)	Description, hardness, thickness, friability, disintegration, dissolution or dissolution profile, assay, degradation products/ related substance, uniformity of dosage units, microbial test	Initial, 30th day, 45th day, 60th day and 90th day

Table A4.1 *continued*

Stage	Test to be carried out as per specification	Study time
Coated tablets (in bulk container)	Description, appearance or visual examination, hardness, thickness, friability, disintegration, dissolution or dissolution profile, assay, degradation products/ related substance, moisture content, microbial test	Initial, 30th day, 45th day, 60th day and 90th day

Reference

1. Supplementary guidelines on GMP: validation, non-sterile process validation. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-ninth report. Geneva: World Health Organization; 2015: Annex 3 (WHO Technical Report Series, No. 992).

Annex 5

Technical supplements to Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products

(WHO Technical Report Series, No. 961, 2011), Annex 9

1. The technical supplement series

This series of technical supplements has been written to amplify the recommendations given in *Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products* (WHO Technical Report Series, No. 961, 2011, Annex 9).[1] This document sets out the principal requirements for the safe storage and distribution of time- and temperature-sensitive pharmaceutical products (TTSPPs).

The introduction to the guidance documents states that: "... supplementary materials will be developed to show how the requirements can practicably be achieved, particularly in resource constrained settings." The technical supplements, which make up this volume, are intended to provide this additional material; each one is linked back to a specific clause or clauses in the parent document. All 16 documents are written in a standard format and each contains a reference section with hyperlinks to relevant supporting materials. Most of these materials are available free online. References to print publications are minimized to avoid the difficulties associated with purchasing books and journals.

1.1 Topics covered

Table A5.1 lists the titles of the supplements and the model guidance sections to which each one refers.

Table A5.1
Titles of supplements and model guidance section to which each refers

Title	Section(s)
1. Selecting sites for storage facilities	Section 2
2. Design of storage facilities	Section 2 to 5
3. Estimating the capacity of storage facilities	Section 3.1 to 3.4
4. Security and fire protection in storage facilities	Section 3.7
5. Maintenance of storage facilities	Section 3.10
6. Temperature monitoring of storage areas	Section 4.5.2, 4.5.4
7. Qualification of temperature-controlled storage areas	Section 4.7

[1] http://www.who.int/medicines/areas/quality_safety/quality_assurance/ModelGuidanceForStorageTransportTRS961Annex9.pdf?ua=1.

Table A5.1 *continued*

Title	Section(s)
8. Temperature mapping of storage areas	Section 4.7
9. Refrigeration equipment maintenance	Section 4.9
10. Checking the accuracy of temperature control and monitoring devices	Section 4.10
11. Qualification of refrigerated road vehicles	Section 6.4, 6.5
12. Temperature-controlled transport operations by road and by air	Section 6.5, 9
13. Qualification of shipping containers	Section 6.8.1 to 6.8.4
14. Transport route profiling qualification	Section 6.8.3, 6.8.4
15. Temperature and humidity monitoring systems for transport operations	Section 6.5, 9
16. Environmental management of refrigerant gases and refrigeration equipment	Section 10.2

1.2 Target readership

The target readership for the model guidance, and for the technical supplements, includes regulators, logisticians and pharmaceutical professionals in industry, government and international agencies.

1.3 Document development and review process

The technical supplements have been written by specialist authors. All 16 supplements passed through the following editorial and public review process.

1. Each document was prepared over the course of several drafts in consultation with the series editor.
2. Acronyms and glossary definitions were harmonized throughout.
3. Public consultation drafts were posted on the WHO website in mid-2014. Review comments were received from a number of people and organizations.
4. Reviews were consolidated by the series editor and sent to the individual authors for initial comment.
5. Amended documents were prepared containing the consolidated comments categorized as "accepted", "rejected" and "for discussion".

These new drafts were sent back to the individual authors for further comment.

6. The series editor prepared final drafts based on the authors' responses and these drafts were checked, reviewed and signed off.
7. On the basis of these final comments, clean versions were prepared for review by the Expert Committee on Specifications for Pharmaceutical Preparations and by the Expert Committee on Biological Standardization.

On the following pages, the contents pages of the 16 technical supplements are reproduced. The full texts will be made available in electronic form on the CD-ROM of *Quality assurance of pharmaceuticals* (2015 and updates) and on the website.[2]

[2] http://www.who.int/medicines/areas/quality_safety/quality_assurance.

Supplement 1

Selecting sites for storage facilities

Technical supplement to

Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products (WHO Technical Report Series, No. 961, 2011), Annex 9.

Contents

Supplement 2

Design and procurement of storage facilities

Technical supplement to

Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products (WHO Technical Report Series, No. 961, 2011), Annex 9.

Contents

Supplement 3

Estimating the capacity of storage facilities

Technical supplement to

Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products (WHO Technical Report Series, No. 961, 2011), Annex 9.

Contents

Supplement 4

Building security and fire protection

Technical supplement to

Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products (WHO Technical Report Series, No. 961, 2011), Annex 9.

Contents

Supplement 5

Maintenance of storage facilities

Technical supplement to

Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products (WHO Technical Report Series, No. 961, 2011), Annex 9.

Contents

Supplement 6

Temperature and humidity monitoring systems for fixed storage areas

Technical supplement to

Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products (WHO Technical Report Series, No. 961, 2011), Annex 9.

Contents

Supplement 7

Qualification of temperature-controlled storage areas

Technical supplement to

Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products (WHO Technical Report Series, No. 961, 2011), Annex 9.

Contents

Supplement 8

Temperature mapping of storage areas

Technical supplement to

Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products (WHO Technical Report Series, No. 961, 2011), Annex 9.

Contents

Supplement 9

Maintenance of refrigeration equipment

Technical supplement to

Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products (WHO Technical Report Series, No. 961, 2011), Annex 9.

Contents

Supplement 10

Checking the accuracy of temperature control and monitoring devices

Technical supplement to

Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products (WHO Technical Report Series, No. 961, 2011), Annex 9.

Contents

Supplement 11

Qualification of refrigerated road vehicles

Technical supplement to

Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products (WHO Technical Report Series, No. 961, 2011), Annex 9.

Contents

Supplement 12

Temperature-controlled transport operations by road and by air

Technical supplement to

Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products (WHO Technical Report Series, No. 961, 2011), Annex 9.

Contents

Supplement 13

Qualification of shipping containers

Technical supplement to

Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products (WHO Technical Report Series, No. 961, 2011), Annex 9.

Contents

Supplement 14

Transport route profiling qualification

Technical supplement to

Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products (WHO Technical Report Series, No. 961, 2011), Annex 9.

Contents

Supplement 15

Temperature and humidity monitoring systems for transport operations

Technical supplement to

Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products (WHO Technical Report Series, No. 961, 2011), Annex 9.

Contents

Supplement 16

Environmental management of refrigeration equipment

Technical supplement to

Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products (WHO Technical Report Series, No. 961, 2011), Annex 9.

Contents

Annex 6

Recommendations for quality requirements when plant-derived artemisinin is used as a starting material in the production of antimalarial active pharmaceutical ingredients[1, 2]

[1] Originally published as Annex 6 in WHO Technical Report Series, No. 970, 2012: Recommendations for quality requirements when artemisinin is used as a starting material in the production of antimalarial active pharmaceutical ingredients.

[2] Also published in the "Supplementary information" section of *The International Pharmacopoeia*.

1. Introduction

The harmonized good manufacturing practices (GMP) (*1*, *2*) describe requirements for the production of active pharmaceutical ingredients (APIs). The applicability of these requirements begins with a defined starting material as follows:

> "An API starting material is a raw material, intermediate, or an API that is used in the production and that is incorporated as a significant structural fragment into the structure of the API. An API starting material can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement, or produced in-house. API starting materials normally have defined chemical properties and structure."

The focus of GMP for APIs is for field inspector use, rather than in applications for marketing authorization. It defines what may be considered as a starting material and provides guidance on where GMP is applied. The GMP guidelines do not apply to steps taken prior to the first introduction of the defined starting material. The manufacturer should designate and document the rationale for the point at which production of the API begins. For a synthesis process, this is known as the point at which the starting materials are entered into processes.

From a regulatory standpoint, the use of API starting materials marks the beginning of the detailed description of the process. The applicant for marketing authorization should propose and justify which substance should be considered as the API starting material, e.g. incorporated as a significant structural fragment into the structure of the active substance.

In practice the designation of a starting material may be difficult. The number of steps separating the starting material from the final API is an issue to be decided on a case-by-case basis, subject to the manufacturer's proposal and assessors' evaluation. Since a designated starting material may be obtained from multiple sources, it is necessary to have well-defined quality requirements to ensure that the APIs produced meet specifications. Establishing these requirements may involve a compromise between the desire for a pure starting material and the impact of this on cost of API production. Impurities can be tolerated in the starting material if the API manufacturing process has been shown to efficiently remove them. Redundant purification steps may reduce the yield of the final API and thus further increase its cost.

Artemisinin derivatives used in artemisinin-based combination therapy (ACT) are synthesized from artemisinin in one or two synthetic steps. Artemisinin is typically produced as an isolate from *Artemisia annua* L. Artemisinin complies with the definition of a "starting material", as defined above and described in certain national, regional and international guidelines. It is:

- a material used in the production of the API that is incorporated into the API as a significant structural element;
- commercially available;
- a compound whose name, chemical structure, chemical and physical characteristics, properties and impurity profile are well defined; and
- obtained by commonly known procedures.

As artemisinin is extracted from plant material and prior intermediates are thus not available, it is logical to designate this compound as the starting material for its derivatives.

A monograph appears in *The International Pharmacopoeia* for artemisinin used as an API. However, at present, artemisinin is mainly used as a starting material for artemisinin-derived APIs, and not as an API.

The level of quality of the artemisinin should be acceptable for its intended use as the starting material for the production of artemisinin derivatives. The specifications presented below take into account an acceptable balance of benefit versus risk between the quality of artemisinin used as a starting material and the quality required for artemisinin derivatives for use as APIs.

However, competent authorities may accept other impurity profile levels depending on the capability of the manufacturing process to lead to artemisinin-derived APIs at least compliant with the relevant monographs of *The International Pharmacopoeia*.

The purpose of this document is to offer a global approach to defining the level of quality requirements of artemisinin when used as a starting material for the production of its API derivatives used in ACT formulations. It does not apply to cases where artemisinin is used as an API. It is intended that the recommendations for requirements outlined in this document will apply to artemisinin extracted from *Artemisia annua* L. regardless of variations in agricultural environment or variations in extraction and purification steps. In addition, in order to ensure appropriate quality of the derived APIs, the manufacturer may add additional tests, such as tests for residual solvents and heavy metals, among others, and/or require tighter specifications. For artemisinin produced using synthetic chemical processes or by fermentation other requirements may be applicable.

2. Characterization of artemisinin

Provided that artemisinin intended for use as a starting material has been correctly identified, the major quality concern is the presence and level of impurities with the potential to affect the purity of subsequent API derivatives.

Impurities may originate from the plant extracts or arise from the purification process or from degradation. Different biosynthetic routes may be used at different stages in the plant's development and there are claims of variability between growing regions and environments. Despite a lack of consensus on a single biosynthetic route, several potential impurities are common to different routes. These include artemisinic acid, dihydroartemisinic acid, arteannuin B and artemisitene. Of these only artemisitene has been reported in isolated artemisinin. Recent work (*3*,*4*) has contributed towards a clearer understanding of existing impurities and their analysis.

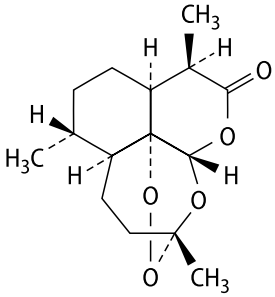
Examination of a wide variety of artemisinin samples produced in various regions indicated the consistent presence of two impurities: artemisitene and an artemisinin diastereomer with the stereochemistry inverted at C-9 (9-epi-artemisinin). A possible concern is that artemisinin impurities may not be detected with high-performance liquid chromatography analysis using ultraviolet detection, as used in the majority of testing laboratories. Recent work (*5*) using more sensitive general detection by mass spectrometry, however, demonstrated that additional impurities occur only in trace amounts. Isolated artemisinin is very stable. The potential degradants proposed on the basis of mechanistic studies do not occur at temperatures below 100 °C. These degradants are not observed in isolated artemisinin.

In the chemical conversion of the artemisinin starting material to its API derivatives (e.g. artesunate), the artemisinin diastereomeric impurity may be converted to a corresponding diastereomer at the C-9 position in the API derivative. However, these resulting diastereomers have not been observed in isolated APIs. The fate of artemisitene is less clear as it may be converted to the same intermediate as artemisinin.

Artemisitene-derived impurities have not been observed in artemisinin derivative APIs. Proposed limits for these impurities are based on historical results. The specifications for artemisinin starting material are based on experience with artemether and artesunate. For a new artemisinin-derived API the suitability of the specifications to control potential impurities arising during its synthesis should be demonstrated.

As the artemisinin extraction processes use solvents like dichloromethane, chloroform, ether and others, residual solvents should be indicated on the certificate of analysis issued by the supplier.

3. Tests and specifications for artemisinin starting material



$C_{15}H_{22}O_5$

Relative molecular mass: 282.3

Chemical name: (*3R*,5a*S*,6*R*,8a*S*,9*R*,12*S*,12a*R*)-3,6,9-trimethyloctahydro-3,12-epoxypyrano[4,3-*j*]-1,2-benzodioxepin-10(3*H*)-one; CAS Reg. No. 63968-64-9.

Description: Colourless needles or a white to almost white to slightly yellow, crystalline powder.

Category: Starting material for the synthesis of artemisinin derivative APIs.

Storage: Artemisinin should be kept in a well-closed container, protected from light.

Requirements

Artemisinin contains not less than 95.0% and not more than the equivalent of 102.0% of $C_{15}H_{22}O_5$ calculated with reference to the dried substance.

Identity tests

Carry out the examination as described under *1.7 Spectrophotometry in the infrared region* of *The International Pharmacopoeia* (*6*). The infrared absorption spectrum is concordant with the spectrum obtained from artemisinin RS or with the *reference spectrum* of artemisinin in *The International Pharmacopoeia*.

Specific optical rotation: Use a 10 mg/mL solution in dehydrated ethanol R; $[\alpha]_D^{20\,°C}$ = +75° to +78°

Loss on drying: Dry to constant mass at 80 °C; it loses not more than 10.0 mg/g.

Related substances

Note: It may be possible to justify other limits when artemisinin as a starting material is used in a particular synthesis and manufacturing process, by validation of the levels and limits of the impurities in the final API.

Carry out the test as described under *1.14.4 High performance liquid chromatography* of *The International Pharmacopoeia* (*6*). Use the chromatographic conditions and prepare solutions (1) and (2) as described below under "Assay". For solution (3) dilute 1 mL of solution (1) to 100 mL with the mobile phase.

Inject separately 20 µL of solutions (1), (2) and (3). Record the chromatograms for about 1.5 times the retention time of artemisinin. In the chromatogram obtained with solution (2) artemisitene (impurity A) is eluted at the relative retention of about 0.79 with reference to artemisinin (retention time about 10 minutes). The test is not valid unless the resolution between the peak of artemisitene and the peak of artemisinin is at least 4. The chromatogram obtained with solution (1) may show a peak due to impurity B eluting at a retention of about 0.85 with reference to artemisinin.

In the chromatogram obtained with solution (1):

- the area of any peak corresponding to impurity A, when multiplied by a correction factor of 0.027, is not greater than 0.15 times the area of the peak in the chromatogram obtained with solution (3) (0.2%);
- the area of any peak corresponding to impurity B is not greater than the area of the peak in the chromatogram obtained with solution (3) (1.0%);
- the area of any peak other than the principal peak is not greater than 0.5 times the area of the peak in the chromatogram obtained with solution (3) (0.5%);
- the sum of the corrected area of any peak corresponding to impurity A and the areas of all the peaks, apart from the principal peak, is not greater than 3 times the area of the peak obtained with solution (3) (3.0%). Disregard any peak with an area less than 0.1 times the area of the principal peak obtained with solution (3) (0.1%).

Assay

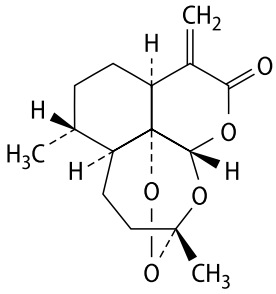
Carry out the test as described under *1.14.4 High performance liquid chromatography* of *The International Pharmacopoeia* (*6*), using a stainless steel column (15 cm × 4.6 mm) packed with 5 µm particles of silica gel, the surface of which has been modified with chemically-bonded octadecylsilyl groups. The mobile phase consists of a 50:50 mixture of acetonitrile and water, pumped at a flow rate of 1.0 mL/minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 210 nm.

Prepare the following solutions. For solution (1) prepare a 5.0 mg/mL solution of the test substance in the mobile phase. For solution (2) prepare a 5.0 mg/mL solution of artemisinin RS in the mobile phase.

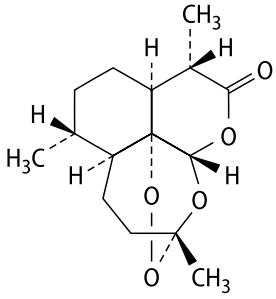
Inject separately 20 µL of solutions (1) and (2). Record the chromatograms for about 1.5 times the retention time of artemisinin. In the chromatogram obtained with solution (2) artemisitene (impurity A) is eluted at the relative retention of 0.79 with reference to artemisinin (retention time about 10 minutes). The test is not valid unless the resolution between the peak of artemisitene and the peak of artemisinin is at least 4. The chromatogram obtained with solution (1) may show a peak due to impurity B eluting at a retention of about 0.85 with reference to artemisinin.

Measure the areas of the peak responses obtained in the chromatograms from solutions (1) and (2) and calculate the content of $C_{15}H_{22}O_5$ with reference to the dried substance.

Impurities



(*3R*,5a*S*,6*R*,8a*S*,12*S*,12a*R*)-3,6-dimethyl-9-methylideneoctahydro-3,12-epoxypyrano[4,3-*j*]-1,2-benzodioxepin-10(*3H*)-one (artemisitene)



(*3R*,5a*S*,6*R*,8a*S*,9*S*,12*S*,12a*R*)-3,6,9-trimethyloctahydro-3,12-epoxypyrano[4,3-*j*]-1,2-benzodioxepin-10(3*H*)-one (9-*epi*-artemisinin)

References

1. WHO good manufacturing practices for active pharmaceutical ingredients. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report*. Geneva, World Health Organization, 2010, Annex 2 (WHO Technical Report Series, No. 957).
2. *International Conference on Harmonisation (ICH) Topic Q7: Note for guidance on good manufacturing practice for active pharmaceutical ingredients*. London, EMEA, 2006 (CPMP/ICH/4106/00); http://www.ema.europa.eu/pdfs/human/ich/410600en.pdf.
3. Lapkin AA et al. Development of HPLC analytical protocols for quantification of artemisinin in biomass and extracts. *Journal of Pharmaceutical and Biomedical Analysis*, 2009, 49:908–915.
4. Stringham RW et al. High performance liquid chromatographic evaluation of artemisinin, raw material in the synthesis of artesunate and artemether. *Journal of Chromatography A*, 2009, 1216:8918–8925.
5. Stringham RW et al. Verification of the identities of impurities in artemisinin and correction of their elution order in high performance liquid chromatography. *Journal of Chromatography A*, 2011, 1218:6838–6842.
6. *The International Pharmacopoeia*, 4th Edition, Vol. 1: General notices; monographs for pharmaceutical substances (A–O) and Vol. 2: Monographs for pharmaceutical substances (P–Z); monographs for dosage forms and radiopharmaceutical preparations; methods of analysis; reagents. Geneva, World Health Organization, 2006, also available in CD-ROM format and online:
   - *The International Pharmacopoeia*, 4th Edition, First Supplement. Geneva, World Health Organization, 2008; http://apps.who.int/phint/en/p/docf/, also available in CD-ROM format;
   - *The International Pharmacopoeia*, 4th Edition, First, Second, Third and Fourth Supplements, 2014, available on CD-ROM.

Annex 7

Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability[1]

[1] Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. In: WHO Expert Committee on Specifications for Pharmaceutical Products: fortieth report. World Health Organization: Geneva; 2006: Annex 7 (WHO Technical Report Series, No. 937).

1. Introduction

These guidelines provide recommendations to regulatory authorities when defining requirements for approval of multisource (generic) pharmaceutical products in their respective countries. The guidance provides appropriate in vivo and in vitro requirements to assure interchangeability of the multisource product without compromising the safety, quality and efficacy of the pharmaceutical product.

National regulatory authorities (NRAs) should ensure that all pharmaceutical products subject to their control conform to acceptable standards of safety, efficacy and quality, and that all premises and practices employed in the manufacture, storage and distribution of these products comply with good manufacturing practice (GMP) standards so as to ensure the continued conformity of the products with these requirements until they are delivered to the end-user.

All pharmaceutical products, including multisource products, should be used in a country only after approval by the national or regional authority. Regulatory authorities should require the documentation of a multisource pharmaceutical product to meet the following:

- GMP;
- QC specifications;
- pharmaceutical product interchangeability.

Multisource pharmaceutical products need to conform to the same appropriate standards of quality, efficacy and safety as those required of the innovator's (comparator) product. In addition, reasonable assurance must be provided that the multisource product is therapeutically equivalent and interchangeable with the comparator product. For some classes of products, including – most evidently – aqueous parenteral solutions, interchangeability is adequately assured by assessment of the composition, implementation of GMP and evidence of conformity with appropriate specifications including relevant pharmacopoeial specifications. For a wide range of pharmaceutical products the concepts and approaches covered by these guidelines will enable NRAs to decide whether a given multisource product can be approved. This guidance is generally applicable to orally-administered multisource products as well as to non-orally-administered pharmaceutical products for which systemic exposure measures are suitable for documenting bioequivalence (e.g. transdermal delivery systems and certain parenteral, rectal and nasal pharmaceutical products). Some information applicable for locally-acting products is also provided in this document. For other classes of products, including many biologicals such as vaccines, animal sera, products derived from human blood and plasma and products manufactured

by biotechnology, as well as non-biological complex products, the concept of interchangeability raises issues that are beyond the scope of this document and these products are consequently excluded from consideration.

To ensure interchangeability, the multisource product must be therapeutically equivalent to the comparator product. Types of in vivo equivalence studies include comparative pharmacokinetic studies, comparative pharmacodynamic studies and comparative clinical studies.

Direct demonstration of therapeutic equivalence through a comparative clinical trial is rarely a practical choice as these trials tend to be insensitive to differences in formulation and usually require a very large number of patients. Further, such studies in humans can be financially daunting, are often unnecessary and may be unethical. For these reasons the science of bioequivalence testing has been developed over the past 50 years. According to the tenets of this science, therapeutic equivalence can be assured when the multisource product is both pharmaceutically equivalent and bioequivalent.

Assuming that, in the same subject, an essentially similar plasma concentration time-course will result in essentially similar concentrations at the site(s) of action and thus in an essentially similar therapeutic outcome, pharmacokinetic data may be used instead of therapeutic results. Further, in selected cases, in vitro comparison of the dissolution profiles of the multisource product with those of the comparator product may be sufficient to provide an indication of equivalence.

It should be noted that interchangeability includes the equivalence of the dosage form as well as of the indications and instructions for use. Alternative approaches to the principles and practices described in this document may be acceptable provided they are supported by adequate scientific justification. These guidelines should be interpreted and applied without prejudice to obligations incurred through the existing international Agreement on Trade-Related Aspects of Intellectual Property Rights (*1*).

2. Glossary

Some important terms used in these guidelines are defined below. They may have different meanings in other contexts.

bioavailability. The rate and extent to which the active moiety is absorbed from a pharmaceutical dosage form and becomes available at the site(s) of action. Reliable measurements of active pharmaceutical ingredient (API) concentrations at the site(s) of action are usually not possible. The substance in the systemic circulation, however, is considered to be in equilibrium with the substance at the site(s) of action. Bioavailability can therefore be defined as the rate and extent to which the API or active moiety is absorbed from a pharmaceutical dosage form

and becomes available in the systemic circulation. Based on pharmacokinetic and clinical considerations it is generally accepted that in the same subject an essentially similar plasma concentration time-course will result in an essentially similar concentration time-course at the site(s) of action.

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

biological pharmaceutical product.[2] A biological pharmaceutical product is a synonym for biological product or biological (as described in the reports of the Expert Committee on Biological Standardization in the World Health Organization (WHO) Technical Report Series). The definition of a pharmaceutical substance used in treatment, prevention or diagnosis as a "biological" has been variously based on criteria related to its source, its amenability to characterization by physicochemical means alone, the requirement for biological assays or arbitrary systems of classification applied by regulatory authorities. For the purposes of WHO, including the current document, the list of substances considered to be biologicals is derived from their earlier definition as "substances which cannot be fully characterized by physicochemical means alone and which therefore require the use of some form of bioassay". However, developments in the utility and applicability of physicochemical analytical methods, improved control of biological and biotechnology-based production methods and an increased applicability of chemical synthesis to larger molecules, have made it effectively impossible to base a definition of a biological on any single criterion related to methods of analysis, source or method of production. Nevertheless many biologicals are produced using in vitro culture systems.

Biopharmaceutics Classification System. The Biopharmaceutics Classification System (BCS) is a scientific framework for classifying APIs based upon their aqueous solubility and intestinal permeability. When combined with the dissolution of the pharmaceutical product and the critical examination of the excipients of the pharmaceutical product, the BCS takes into account the major factors that govern the rate and extent of API absorption (exposure) from immediate-release oral solid dosage forms: excipient composition, dissolution, solubility and intestinal permeability.

[2] Developers of such pharmaceutical products that do not fit the definition of biological pharmaceutical products provided in this document should consult the relevant NRA for product classification and the licensing application pathway.

biowaiver. The term biowaiver is applied to a regulatory pharmaceutical product approval process when the dossier (application) is approved based on evidence of equivalence other than through in vivo equivalence testing.

comparator product. The comparator product is a pharmaceutical product with which the multisource product is intended to be interchangeable in clinical practice. The comparator product will normally be the innovator product for which efficacy, safety and quality have been established. If the innovator product is no longer marketed in the jurisdiction, the selection principle as described in *Guidance on the selection of comparator pharmaceutical products for equivalence assessment of interchangeable multisource (generic) products* (WHO Technical Report Series, No. 992, Annex 8 (2015)) should be used to identify a suitable alternative comparator product.

dosage form. The form of the completed pharmaceutical product, e.g. tablet, capsule, elixir or suppository.

equivalence requirements. In vivo and/or in vitro testing requirements for approval of a multisource pharmaceutical product for a marketing authorization.

equivalence test. A test that determines the equivalence between the multisource product and the comparator product using in vivo and/or in vitro approaches.

fixed-dose combination. A combination of two or more APIs in a fixed ratio of doses. This term is used generically to mean a particular combination of APIs irrespective of the formulation or brand. It may be administered as single-entity products given concurrently or as a finished pharmaceutical product (FPP).

fixed-dose combination finished pharmaceutical product. An FPP that contains two or more APIs.

generic product. *See* multisource pharmaceutical products.

innovator pharmaceutical product. Generally the innovator pharmaceutical product is that which was first authorized for marketing, on the basis of complete documentation of quality, safety and efficacy.

interchangeable pharmaceutical product. An interchangeable pharmaceutical product is one which is therapeutically equivalent to a comparator product and can be interchanged with the comparator in clinical practice.

in vitro equivalence dissolution test. An in vitro equivalence test is a dissolution test that includes comparison of the dissolution profile between the multisource product and the comparator product, typically in at least three media: pH 1.2, pH 4.5 and pH 6.8 buffer solutions.

in vitro quality control dissolution test. A dissolution test procedure identified in the pharmacopoeia for routine QC of product batches, generally a one time-point dissolution test for immediate-release products and a three or more time-points dissolution test for modified-release products.

multisource pharmaceutical products. Pharmaceutically equivalent or pharmaceutically alternative products that may or may not be therapeutically

equivalent. Multisource pharmaceutical products that are therapeutically equivalent are interchangeable.

non-biological. Not involving or derived from biology or living organisms.

pharmaceutical alternatives. Products are pharmaceutical alternative(s) if they contain the same active pharmaceutical moiety or moieties but differ in dosage form (e.g. tablets versus capsules), strength, and/or chemical form (e.g. different salts or different esters). Pharmaceutical alternatives deliver the same active moiety by the same route of administration but are otherwise not pharmaceutically equivalent. They may or may not be bioequivalent or therapeutically equivalent to the comparator product.

pharmaceutical equivalence. Products are pharmaceutical equivalents if they contain the same molar amount of the same APIs in the same dosage form, if they meet comparable standards and if they are intended to be administered by the same route. Pharmaceutical equivalence does not necessarily imply therapeutic equivalence, as differences in the API solid state properties, the excipients and/or the manufacturing process and other variables can lead to differences in product performance.

quantitatively similar amounts (concentrations) of excipients. The relative amount of excipient present in two solid oral FPPs is considered to be quantitatively similar if the differences in amount fall within the limits shown in Table A7.1.

Table A7.1

Limits on the relative difference in the amount of excipient in two solid oral finished pharmaceutical products for the products to be considered quantitatively similar in that excipient

Excipient type	Percentage difference (w/w) out of total product (core) weight
Filler	5.0
Disintegrant	
Starch	3.0
Other	1.0
Binder	0.5
Lubricant	
Calcium or magnesium stearate	0.25
Other	1.0
Glidant	
Talc	1.0
Other	0.1

If an excipient serves multiple functions (e.g. microcrystalline cellulose as a filler and as a disintegrant) then the most conservative recommended range should be applied (e.g. ± 1.0% for microcrystalline cellulose should be applied in this example). The relative concentration of an excipient present in two aqueous solution FPPs is considered to be similar if the difference is ≤ 10%.

therapeutic equivalence. Two pharmaceutical products are considered to be therapeutically equivalent if they are pharmaceutically equivalent or pharmaceutical alternatives and, after administration in the same molar dose, their effects, with respect to both efficacy and safety, are essentially the same when administered to patients by the same route under the conditions specified in the labelling. This can be demonstrated by appropriate equivalence studies, such as pharmacokinetic, pharmacodynamic, clinical or in vitro studies.

3. Documentation of equivalence for marketing authorization

Multisource pharmaceutical products must be shown, either directly or indirectly, to be therapeutically equivalent to the comparator product if they are to be considered interchangeable. Suitable test methods to assess equivalence are:

- comparative pharmacokinetic studies in humans, in which the API and/or its metabolite(s) are measured as a function of time in an accessible biological fluid such as blood, plasma, serum or urine to obtain pharmacokinetic measures, such as AUC and C_{max} that reflect the systemic exposure;
- comparative pharmacodynamic studies in humans;
- comparative clinical trials;
- comparative in vitro tests.

The applicability of each of these four methods is discussed below. Detailed information is provided on conducting an assessment of equivalence studies using pharmacokinetic measurements and in vitro methods, which are currently the methods most often used to document equivalence for most orally-administered pharmaceutical products for systemic exposure.

Acceptance of any test procedure in the documentation of equivalence between two pharmaceutical products by an NRA depends on many factors, including the characteristics of the API and the pharmaceutical product. Where an API produces measurable concentrations in an accessible biological fluid, such as plasma, comparative pharmacokinetic studies can be performed. This type of study is considered to be the gold standard in equivalence testing; however, where

appropriate, in vitro testing, e.g. BCS-based biowaivers for immediate-release pharmaceutical products, can also assure equivalence between the multisource product and the comparator product (see sections 5 and 10). Where an API does not produce measurable concentrations in an accessible biological fluid and a BCS-based biowaiver is not an option, comparative pharmacodynamics studies may be an alternative method for documenting equivalence. Further, in certain cases when it is not possible to assess equivalence through other methods, comparative clinical trials may be considered appropriate.

The criteria that indicate when equivalence studies are necessary are discussed in sections 4 and 5 of these guidelines.

4. When equivalence studies are not necessary

In the following circumstances, multisource pharmaceutical products are considered to be equivalent without the need for further documentation:

(a) when the pharmaceutical product is to be administered parenterally (e.g. intravenously, subcutaneously or intramuscularly) as an aqueous solution containing the same API in the same molar concentration as the comparator product and the same or similar excipients in comparable concentrations to those in the comparator product. Certain excipients (e.g. buffer, preservative and antioxidant) may be different provided it can be shown that the change(s) in these excipients would not affect the safety and/or efficacy of the pharmaceutical product. The same principles are applicable for parenteral oily solutions but, in this case, the use of the same oily vehicle is essential. Similarly, for micellar solutions, solutions containing complexing agents or solutions containing co-solvents of the same qualitative and quantitative composition of the functional excipients are necessary in order to waive equivalence studies and the change of other excipients should be critically reviewed;

(b) when pharmaceutically-equivalent products are solutions for oral use (e.g. syrups, elixirs and tinctures), contain the API in the same molar concentration as the comparator product, contain the same functional excipients in similar concentrations (if the API is BCS Class I) and the same excipients in similar concentrations (for APIs from other BCS classes);

(c) when pharmaceutically-equivalent products are in the form of powders for reconstitution as an aqueous solution and the resultant solution meets either criterion (a) or criterion (b) above;

(d) when pharmaceutically-equivalent products are gases;

(e) when pharmaceutically-equivalent products are otic or ophthalmic products prepared as aqueous solutions and contain the same API(s) in the same molar concentration and the same excipients in similar concentrations. Certain excipients (e.g. preservative, buffer, substance to adjust tonicity or thickening agent) may be different provided their use is not expected to affect bioavailability, safety and/or efficacy of the product;

(f) when pharmaceutically-equivalent products are topical products prepared as aqueous solutions and contain the same API(s) in the same molar concentration and the same excipients in similar concentrations (note that a waiver would not apply to other topical dosage forms like gels, emulsions or suspensions, but might be applicable to oily solutions if the vehicle composition is sufficiently similar);

(g) when pharmaceutically-equivalent products are aqueous solutions for nebulization or nasal drops, intended to be administered with essentially the same device, contain the same API(s) in the same concentration and contain the same excipients in similar concentrations (note that this waiver does not apply to other dosage forms like suspensions for nebulization, nasal drops where the API is in suspension, nasal sprays in solution or suspension, dry powder inhalers or pressurized metered dose inhalers in solution or suspensions). The pharmaceutical product may include different excipients provided their use is not expected to affect bioavailability, safety and/or efficacy of the product.

For situations (b), (c), (e), (f) and (g) above it is incumbent upon the applicant to demonstrate that the excipients in the pharmaceutically-equivalent product are the same and that they are in concentrations similar to those in the comparator product or, where applicable (i.e. (a), (e) and (g)), that their use is not expected to affect the bioavailability, safety and/or efficacy of the product. In the event that the applicant cannot provide this information and the NRA does not have access to the relevant data, it is incumbent upon the applicant to perform appropriate studies to demonstrate that differences in excipients or devices do not affect product performance.

5. When equivalence studies are necessary and types of study required

Except for the cases discussed in section 4, these guidelines recommend that documentation of equivalence with the comparator product be required by registration authorities for a multisource pharmaceutical product. Studies must be carried out using the product intended for marketing (see also section 7.3).

5.1 In vivo studies

For certain APIs and dosage forms, in vivo documentation of equivalence, through either a pharmacokinetic comparative bioavailability (bioequivalence) study, a comparative pharmacodynamic study or a comparative clinical trial, is regarded as especially important. In vivo documentation of equivalence is necessary when there is a risk that possible differences in bioavailability may result in therapeutic inequivalence (*2*). Examples are listed below.

(a) oral, immediate-release pharmaceutical products with systemic action, except for the conditions outlined in section 10;

(b) non-oral, non-parenteral pharmaceutical products designed to act systemically (such as transdermal patches, suppositories, nicotine chewing gum, testosterone gel and skin-inserted contraceptives);

(c) modified-release pharmaceutical products designed to act systemically, except for the conditions outlined in section 10;

(d) fixed-dose combination (FDC) products with systemic action, where at least one of the APIs requires an in vivo study (*3*);

(e) non-solution pharmaceutical products, which are for non-systemic use (e.g. for oral, nasal, ocular, dermal, rectal or vaginal application) and are intended to act without systemic absorption.

In the case of non-solution pharmaceutical products for non-systemic use, the equivalence is established through, e.g. comparative clinical or pharmacodynamic studies, local availability studies and/or in vitro studies. In certain cases, measurement of the concentration of the API may still be required for safety reasons, i.e. in order to assess unintended systemic absorption.

5.2 In vitro studies

For certain APIs and dosage forms, in vitro documentation of equivalence may be appropriate. In vitro approaches for systemically-acting oral products are discussed in section 10.

6. In vivo equivalence studies in humans

6.1 General considerations

6.1.1 Provisions for studies in humans

Pharmacokinetic, pharmacodynamic and comparative clinical trials are clinical studies and should therefore be carried out in accordance with the provision and prerequisites for a clinical study, as outlined in the WHO *Guidelines for good clinical practice for trials on pharmaceutical products* (*4*) and with WHO good

laboratory practices (*5*). Additional guidance for organizations performing in vivo equivalence studies is available from WHO (*6*).

All research involving human subjects should be conducted in accordance with the ethical principles contained in the current version of the Declaration of Helsinki, including respect for persons, beneficence ("maximize benefits and minimize harms and wrongs") and non-maleficence ("do no harm"), as defined by the International Ethical Guidelines for Biomedical Research Involving Human Subjects issued by the Council for International Organizations of Medical Sciences (CIOMS), or laws and regulations of the country in which the research is conducted, whichever represents the greater protection for study subjects.

6.1.2 Justification of human bioequivalence studies

Most pharmacokinetic and pharmacodynamic equivalence studies are non-therapeutic studies in which no direct clinical benefit accrues to the subject.

It is important for anyone preparing a trial of a medicinal product in humans that the specific aims, problems and risks or benefits of the proposed human study be thoroughly considered and that the chosen design be scientifically sound and ethically justified. It is assumed that people involved in the planning of a study are familiar with the pharmacokinetic theories underlying bioavailability and bioequivalence studies. The overall design of the bioequivalence study should be based on the knowledge of the pharmacokinetics, pharmacodynamics and therapeutics of the API. Information about manufacturing procedures and data from tests performed on the product batch to be used in the study should establish that the product under investigation is of suitable quality.

6.1.3 Selection of investigators

The investigator(s) should have the appropriate expertise, qualifications and competence to undertake the proposed study. Prior to the trial, the investigator(s) and the sponsor should draw up an agreement on the protocol, monitoring, auditing, standard operating procedures (SOPs) and the allocation of trial-related responsibilities. The identity and duties of the individuals responsible for the study and safety of the subjects participating in the study must be specified. The logistics and premises of the trial site should comply with requirements for the safe and efficient conduct of the trial.

6.1.4 Study protocol

A bioequivalence study should be carried out in accordance with a protocol agreed upon and signed by the investigator and the sponsor. The protocol and its attachments and/or appendices should state the aim of the study and the procedures to be used, the reasons for proposing the study to be undertaken in humans, the nature and degree of any known risks, assessment methodology,

criteria for acceptance of bioequivalence, the groups from which it is proposed that trial subjects be selected and the means for ensuring that they are adequately informed before they give their consent. The investigator is responsible for ensuring that the protocol is strictly followed. Any change(s) required must be agreed on and signed by the investigator and sponsor and appended as amendments, except when necessary to eliminate an apparent immediate hazard or danger to a trial subject.

The protocol, attachments and appendices should be scientifically and ethically appraised by one or, if required by local laws and regulations, more review bodies (e.g. institutional review board, peer review committee, ethics committee or NRA) constituted appropriately for these purposes and independent of the investigator(s) and sponsor.

The signed and dated study protocol should be approved by the NRA before commencing the study, if required by national and regional laws and regulations. The study report forms an integral part of the registration dossier of the multisource product in order to obtain the marketing authorization for the multisource product.

7. Pharmacokinetic comparative bioavailability (bioequivalence) studies in humans

7.1 Design of pharmacokinetic studies

Bioequivalence studies are designed to compare the in vivo performance of a multisource product with that of a comparator product. Such studies on products designed to deliver the API for systemic exposure serve two purposes:

- as a surrogate for clinical evidence of the safety and efficacy of the multisource product;
- as an in vivo measure of pharmaceutical quality.

The design of the study should maximize the sensitivity to detect any difference between products, minimize the variability that is not caused by formulation effects and eliminate bias as far as possible. Test conditions should reduce variability within and between subjects. In general, for a bioequivalence study involving a multisource product and a comparator product, a randomized, two-period, two-sequence, single-dose, cross-over study conducted with healthy volunteers is the preferred study design. In this design each subject is given the multisource product and the comparator product in randomized order. An adequate wash-out period should follow the administration of each product.

It should be noted, however, that under certain circumstances an alternative, well-established and statistically appropriate study design may be more suitable.

7.1.1 Alternative study designs for studies in patients

For APIs that are very potent or too toxic to administer in the highest strength to healthy volunteers (e.g. because of the potential for serious adverse events or because the trial necessitates a high dose), it is recommended that the study be conducted using the API at a lower strength in healthy volunteers. For APIs that show unacceptable pharmacological effects in healthy volunteers, even at lower strengths, a study conducted in patients may be required. Depending on the dosing posology this may be a multiple-dose, steady-state study. As above, such studies should employ a cross-over design if possible; however, a parallel group design study in patients may be required in some situations. The use of such an alternative study design should be fully justified by the sponsor and should include patients whose disease process is stable for the duration of the bioequivalence study if possible.

7.1.2 Considerations for active pharmaceutical ingredients with long elimination half-lives

A single-dose, cross-over bioequivalence study for an orally-administered product with a long elimination half-life is preferred, provided an adequate wash-out period between administrations of the treatments is possible. The interval between study days should be long enough to permit elimination of essentially all of the previous dose from the body. Ideally the interval should not be less than five terminal elimination half-lives of the active compound or metabolite, if the latter is measured. If the cross-over study is problematic owing to a very long elimination half-life, a bioequivalence study with a parallel design may be more appropriate. A parallel design may also be necessary when comparing some depot formulations.

For both cross-over and parallel-design studies of oral products, sample collection time should be adequate to ensure completion of gastrointestinal (GI) transit (approximately 2–3 days) of the pharmaceutical product and absorption of the API. Blood sampling should be conducted for up to 72 hours following administration, but sampling beyond this time is not generally necessary for immediate-release products.

The number of subjects should be derived from statistical calculations, but generally more subjects are needed for a parallel study design than for a cross-over study design.

7.1.3 Considerations for multiple-dose studies

In certain situations multiple-dose studies may be considered appropriate. Multiple-dose studies in patients are most useful in cases where the API being studied is considered to be too potent and/or too toxic to be administered to healthy volunteers, even in single doses (see also section 7.1.1). In this case

a multiple-dose, cross-over study in patients may be performed without interrupting therapy.

The dosage regimen used in multiple-dose studies should follow the usual dosage recommendations.

Other situations in which multiple-dose studies may be appropriate are as follows:

- cases where the analytical sensitivity is too low to adequately characterize the pharmacokinetic profile after a single dose;
- for extended-release dosage forms with a tendency to accumulate (in addition to single-dose studies).

In steady-state studies, the wash-out of the last dose of the previous treatment can overlap with the approach to steady state of the second treatment, provided the approach period is sufficiently long (at least five times the terminal half-life). Appropriate dosage administration and sampling should be carried out to document the attainment of a steady state.

7.1.4 Considerations for modified-release products

Modified-release products include extended-release products and delayed-release products. Extended-release products are variously known as controlled-release, prolonged-release and sustained-release products.

Owing to the more complex nature of modified-release products relative to immediate-release products, additional data are required to ensure the bioequivalence of two modified-release products. Factors such as the co-administration of food, which influences API bioavailability and also, in certain cases, bioequivalence, must be taken into consideration. The presence of food can affect product performance both by influencing the release of the API from the formulation and by causing physiological changes in the GI tract. In this regard a significant concern with regard to modified-release products is the possibility that food may trigger a sudden and abrupt release of the API leading to "dose dumping". This would most likely be manifested as a premature and abrupt rise in the plasma concentration time profile. Therefore, bioequivalence studies conducted under both fasted and fed conditions are required for orally-administered, modified-release pharmaceutical products.

Unless single-dose studies are not possible for reasons such as those discussed in section 7.1.1, single-dose, cross-over bioequivalence studies conducted under both fasted and fed conditions comparing the highest strength of the multisource product and the comparator product must be performed to demonstrate bioequivalence. Single-dose studies are preferred to multiple-dose studies as single-dose studies are considered to provide more sensitive

measurement of the release of API from the pharmaceutical product into the systemic circulation. In addition to single-dose studies, multiple-dose studies may be considered for extended-release dosage forms with a tendency to accumulate, e.g. after a single dose of the highest strength the AUC for the dosing interval covers < 90% of AUC extrapolated to infinity.

The comparator product in these studies should be a pharmaceutically-equivalent, modified-release product. The bioequivalence criteria for modified-release products are essentially the same as for conventional-release dosage forms except that acceptance criteria should also be applied to C_{min} (C_{tau}) in the case of multiple-dose studies. As release mechanisms of pharmaceutical products become more complex, e.g. products with an immediate-release and modified-release component, additional parameters such as partial AUC measures may be necessary to ensure the bioequivalence of two products.

The fed-state bioequivalence study should be conducted after the administration of an appropriate standardized meal at a specified time (usually not more than 30 minutes) before taking the pharmaceutical product. A meal that will promote the greatest change in GI tract conditions relative to the fasted state should be given. See section 7.4.3 for more recommendations for the content of the meal. The composition of the meal should take local diet and customs into consideration. The composition and caloric breakdown of the test meal should be provided in the study protocol and report.

7.2 Subjects

7.2.1 Number of subjects

The number of subjects required for a bioequivalence study is determined by:

- the error variance (coefficient of variation) associated with the primary parameters to be studied, as estimated from a pilot experiment, from previous studies or from published data;
- the significance level desired (5%);
- the statistical power desired;
- the mean deviation from the comparator product compatible with bioequivalence and with safety and efficacy;
- the need for the 90% confidence interval around the geometric mean ratio to be within bioequivalence limits, normally 80–125%, for log-transformed data.

The number of subjects to be recruited for the study should be estimated by considering the standards that must be met using an appropriate method (see, for example, Julious 2004 (*7*)). In addition, a number of extra subjects should be

recruited, dosed appropriately, and their samples analysed based on the expected rate of drop-outs and/or withdrawals, which depends on the safety and tolerability profile of the API. The number of subjects recruited should always be justified by the sample-size calculation provided in the study protocol. A minimum of 12 subjects is required.

In some situations, reliable information concerning the expected variability in the parameters to be estimated may not be available. In such situations a two-stage sequential study design can be employed as an alternative to conducting a pilot study (see section 7.6.1 for more information).

7.2.2 Drop-outs and withdrawals

Sponsors should select a sufficient number of study subjects to allow for possible drop-outs or withdrawals. Because replacement of subjects during the study could complicate the statistical model and analysis, drop-outs generally should not be replaced. Reasons for withdrawal (e.g. adverse reaction or personal reasons) must be reported. If a subject is withdrawn due to an adverse event after receiving at least one dose of the study medication the subject's plasma/serum concentration data should be provided.

The concentration–time profiles of subjects who exhibit pre-dose concentrations higher than 5% of the corresponding C_{max} should be excluded from the statistical analysis. The concentration–time profiles of subjects who exhibit pre-dose concentrations equal to or less than 5% of the corresponding C_{max} should be included in the statistical analysis without correction.

7.2.3 Exclusion of subject data

Extreme values can have a significant impact on bioequivalence study data because of the relatively small number of subjects typically involved; however, it is rarely acceptable to exclude data. Potential reasons for excluding subject data and the procedure to be followed should be included in the study protocol. Exclusion of data for statistical or pharmacokinetic reasons alone is not acceptable. Retesting of subjects is not recommended.

7.2.4 Selection of subjects

Bioequivalence studies should generally be performed with healthy volunteers. Clear criteria for inclusion and exclusion should be stated in the study protocol. If the pharmaceutical product is intended for use in both sexes, the sponsor should include both males and females in the study. The potential risk to women will need to be considered on an individual basis and, if necessary, they should be warned of any possible dangers to the fetus if they should become pregnant. The investigators should ensure that female volunteers are not pregnant or likely to become pregnant during the study. Confirmation should be obtained

by urine tests just before administration of the first and last doses of the product under study.

Generally subjects should be between the ages of 18 and 55 years and their weight should be within the normal range with a body mass index (BMI) between 18 and 30 kg/m². The subjects should have no history of alcohol or drug-abuse problems and should preferably be non-smokers.

The volunteers should be screened for their suitability using standard laboratory tests, a medical history and a physical examination. If necessary, special medical investigations may be carried out before and during studies, depending on the pharmacology of the individual API being investigated, e.g. an electrocardiogram if the API has a cardiac effect. The ability of the volunteers to understand and comply with the study protocol has to be assessed. Subjects who are being or have previously been treated for any GI problems or convulsive, depressive or hepatic disorders, and in whom there is a risk of a recurrence during the study period, should be excluded.

If a parallel-design study is planned, standardization of the two groups of subjects is important in order to minimize variation not attributable to the investigational products (see section 7.2.6).

If the aim of the bioequivalence study is to address specific questions (e.g. bioequivalence in a special population) the selection criteria should be adjusted accordingly.

7.2.5 Monitoring the health of subjects during the study

In keeping with GCP (*4*) the health of volunteers should be monitored during the study so that the onset of side-effects, toxicity or any intercurrent disease may be recorded and appropriate measures taken. The incidence, severity, seriousness and duration of any adverse event observed during the study must be reported. The probability that an adverse event is due to the FPP should be judged by the investigator.

Health monitoring before, during and after the study must be carried out under the supervision of a qualified medical practitioner licensed in the jurisdiction in which the study is conducted.

7.2.6 Considerations for genetic phenotyping

Phenotyping for metabolizing activity can be important for studies with high-clearance APIs that are metabolized by enzymes that are subject to genetic polymorphism, e.g. propranolol. In such cases slow metabolizers will have a higher bioavailability of the API while the bioavailability of possible active metabolites will be lower. Phenotyping of subjects can be considered for studies of APIs that show phenotype-linked metabolism and for which a parallel group design is to be used, because it allows fast and slow metabolizers to be evenly distributed between the two groups of subjects.

Phenotyping could also be important for safety reasons, determination of sampling times and wash-out periods in cross-over design studies.

7.3 Investigational product

7.3.1 Multisource pharmaceutical product

The multisource pharmaceutical product used in the bioequivalence studies for registration purposes should be identical to the planned commercial pharmaceutical product. Therefore, not only the composition and quality characteristics (including stability), but also the manufacturing methods (including equipment and procedures) should be the same as those to be used in the future routine production runs. Test products must be manufactured under GMP regulations. Batch-control results, lot number, manufacturing date and, if possible, expiry date for the multisource product should be stated.

Samples should ideally be taken from batches of industrial scale. When this is not feasible, pilot or small-scale production batches may be used, provided that they are not smaller than 10% of expected full production batches, or 100 000 units, whichever is larger, and are produced with the same formulation and similar equipment and process to that planned for commercial production batches. A biobatch of less than 100 000 units may be accepted provided that this is the proposed production batch size, with the understanding that future scale-up for production batches will not be accepted unless supported by in vitro and/or in vivo data as applicable.

7.3.2 Choice of comparator product

The innovator pharmaceutical product is usually the most logical comparator product for a multisource pharmaceutical product because its quality, safety and efficacy should have been well assessed and documented in premarketing studies and postmarketing monitoring schemes. Preferably this will mean employing the innovator product available on the market when studying multisource products for national and regional approval. There will be situations, however, where this is not feasible. Detailed guidance for the selection of comparator products for use in national and regional applications is provided in the comparator guidance (*8*).

It is recommended that potency and in vitro dissolution characteristics of the multisource and the comparator pharmaceutical products be ascertained prior to the performance of an equivalence study. Content of the API(s) of the comparator product should be close to the label claim and the difference between two products being compared should not be more than ± 5%. If, because of the lack of availability of different batches of the comparator product, it is not possible to study batches with potencies within ± 5%, potency correction may be required on the statistical results from the bioequivalence study.

7.4 Study conduct

7.4.1 Selection of strength

In bioequivalence studies the molar equivalent dose of multisource and comparator product must be used.

For a series of strengths that can be considered proportionally formulated (see section 10.3) the strength with the greatest sensitivity for bioequivalence assessment should be administered as a single unit. This will usually be the highest marketed strength. A higher dose, i.e. more than one dosage unit, may be employed when analytical difficulties exist. In this case, the total single dose should not exceed the maximal daily dose of the dosage regimen. In certain cases a study performed with a lower strength can be considered acceptable if this lower strength is chosen for reasons of safety or if the API is highly soluble and its pharmacokinetics are linear over the therapeutic range.

7.4.1.1 Non-linear pharmacokinetics

When the API in a series of strengths, which are considered proportionally formulated, exhibits non-linear pharmacokinetics over the range of strengths, special consideration is necessary when selecting the strength for study.

For APIs exhibiting non-linear pharmacokinetics within the range of strengths resulting in greater than proportional increases in AUC with increasing dose, the comparative bioavailability study should be conducted on at least the highest marketed strength.

For APIs with non-linear pharmacokinetics within the range of strengths due to saturable absorption and resulting in less than proportional increases in AUC with increasing dose, the bioequivalence study should be conducted on at least the lowest strength (or a strength in the linear range).

For APIs with non-linear pharmacokinetics within the range of strengths due to limited solubility of the API and resulting in less than proportional increases in AUC with increasing dose, bioequivalence studies should be conducted on at least the lowest strength (or a strength in the linear range) and the highest strength.

7.4.2 Study standardization

Standardization of study conditions is important to minimize variability other than in the pharmaceutical products. Standardization between study periods is critical to a successful study. Standardization should cover exercise, diet, fluid intake and posture, as well as the restriction of the intake of alcohol, caffeine, certain fruit juices and concomitant medicines for a specified period before and during the study.

Volunteers should not take any other medicine, alcoholic beverages or over-the-counter medicines and supplements for an appropriate interval before,

or during, the study. In the event of emergency the use of any non-study medicine must be reported (dose and time of administration).

Physical activity and posture should be standardized as far as possible to limit their effects on GI blood flow and motility. The same pattern of posture and activity should be maintained for each day of the study. The time of day at which the study product is to be administered should be specified.

7.4.3 Co-administration of food and fluid with the dose

FPPs are usually given after an overnight fast of at least 10 hours and participants are allowed free access to water. On the morning of the study no water is allowed during the hour prior to FPP administration. The dose should be taken with a standard volume of water (usually 150–250 mL). Two hours after FPP administration, water is again permitted as often as desired. A standard meal is usually provided four hours after FPP administration. All meals should be standardized and the composition stated in the study protocol and report.

There are situations when the investigational products should be administered following consumption of a meal (under fed conditions). These situations are described below.

7.4.3.1 Immediate-release formulations

Fasted-state studies are generally preferred. However, when the product is known to cause GI disturbances if given to subjects in the fasted state, or if the labelling of the comparator product restricts administration to subjects in the fed state, then a fed-state study becomes the preferred approach.

For products with specific formulation characteristics (e.g. microemulsions, solid dispersions), bioequivalence studies performed under both fasted and fed conditions are required, unless the product is only taken in a fasted or fed state.

Typically a meal meeting the composition recommendations identified in section 7.4.3.2 should be employed in fed-state studies. The exact composition of the meal may depend on local diet and customs as determined by the NRA. For studies conducted with immediate-release products there may be situations where it is appropriate to employ a pre-dose meal with a different caloric/fat content from a meal meeting the composition recommendations identified in section 7.4.3.2.

The test meal should be consumed beginning 30 minutes prior to administration of the FPP.

7.4.3.2 Modified-release formulations

In addition to a study conducted under fasted conditions, food-effect studies are necessary for all multisource, modified-release formulations to ensure that

the interaction between the varying conditions in the GI tract and the product formulations does not differentially impact the performance of the multisource and comparator products. The presence of food can affect product performance both by influencing the release of the API from the formulation and by causing physiological changes in the GI tract. A significant concern with regard to modified-release products is the possibility that food may trigger a sudden and abrupt release of the API leading to "dose dumping".

In these cases the objective is to select a meal that will challenge the robustness of the new multisource formulation to prandial effects on bioavailability. To achieve this, a meal that will provide a maximal perturbation to the GI tract relative to the fasted state should be employed, e.g. a high-fat (approximately 50% of the total caloric content of the meal), high-calorie (approximately 800 to 1000 kilocalories) test meal has been recommended (*2*). The meal selected should take into account local customs and diet. The caloric breakdown of the test meal should be provided in the study report.

The subject should start eating the meal 30 minutes before the FPP is administered and complete eating the meal prior to FPP administration.

7.4.4 Wash-out interval

The interval (wash-out period) between doses of each formulation should be long enough to permit the elimination of essentially all of the previous dose from the body. The wash-out period should be the same for all subjects and should normally be more than five times the median terminal half-life of the API. Consideration should be given to extending this period in some situations, e.g. if active metabolites with longer half-lives are produced or if the elimination rate of the API has high variability between subjects. In this second case a longer wash-out period should be considered to allow for the slower elimination in subjects with lower elimination rates. Just prior to administration of the treatment during the second study period, blood samples should be collected and assayed to determine the concentration of the API or metabolites. The minimum wash-out period should be at least seven days unless a shorter period is justified by a short half-life. The adequacy of the wash-out period can be estimated from the pre-dose concentrations of the API in the second study period and should be less than 5% of the observed C_{max}.

7.4.5 Sampling times

Blood samples should be taken at a frequency sufficient for assessing C_{max}, AUC and other parameters. Sampling points should include a pre-dose sample, at least 1–2 points before C_{max}, 2 points around C_{max} and 3–4 points during the elimination phase. Consequently at least seven sampling points will be necessary for estimation of the required pharmacokinetic parameters.

For most APIs the number of samples necessary will be higher to compensate for between-subject differences in absorption and elimination rate and thus enable accurate determination of the maximum concentration of the API in the blood (C_{max}) and terminal elimination rate constant in all subjects. Generally, sampling should continue for long enough to ensure that 80% of the $AUC_{0-\infty}$ can be accrued but it is not necessary to sample for more than 72 hours. The exact duration of sample collection depends on the nature of the API and the input function from the administered dosage form.

7.4.6 Sample fluids and their collection

Under normal circumstances blood should be the biological fluid sampled to measure the concentrations of the API. In most cases the API or its metabolites are measured in serum or plasma. If it is not possible to measure the API in blood, plasma or serum, the API is excreted unchanged in the urine and there is a proportional relationship between plasma and urine concentrations; urine can be sampled for the purpose of estimating exposure. The volume of each urine sample must be measured at the study centre, where possible immediately after collection, and the measurements included in the report. The number of samples should be sufficient to allow the estimation of pharmacokinetic parameters. However, in most cases the exclusive use of urine excretion data should be avoided as this does not allow estimation of the t_{max} and the maximum concentration. Blood, plasma, serum and urine samples should be processed and stored under conditions that have been shown not to cause degradation of the analytes. Details of these conditions should be included in the analytical validation report (see section 7.5).

The sample collection methodology must be specified in the study protocol.

7.4.7 Parameters to be assessed

In bioavailability studies, the shape and area under the plasma concentration versus time curves are mostly used to assess rate (C_{max}, t_{max}) and extent (AUC) of exposure. Sampling points or periods should be chosen such that the concentration versus time profile is sufficiently defined to allow calculation of relevant parameters. For single-dose studies, the following parameters should be measured or calculated:

- area under the plasma, serum or blood concentration–time curve from time zero to time *t* (AUC_{0-t}), where *t* is the last sampling time-point with a measurable concentration of the API in the individual formulation tested. The method of calculating AUC values should be specified. Non-compartmental methods should be used for pharmacokinetic calculations in bioequivalence studies;

- C_{max} is the maximum or peak concentration observed representing peak exposure of API (or metabolite) in plasma, serum or whole blood.

Usually AUC_{0-t} and C_{max} are considered to be the most relevant parameters for assessment of bioequivalence. In addition it is recommended that the following parameters be estimated:

- area under the plasma, serum or blood concentration–time curve from time zero to time infinity ($AUC_{0-\infty}$) representing total exposure, where $AUC_{0-\infty} = AUC_{0-t} + C_{last} / K_e$; C_{last} is the last measurable analyte concentration and K_e is the terminal or elimination rate constant calculated according to an appropriate method;
- t_{max} is the time after administration of the FPP at which C_{max} is observed.

For additional information the elimination parameters can be calculated:

- $t_{1/2}$ is the plasma (serum, whole blood) half-life.

For multiple-dose studies conducted with modified-release products, the following parameters should be calculated:

- AUCτ is AUC over one dosing interval (τ) at steady state;
- C_{max};
- C_{min} (C_{tau}) is concentration at the end of a dosing interval;
- peak trough fluctuation is percentage difference between C_{max} and C_{min}.

As release mechanisms of pharmaceutical products become more complex, e.g. products with an immediate-release and a modified-release component, additional parameters such as partial AUC measures may be necessary to ensure the bioequivalence of two products.

When urine samples are used, cumulative urinary recovery (Ae) and maximum urinary excretion rate are employed instead of AUC and C_{max}.

7.4.8 Studies of metabolites

Generally evaluation of bioequivalence will be based on the measured concentrations of the API released from the dosage form rather than the metabolite. The concentration–time profile of the API is more sensitive to changes in formulation performance than a metabolite which is more reflective of metabolite formation, distribution and elimination.

In rare cases it may be necessary to measure concentrations of a primary active metabolite rather than those of the API if concentrations of the API are too low to allow reliable analytical measurement in blood, plasma or serum for

an adequate length of time, or when the parent compound is unstable in the biological matrix.

It is important to decide beforehand and state in the study protocol, which chemical entities (API or metabolite) will be analysed in the samples and to identify the analyte whose data will be used to assess bioequivalence.

It is important to note that measurement of one analyte, API or metabolite carries the risk of making a type-1 error (the consumer's risk) to remain at the 5% level. However, if more than one of several analytes is selected retrospectively as the bioequivalence determinant, then both the consumer and producer risks change (*9*). The analyte whose data will be used to assess bioequivalence cannot be changed retrospectively.

When measuring active metabolites, wash-out period and sampling times may need to be adjusted to enable adequate characterization of the pharmacokinetic profile of the metabolite.

7.4.9 Measurement of individual enantiomers

A non-stereoselective assay is acceptable for most bioequivalence studies. A stereospecific assay measuring the individual enantiomers should be employed when the enantiomers exhibit different pharmacokinetic properties, different pharmacodynamic properties and the exposure of the enantiomers, as estimated by their AUC ratio or C_{max} ratio, changes when there is a change in the rate of absorption.

7.5 Quantification of active pharmaceutical ingredient

For the measurement of concentrations of the active compound and/or metabolites in biological matrices, such as serum, plasma, blood and urine, the applied bioanalytical method should be well-characterized, fully validated and documented to a satisfactory standard in order to yield reliable results.

The validation of bioanalytical methods and the analysis of subject samples for clinical trials in humans should be performed following the principles of good clinical practice (GCP), good laboratory practice (GLP) and the most up-to-date guidelines from stringent regulatory authorities (SRAs) on the topic of bioanalytical method validation.

State-of-the-art principles and procedures for bioanalytical method validation and analysis of study samples should be employed.

The main characteristics of a bioanalytical method that are essential to ensure the acceptability of the performance and the reliability of analytical results are:

- selectivity;
- lower limit of quantification;

- the response function and calibration range (calibration curve performance);
- accuracy;
- precision;
- matrix effects;
- stability of the analyte(s) in the biological matrix;
- stability of the analyte(s) and of the internal standard in the stock and working solutions, and in extracts throughout the entire period of storage and processing conditions.

In general:

- the analytical method should be able to differentiate the analyte(s) of interest and, if employed, the internal standard (IS) from endogenous components in the matrix or other components in the sample;
- the lower limit of quantification (LLOQ), being the lowest concentration of analyte in a sample, should be estimated to prove that the analyte at this concentration can be quantified reliably, with an acceptable accuracy and precision;
- the response of the instrument with regard to the concentration of analyte should be known and should be evaluated over a specified concentration range. The calibration curve should be prepared in the same matrix as the matrix of the intended subject samples by spiking the blank matrix with known concentrations of the analyte. A calibration curve should consist of a blank sample, a zero sample and 6–8 non-zero samples covering the expected range;
- within-run and between-run accuracy and precision should be assessed on samples spiked with known amounts of the analyte, the QC samples, at a minimum of three different concentrations;
- matrix effects should be investigated when using mass spectrometric methods;
- stability of the analyte in the stock solution and in the matrix should be proven covering every step taken during sample preparation and sample analysis, as well as the storage conditions used;
- when more than one analyte is present in subject samples, it is recommended to demonstrate the stability of the analytes in the matrix in the presence of the other analytes under standard conditions such as freeze–thaw testing, short-term room temperature storage and long-term freezer storage;

- where changes are made to an analytical method that has already been validated, a full validation may not be necessary depending on the nature of the changes implemented. A partial validation may be acceptable;
- a cross-validation is needed in cases where data are obtained from different methods within and across studies or when data are obtained within a study from different laboratories applying the same method;
- analysis of subject samples should be carried out after validation of the analytical method. Before the start of the analysis of the subject samples, the performance of the bioanalytical method should have been verified;
- calibration and QC standards should be processed in an identical manner and at the same time as the subjects' samples from the same run;
- reasons for reanalysis, reinjection and reintegration of subject samples should be predefined in the protocol, study plan or SOP. Reinjection of a full analytical run or of individual calibration standard samples or QC samples, simply because the calibration or QCs failed, without any identified analytical cause, is considered unacceptable. For bioequivalence studies, reanalysis, reinjection or reintegration of subject samples for reasons related to pharmacokinetic fit is normally not acceptable as this may affect and bias the outcome of such a study;
- when analysing subject samples, the precision and accuracy of the method should be confirmed by reanalysing subject samples in a separate analytical run on a different day (incurred samples reanalysis (ISR)). ISR should be performed for each bioequivalence trial. The extent of testing done should be based on an in-depth understanding of the analytical method and analyte used;
- the samples from one subject (all periods) should be analysed in the same analytical run if possible.

Validation procedures, methodology and acceptance criteria should be specified in the analytical protocol and/or the SOP. All experiments used to support claims or draw conclusions about the validity of the method should be described in a report (method validation report).

The results of subject sample determination should be given in the analytical report together with calibration and QC sample results, repeat analyses, reinjections and reintegrations (if any) and a representative number of sample chromatograms.

7.6 Statistical analysis

The primary concern in bioequivalence assessment is to limit the risk of a false declaration of equivalence. Statistical analysis of the bioequivalence trial should demonstrate that a clinically significant difference in bioavailability between the multisource product and the comparator product is unlikely. The statistical procedures should be specified in the protocol before the data collection starts.

The statistical method for testing bioequivalence is based on the determination of the 90% confidence interval around the ratio of the log-transformed population means (multisource/comparator) for the pharmacokinetic parameters under consideration and by carrying out two one-sided tests at the 5% level of significance (*10*). To establish bioequivalence, the calculated confidence interval should fall within a preset bioequivalence limit. The procedures should lead to a decision scheme which is symmetrical with respect to the formulations being compared (i.e. leading to the same decision whether the multisource formulation is compared to the comparator product or the comparator product to the multisource formulation).

All concentration-dependent pharmacokinetic parameters (e.g. AUC and C_{max}) should be log-transformed using either common logarithms to the base 10 or natural logarithms. The choice of either common or natural logs should be consistent and should be stated in the study report.

Logarithmically transformed, concentration-dependent pharmacokinetic parameters should be analysed using analysis of variance (ANOVA). Normally the ANOVA model should include formulation, period, sequence and subject factors.

Parametric methods, i.e. those based on normal distribution theory, are recommended for the analysis of log-transformed bioequivalence measures.

The general approach is to construct a 90% confidence interval for the quantity $\mu T - \mu R$ and to reach a conclusion of pharmacokinetic equivalence if this confidence interval is within the stated limits. The nature of parametric confidence intervals means that this is equivalent to carrying out two one-sided tests of the hypothesis at the 5% level of significance (*10*, *11*). The antilogs of the confidence limits obtained constitute the 90% confidence interval for the ratio of the geometric means between the multisource and comparator products.

The same procedure should be used for analysing parameters from steady-state trials or cumulative urinary recovery if required.

For t_{max} descriptive statistics should be given. Where t_{max} is considered clinically relevant, median and range of t_{max} should be compared between test and comparator to exclude numerical differences with clinical importance. A formal statistical comparison is rarely necessary. Generally the sample size is not calculated to have enough statistical power for t_{max}. However, if t_{max} is to be subjected to a statistical analysis, this should be based on non-parametric

methods and should be applied to untransformed data. A sufficient number of samples around predicted maximal concentrations should have been taken to improve the accuracy of the t_{max} estimate. For parameters describing the elimination phase ($t_{1/2}$) only descriptive statistics should be given.

See section 7.2.3 for information on the handling of extreme data. Exclusion of data for statistical or pharmacokinetic reasons alone is not acceptable.

7.6.1 Two-stage sequential design

In some situations reliable information concerning the expected variability in the parameters to be estimated may not be available. In such situations a two-stage sequential study design can be employed such that an accurate estimate of the variability can be determined in the first stage of the study. The number of subjects employed in the first stage is generally based on the most likely intra-subject variance estimate with some added subjects to compensate for drop-outs. The analysis undertaken at the end of the first stage is treated as an interim analysis. If bioequivalence is proven at this point the study can be terminated. If bioequivalence is not proven at the end of the first stage, the second stage is conducted employing an appropriate number of additional subjects as determined based on the variance estimates and point estimate calculated from the stage 1 data. At the end of the second stage, the results from both groups combined are used in the final analysis. In order to use a two-stage design, adjustments must be made to protect the overall Type 1 error rate and maintain it at 5%. To do this, both the interim and final analyses must be conducted at adjusted levels of significance with the confidence intervals calculated using the adjusted values.

It is recommended that the same alpha for both stages be employed. This gives an alpha of 0.0294 for this case (*12*), however, the amount of alpha to be spent at the time of the interim analysis can be set at the study designer's discretion. For example, the first stage may be planned as an analysis where no alpha is spent in the interim analysis since the objective of the interim analysis is to obtain information on the point estimate difference and variability and where all the alpha is spent in the final analysis with the conventional 90% confidence interval. In this case no test against the acceptance criteria is made during the interim analysis and bioequivalence cannot be proven at that point. The proposed statistical plan must be clearly defined in the study protocol, including the adjusted significance level that is to be employed during each analysis.

A factor for stage should be included in the ANOVA model for the final analysis of the combined data from the two stages.

This approach can be employed in both cross-over and parallel study designs.

7.7 Acceptance ranges

AUC_{0-t}-ratio

The 90% confidence interval for this measure of relative bioavailability should lie within a bioequivalence range of 80.00–125.00%. If the API is determined to possess a narrow therapeutic index (NTI) the bioequivalence acceptance range should be restricted 90.00–111.11%.

The same criterion applies to the parameter AUCτ in multiple-dose studies and for partial AUCs if they are necessary for comparative testing of a modified-release product.

C_{max}-ratio

For maximal concentration data, the acceptance limit of 80.00–125.00% should be applied to the 90% confidence interval for the mean C_{max}-ratio. However, this measure of relative bioavailability is inherently more variable than, for example, the AUC-ratio, and in certain cases this variability can make proving bioequivalence challenging. See section 7.9.3 for information on an approach for proving bioequivalence when the intrasubject variability for the C_{max} parameter is high. If the API is determined to possess a narrow therapeutic index, the bioequivalence acceptance range may need to be restricted to 90.00–111.11%, if appropriate.

The same criterion applies to the parameters C_{max} and C_{tau} in multiple-dose studies.

t_{max}-difference

Statistical evaluation of t_{max} makes sense only if there is a clinically relevant claim for rapid onset of action or concerns about adverse effects. In such a case, comparison of the median and range data for each product should be undertaken.

For other pharmacokinetic parameters the same considerations as outlined above apply.

7.8 Reporting of results

The report of a bioequivalence study should give the complete documentation of its protocol, conduct and evaluation complying with GCP and GLP rules. The relevant International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guideline (*13*) can be used in the preparation of the study report. The responsible investigator(s) should sign the respective sections of the report. Names and affiliations of the responsible investigator(s), site of the study and period of its execution should be stated.

The names and batch numbers of the pharmaceutical products used in the study as well as the composition(s) of the tests product(s) should be given. Results of in vitro dissolution tests conducted in media with pHs of 1.2, 4.5 and 6.8 and the QC media, if different, should be provided. In addition, the applicant should submit a signed statement confirming that the test product is identical to the pharmaceutical product that is submitted for registration.

The bioanalytical validation report should be attached. This report should include the information recommended in the SRA guidance chosen as a guide for the bioanalytical portion of a study (see section 7.5).

All results should be presented clearly. All concentrations measured in each subject and the sampling time should be tabulated for each formulation. Tabulated results showing API concentration analyses according to analytical run (including runs excluded from further calculations, together with all calibration standards and QC samples from the respective run) should also be presented. The tabulated results should present the date of run, subject, study period, product administered (multisource or comparator) and time elapsed between FPP administration and blood sampling, in a clear format. The procedure for calculating the parameters used (e.g. AUC) from the raw data should be stated. Any deletion of data should be documented and justified.

Individual blood concentration/time curves should be plotted on a linear/linear and log/linear scale. All individual data and results should be given, including information on subjects who dropped out. The drop-outs and/or withdrawn subjects should be reported and accounted for. All adverse events that occurred during the study should be reported together with the study physician's classification of the events. Further, any treatments given to address adverse events should be reported.

Results of all measured and calculated pharmacokinetic parameters should be tabulated for each subject–formulation combination together with descriptive statistics. The statistical report should be sufficiently detailed to enable the statistical analyses to be repeated if necessary. If the statistical methods applied deviate from those specified in the study protocol the reasons for the deviations should be stated.

7.9 Special considerations

7.9.1 Fixed-dose combination products

If the bioequivalence of FDC products is assessed by in vivo studies, the study design should follow the same general principles as described in previous sections. The multisource FDC product should be compared with the pharmaceutically-equivalent comparator FDC product. In certain cases (e.g. when no comparator FDC product is available on the market) separate products administered in free

combination can be used as a comparator (*3*). Sampling times should be chosen to enable the pharmacokinetic parameters of all APIs to be adequately assessed. The bioanalytical method should be validated with respect to all analytes measured in the presence of the other analytes. Statistical analyses should be performed with pharmacokinetic data collected on all active ingredients; the 90% confidence intervals of test/comparator ratio of all active ingredients should be within acceptance limits.

7.9.2 Clinically important variations in bioavailability

Innovators should make every effort to provide formulations with good bioavailability characteristics. If a better formulation is later developed by the innovator, this should then serve as the comparator product. A new formulation with a bioavailability outside the acceptance range for an existing pharmaceutical product is not interchangeable by definition.

7.9.3 "Highly variable active pharmaceutical ingredients"

A "highly variable API" has been defined as an API with an intrasubject variability of > 30% in terms of the ANOVA-CV (*14*). Proving the bioequivalence of FPPs containing highly variable APIs can be problematic because the higher the ANOVA-CV, the wider the 90% confidence interval. Thus large numbers of subjects must be enrolled in studies involving highly variable APIs to achieve adequate statistical power.

Although there is variability in how regulatory authorities deal with the issue of highly variable APIs, the most rigorous of the current approaches involve the scaling of bioequivalence acceptance criteria based on the intra-subject standard deviation observed in the relevant parameters for the comparator product (*15–17*). Of the two most common assessment parameters C_{max} is subject to the highest variability and hence is the parameter for which a modified approach is most needed.

For highly variable FPPs it is recommended that a three-way partial replicate (where the comparator product is administered twice) or a four-way fully replicated cross-over bioequivalence study be conducted and reference-scaled average bioequivalence be employed to widen the acceptance interval for the C_{max} parameter, if the intrasubject variability for C_{max} following replicate administrations of the comparator product is > 30%. If this is the case the acceptance criteria for C_{max} can be widened to a maximum of 69.84–143.19%. The applicant should justify that the calculated intrasubject variability is a reliable estimate and that it is not the result of outliers.

The extent of the widening of the acceptance interval for C_{max} is defined based upon the intrasubject variability seen in the bioequivalence study using scaled-average-bioequivalence according to [U, L] = exp [± k·sWR], where U

is the upper limit of the acceptance range, L is the lower limit of the acceptance range, k is the regulatory constant set to 0.760 and s_{WR} is the intrasubject standard deviation of the log-transformed values of C_{max} of the reference product. Table A7.2 gives examples of how different levels of variability lead to different acceptance limits using this methodology.

Table A7.2
Acceptance limits for different levels of variability

Intrasubject CV (%)	Lower limit	Upper limit
30	80.00	125.00
35	77.23	129.48
40	74.62	134.02
45	72.15	138.59
≥50	69.84	143.19

$$CV(\%) = \sqrt{(e^{S_{WR}^2}) - 1}$$

The geometric mean ratio (GMR) for C_{max} should lie within the conventional acceptance range 80.00–125.00%.

The standard bioequivalence acceptance criterion for AUC should be maintained without scaling. If the intrasubject variability for C_{max}, following replicate administration of the comparator, is found to be <30%, standard bioequivalence acceptance criteria should be applied to both AUC and C_{max} without scaling.

For multipledose studies, a similar approach can be applied to the following parameters if the intrasubject variability for the parameter is found to be >30%: C_{max}, C_{tau} and partial AUCs if required. The standard bioequivalence acceptance criterion will apply to AUCτ without scaling.

The approach to be employed should be clearly defined prospectively in the study protocol. The regulatory authority of the country to which the study data will be submitted should be consulted before commencing the study to confirm that the proposed approach is acceptable for that jurisdiction.

8. Pharmacodynamic equivalence studies

Studies in healthy volunteers or patients using pharmacodynamic measurements may be used for establishing equivalence between two pharmaceutical

products when the pharmacokinetic approach is not feasible. Pharmacodynamic equivalence studies may become necessary if quantitative analysis of the API and/or metabolite(s) in blood, serum, plasma or urine cannot be made with sufficient accuracy and sensitivity; however, this is extremely unlikely given current technology. Furthermore, pharmacodynamic equivalence studies in humans are required if measurements of API concentrations cannot be used as surrogate end-points for the demonstration of efficacy and safety of the particular pharmaceutical product as is the case with pharmaceutical products designed to act locally. However, local availability studies based on pharmacokinetic studies alone or in combination with in vitro dissolution studies are being considered as surrogate end-points for the demonstration of equivalent biopharmaceutical quality and release at the site of action for some products acting locally. In addition, bioequivalence studies are also required in order to demonstrate equivalent systemic exposure for systemic safety purposes.

Pharmacodynamic studies are not recommended for orally-administered, pharmaceutical products for systemic action when the API is absorbed into the systemic circulation and a pharmacokinetic approach can be used to assess systemic exposure and establish bioequivalence. This is because the sensitivity to detect differences between products in their biopharmaceutical quality, release and absorption is lower with pharmacodynamic or clinical end-points. As the dose–response curve for pharmacodynamics or clinical end-points is usually flatter than the relationship between dose and pharmacokinetic parameters, it is essential to ensure the internal validity of the study by showing assay sensitivity, i.e. the ability to distinguish the response obtained by adjacent doses (two-fold or even four-fold difference in dose). It is essential to perform the comparison at the dose level at which the dose response is steepest, which may require firstly doing a pilot study for its identification. Furthermore, variability in pharmacodynamic measures is usually greater than that in pharmacokinetic measures. In addition, pharmacodynamic measures are often subject to significant placebo effects, which add to the variability and complicate experimental design. The result is often that huge numbers of patients would have to be enrolled in pharmacodynamic studies to achieve adequate statistical power.

If pharmacodynamic studies are to be used they must be performed as rigorously as bioequivalence studies and the principles of GCP must be followed (*4*).

The following requirements must be recognized when planning, conducting and assessing the results of a study intended to demonstrate equivalence by measuring pharmacodynamic responses:

- the response measured should be a pharmacological or therapeutic effect which is relevant to the claims of efficacy and/or safety;

- the methodology must be validated for precision, accuracy, reproducibility and specificity;
- neither the multisource product nor the comparator product should produce a maximal response during the course of the study since it may be impossible to detect differences between formulations given in doses which give maximum or near maximum effects. Investigation of dose–response relationships may be a necessary part of the design;
- the response should be measured quantitatively, preferably under double-blind conditions, and be recordable by an instrument that produces and records the results of repeated measurements to provide a record of the pharmacodynamic events, which are substitutes for measurements of plasma concentrations. Where such measurements are not possible, recordings on visual analogue scales may be used. Where the data are limited to qualitative (categorized) measurements, appropriate special statistical analysis will be required;
- participants should be screened prior to the study to exclude non-responders. The criteria by which responders are distinguished from non-responders must be stated in the protocol;
- in situations where an important placebo effect can occur, comparison between pharmaceutical products can only be made by a priori consideration of the potential placebo effect in the study design. This may be achieved by adding a third phase with placebo treatment during the design of the study;
- the underlying pathology and natural history of the condition must be considered in the study design. There should be confirmation that the baseline conditions are reproducible;
- a cross-over design can be used. Where this is not appropriate, a parallel group study design should be chosen.

The basis for the selection of the multisource and comparator products should be the same as described in section 7.3.

In studies in which continuous variables can be recorded, the time-course of the intensity of the action can be described in the same way as in a study in which plasma concentrations are measured and parameters can be derived that describe the area under the effect–time curve, the maximum response and the time at which the maximum response occurred.

The comparison between the multisource and the comparator product can be performed in two different ways:

(a) *dose-scale analysis or relative potency*: this is defined as the ratio of the potency of the multisource product to that of the comparator

product. It is a way of summarizing the relationship between the dose–response curves of the multisource and comparator product;

(b) *response-scale analysis*: this consists of demonstration of equivalence (for at least two dose levels) at the pharmacodynamic end-point.

For either approach to be acceptable a minimum requirement is that the study has assay sensitivity. To meet this requirement, at least two non-zero levels need to be studied and one dose level needs to be shown to be superior to the other. Therefore, it is recommended that unless otherwise justified more than one dose of both the multisource and comparator products are studied. However, it is essential that doses on the steep part of the dose–response curve are studied. If the chosen dose is too low on the dose–response curve, then demonstrating equivalence between two products is not convincing, as this dose could be subtherapeutic. Equally if a dose at the top of the dose–response curve is included, similar effects will be seen for doses much higher than that studied and hence demonstrating equivalence at this dose level would also not be convincing.

The results using both approaches should be provided. In both cases the observed confidence intervals comparing multisource and comparator products should lie within the chosen equivalence margins to provide convincing evidence of equivalence. As for bioequivalence studies, 90% confidence intervals should be calculated for relative potency whereas 95% confidence intervals should be calculated for the response-scale analysis. It should be noted that the acceptance range as applied for bioequivalence assessment may not be appropriate. For both approaches the chosen equivalence ranges should be prespecified and appropriately justified in the protocol.

9. Clinical equivalence studies

In some instances (see example (e) in section 5.1, In vivo studies) plasma concentration time–profile data may be not suitable for assessing equivalence between two formulations. Although in some cases pharmacodynamic equivalence studies can be an appropriate tool for establishing equivalence, in others this type of study cannot be performed because of a lack of meaningful pharmacodynamic parameters that can be measured; a comparative clinical trial then has to be performed to demonstrate equivalence between two formulations. However, it is preferable to assess equivalence by performing a pharmacokinetic equivalence study rather than a clinical trial that is less sensitive and would require a huge number of subjects to achieve adequate statistical power. For example, it has been calculated that 8600 patients would be required to give adequate statistical power to detect a 20% improvement in response to the study API compared with placebo (*18*,*19*). Similarly it was calculated that 2600 myocardial infarct patients would be required to show a 16% reduction in risk. A comparison of

two formulations of the same API based on such end-points would require even greater numbers of subjects (*19*).

If a clinical equivalence study is considered as being undertaken to prove equivalence, the same statistical principles apply as for the bioequivalence studies, although a 95% confidence interval might be necessary for pharmacodynamic and clinical end-points in contrast to the 90% confidence level employed conventionally for pharmacokinetic studies. The number of patients to be included in the study will depend on the variability of the target parameters and the acceptance range and is usually much higher than the number of subjects needed in bioequivalence studies.

The methodology for establishing equivalence between pharmaceutical products by means of a clinical trial with a therapeutic end-point conducted in patients is not yet as far advanced as that for bioequivalence studies. However, some important items that need to be defined in the protocol can be identified as follows:

- the target parameters that usually represent relevant clinical end-points from which the onset, if applicable and relevant, and intensity of the response are to be derived;
- the size of the acceptance range has to be defined case by case, taking into consideration the specific clinical conditions. These include, among others, the natural course of the disease, the efficacy of available treatments and the chosen target parameter. In contrast to bioequivalence studies (where a conventional acceptance range is applied) the size of the acceptance range in clinical trials should be set individually according to the therapeutic class and indication(s);
- the presently used statistical method is the confidence interval approach;
- the confidence intervals can be derived from either parametric or non-parametric methods;
- where appropriate a placebo arm should be included in the design;
- in some cases it is relevant to include safety end-points in the final comparative assessments.

The selection basis for the multisource and comparator products should be the same as described in section 7.3.

10. In vitro equivalence testing

Over the past three decades dissolution testing has evolved into a powerful tool for characterizing the quality of oral pharmaceutical products. The dissolution test, at first exclusively a QC test, is now emerging as a surrogate equivalence

test for certain categories of orally-administered, pharmaceutical products. For these products (typically solid oral dosage forms containing APIs with suitable properties) similarity in in vitro dissolution profiles, in addition to excipient comparisons and a risk–benefit analysis, can be used to document equivalence of a multisource product with a comparator product.

It should be noted that although the dissolution tests recommended in *The International Pharmacopoeia* (Ph.Int.) (*20*) for QC have been designed to be compatible with the biowaiver dissolution tests, they do not fulfil all the requirements for evaluating equivalence of multisource products with comparator products. Dissolution tests for QC purposes, including those described in other pharmacopoeias, do not address all test conditions required for evaluating equivalence of multisource products and should not be applied for this purpose.

10.1 In vitro equivalence testing in the context of the Biopharmaceutics Classification System

10.1.1 Biopharmaceutics Classification System

The BCS is based on aqueous solubility and intestinal permeability of the API. It classifies the API into one of four classes:

— Class 1: high solubility, high permeability;
— Class 2: low solubility, high permeability;
— Class 3: high solubility, low permeability;
— Class 4: low solubility, low permeability.

Combining the dissolution results and a critical examination of the excipients of the pharmaceutical product with these two properties of the API takes the four major factors that govern the rate and extent of API absorption from immediate-release, solid dosage forms into account (*21*). On the basis of their dissolution properties, immediate-release dosage forms can be categorized as having "very rapid", "rapid", or "not rapid" dissolution characteristics.

On the basis of solubility and permeability of the API, excipient nature, excipient content and dissolution characteristics of the dosage form, the BCS approach provides an opportunity to waive in vivo bioequivalence testing for certain categories of immediate-release FPPs. Oral FPPs containing an API possessing a narrow therapeutic index are not eligible for a so-called biowaiver based on the BCS approach.

10.1.1.1 High solubility

An API is considered highly soluble when the highest single therapeutic dose as determined by the relevant regulatory authority, typically defined by the labelling for the innovator product, is soluble in 250 mL or less of aqueous

media over the pH range of 1.2–6.8. The pH-solubility profile of the API should be determined at 37 ± 1 °C in aqueous media. A minimum of three replicate determinations of solubility at each pH condition is recommended.

10.1.1.2 High permeability

An API is considered highly permeable when the extent of absorption in humans is 85% or more based on a mass balance determination or in comparison with an intravenous comparator dose. Ideally the mass balance study or comparison with an intravenous comparator dose would be conducted at the same dose as that used for the solubility classification. If this is not possible, dose linearity of pharmacokinetics should be used to justify the use of other doses.

Absolute bioavailability or mass balance study data obtained from published literature may be accepted as evidence if it can be clearly established that the data were derived from appropriately designed studies.

In vivo intestinal perfusion in humans is an acceptable alternative test method.

When this method is used for permeation studies, suitability of the methodology should be demonstrated, including determination of permeability relative to that of a reference compound whose fraction of dose absorbed has been documented to be at least 85%, as well as use of a negative control.

Supportive data can be provided by the following additional test methods:

(i) in vivo or in situ intestinal perfusion using animal models;

(ii) in vitro permeation across a monolayer of cultured epithelial cells (e.g. Caco-2) using a method validated using APIs with known permeabilities, although data from neither method (i) nor (ii) would be considered acceptable on a stand-alone basis.

In these experiments, high permeability is assessed with respect to the high permeability of a series of reference compounds with documented permeabilities and values of the absorbed fraction, including some for which fraction of dose absorbed is at least 85% (*22*).

10.1.2 Determination of dissolution characteristics of multisource products in consideration of a biowaiver based on the Biopharmaceutics Classification System

For exemption from an in vivo bioequivalence study, an immediate-release, multisource product should exhibit very rapid or rapid in vitro dissolution characteristics (see sections 10.1.2.1 and 10.1.2.2), depending on the BCS properties of the API. In vitro data should also demonstrate the similarity of dissolution profiles between the multisource and comparator products.

10.1.2.1 Very rapidly dissolving

A multisource product is considered to be very rapidly dissolving when no less than 85% of the labelled amount of the API dissolves in 15 minutes at 37 ± 1 °C using a paddle apparatus at 75 rpm or a basket apparatus at 100 rpm in a volume of 900 mL or less in each of the following media:

- pH 1.2 HCl solution or buffer;
- a pH 4.5 acetate buffer;
- a pH 6.8 phosphate buffer.

Pharmacopoeial buffers (e.g. Ph.Int.) are recommended for use at these three pH values. Surfactants should not be used in the dissolution media. Enzymes (pepsin at pH 1.2 and pancreatin at pH 6.8) may be used if the pharmaceutical product contains gelatin (e.g. capsules or caplets) due to the possibility of cross-linking.

(See also section 10.2, dissolution profile comparison.)

10.1.2.2 Rapidly dissolving

A multisource product is considered to be rapidly dissolving when no less than 85% of the labelled amount of the API dissolves in 30 minutes at 37 ± 1 °C using a paddle apparatus at 75 rpm or a basket apparatus at 100 rpm in a volume of 900 mL or less in each of the following media:

- pH 1.2 HCl solution or buffer;
- pH 4.5 acetate buffer;
- pH 6.8 phosphate buffer.

Surfactants should not be used in the dissolution media. Enzymes (pepsin at pH 1.2 and pancreatin at pH 6.8) may be used if the pharmaceutical product contains gelatin (e.g. capsules or caplets) due to the possibility of cross-linking.

10.2 Qualification for a biowaiver based on the Biopharmaceutics Classification System

A biowaiver based on the BCS considers:

(a) the solubility and intestinal permeability of the API (see section 10.1);

(b) the similarity of the dissolution profiles of the multisource and comparator products in pH 1.2, 4.5 and 6.8 media (see below);

(c) the excipients used in the formulation (see below);

(d) the risks of an incorrect biowaiver decision in terms of the therapeutic index of and clinical indications for the API (see section 5.1 for cases where an in vivo study would be required to demonstrate bioequivalence).

Only when there is an acceptable risk–benefit balance in terms of public health and risk to the individual patient should bioequivalence testing be waived and the in vitro methods described in this section applied as a test of product equivalence.

Risk reduction and assessment of excipients

The risk of reaching an incorrect decision that the multisource product is equivalent to the comparator product can be reduced by correct classification of the API and by following the recommendations for dissolution testing and comparison of the dissolution profiles. In all cases it should be further demonstrated that the excipients included in the formulation of the multisource product are well established for use in products containing that API and that the excipients used will not lead to differences between the comparator and multisource product with respect to processes affecting absorption (e.g. by effects on GI motility or interactions with transport processes) or which might lead to interactions that alter the pharmacokinetics of the API.

In all cases, well-established excipients in usual amounts should be used in multisource products. Excipients that might affect the bioavailability of the API, e.g. mannitol, sorbitol or surfactants, should be identified and an assessment of their impact provided. These critical excipients should not differ qualitatively and must be quantitatively similar between the test product and comparator product.

For biowaivers for products containing Class 1 APIs there is some flexibility in the excipients employed, with the exception of critical excipients as discussed above. It is recommended that the excipients employed be present in the comparator product or be present in other products which contain the same API as the multisource product and which have marketing authorizations in ICH-associated countries.

For biowaivers for products containing Class 3 APIs all excipients in the proposed product formulation should be qualitatively the same and quantitatively similar to that of the comparator product, as defined by the WHO quality limits on allowable quantitative changes in excipients for a variation (*23*).

As a general rule, the closer the composition of the multisource product to that of the comparator product with regard to excipients, the lower the risk of an inappropriate decision on equivalence using a biowaiver based on the BCS.

Sub- and supra-bioavailable products

A further consideration is the potential risk to public health and to the individual patient, should an inappropriate decision with respect to bioequivalence be reached. Essentially there are two possible negative outcomes.

The first arises when the multisource product is sub-bioavailable. In this case substitution of the comparator with the multisource product could lead to reduced therapeutic efficacy. APIs which must reach a certain concentration to be effective (e.g. antibiotics) are most susceptible to problems of sub-bioavailability.

The second negative outcome arises when the multisource product is supra-bioavailable. In this case substitution of the comparator with the multisource product could lead to toxicity. APIs which exhibit toxic effects at concentrations close to the therapeutic range are most susceptible to problems of supra-bioavailability. For these reasons therapeutic index is an important consideration in determining whether the biowaiver based on BCS can be applied or not.

Dissolution profile comparison

Approval of multisource formulations using comparative in vitro dissolution studies should be based on the generation of comparative dissolution profiles rather than a single-point dissolution test. For details refer to Appendix 1.

10.2.1 Dissolution criteria for biowaivers based on the Biopharmaceutics Classification System according to the properties of active pharmaceutical ingredients

The major application of BCS is to provide criteria for biowaiver of multisource products. It is recommended that products containing the following BCS classes of APIs be eligible for a biowaiver:

- BCS Class 1 APIs, if the multisource and comparator product are *very rapidly dissolving or similarly rapidly dissolving*;
- BCS Class 3 APIs, if the multisource and comparator product are *very rapidly dissolving*.

In summary, biowaivers for solid oral dosage forms based on BCS can be considered under the following conditions.

1. Dosage forms of APIs that are highly soluble, highly permeable (BCS Class 1) with acceptable excipient content and favourable risk–benefit analysis and which are rapidly dissolving, are eligible for a biowaiver based on the BCS provided:

(i) the dosage form is *rapidly dissolving* (as defined in section 10.1.2.2) and the dissolution profile of the multisource product is similar to that of the comparator product in aqueous buffers at pH 1.2, pH 4.5 and pH 6.8 using the paddle method at 75 rpm or the basket method at 100 rpm and meets the criteria of dissolution profile similarity, $f_2 \geq 50$ (or equivalent statistical criterion);

(ii) if both the comparator and the multisource dosage forms are *very rapidly dissolving* (as defined in section 10.1.2.1) the two products are deemed equivalent and a profile comparison is not necessary.

2. Dosage forms of APIs that are highly soluble and have low permeability (BCS Class 3) are eligible for biowaivers provided all the criteria (a–d) listed in section 10.2 are met and the risk–benefit is additionally addressed in terms of extent, site and mechanism of absorption.

In general, the risks of reaching an inappropriate biowaiver decision need to be more critically evaluated when the extent of absorption is lower (especially if absolute bioavailability < 50%); therefore it is essential that the excipients in the proposed product formulation be scrutinized carefully. In order to minimize the risk of an inappropriate decision, excipients in the proposed product formulation should be qualitatively the same and quantitatively similar to that of the comparator.

If it is deemed that the risk of reaching an inappropriate biowaiver decision and its associated risks to public health and for individual patients is acceptable, the multisource product is eligible for a biowaiver based on BCS when both the comparator and the multisource dosage forms are *very rapidly dissolving* (85% dissolution in 15 minutes as described in section 10.1.2.1).

10.3 In vitro equivalence testing based on dose-proportionality of formulations

Under certain conditions, approval of different strengths of a multisource product can be considered on the basis of dissolution profiles if the formulations have proportionally similar compositions.

10.3.1 Proportional formulations

For the purpose of this guidance proportional formulations can be defined in two ways, based on the strength of dosage forms.

(i) All active and inactive ingredients are exactly in the same proportions in the different strengths (e.g. a tablet of 50 mg strength has exactly half of all the active and inactive ingredients contained in a tablet of 100 mg

strength and twice what would be contained in a tablet of 25 mg strength). For immediate-release products, coating components, capsule shell, colour agents and flavours are not generally required to meet this requirement.

(ii) For an FPP, where the amount of the API in the dosage form is relatively low (up to 10 mg per dosage unit or not more than 5% of the weight of the dosage form), the total weight of the dosage form remains similar for all strengths.

For (ii) a waiver is considered:

- if the amounts of the different excipients or capsule contents are the same for the strengths concerned and only the amount of the API has changed;
- if the amount of filler is changed to account for the change in amount of API: the amounts of other core excipients or capsule content should be the same for the strengths concerned.

10.3.2 Qualification for biowaivers based on dose-proportionality of formulations

10.3.2.1 Immediate-release tablets

A biowaiver based on dose-proportionality of formulations for a series of strengths of a multisource product, when the pharmaceutical products are manufactured with the same manufacturing process, may be granted when:

(i) an in vivo equivalence study has been performed on at least one of the strengths of the formulation. As described in section 7.4.1, the strength studied will usually be the highest strength, unless a lower strength is chosen for reasons of safety or the API is highly soluble and displays linear pharmacokinetics);

(ii) all strengths are proportionally similar in formulation to that of the strength studied;

(iii) the dissolution profiles for the different strengths are similar at pH 1.2, 4.5, 6.8 and for the QC media, unless justified by the absence of sink conditions. If the different strengths of the test product do not show similar dissolution profiles owing to the absence of sink conditions in any of the above media, this should be substantiated by showing similar dissolution profiles when testing the same dose per vessel (e.g. two tablets of 5 mg versus one tablet of 10 mg) or by showing the same behaviour in the comparator product.

As for the BCS-based biowaiver, if both strengths release 85% or more of the label amount of the API in 15 minutes, using all three dissolution media as recommended in section 10.2, the profile comparison with an f_2 test is unnecessary.

In the case where an immediate-release dosage form with several strengths deviates from proportionality a bracketing approach is possible, so that only two strengths representing the extremes need to be studied in vivo.

If approval of one strength of a product is based on a BCS-based biowaiver instead of an in vivo equivalence study, other strengths in the series of strengths should also be assessed based on BCS-based biowaivers as opposed to a biowaiver based on dose proportionality.

10.3.2.2 Delayed-release tablets and capsules

For delayed-release tablets, for a series of strengths of a multisource product where the strengths are proportionally similar in formulation to that of the strength studied in an in vivo equivalence study, a lower strength can be granted a biowaiver if it exhibits similar dissolution profiles, $f_2 \geq 50$, in the recommended test condition for delayed-release product, e.g. dissolution test in acid medium (pH 1.2) for 2 hours followed by dissolution in pH 6.8. When evaluating proportionality in composition, it is recommended to consider the proportionality of gastro-resistant coating with respect to the surface area (not to core weight) to have the same gastro-resistance (mg/cm²).

For delayed-release capsules where different strengths have been achieved solely by means of adjusting the number of beads containing the API, similarity in the dissolution profile of the new (lower) strength to that of the approved strength ($f_2 > 50$) under the test conditions recommended for delayed-release products (see above) is sufficient for a biowaiver.

10.3.2.3 Extended-release tablets and capsules

(a) For extended-release tablets, when there is a series of strengths of a multisource product that are proportionally similar in their active and inactive ingredients and have the same API-release mechanism, in vivo bioequivalence studies should be conducted with the highest proposed strength. Subsequently, lower strengths in the series can be granted a biowaiver if they exhibit similar dissolution profiles to the highest strength, $f_2 \geq 50$, in three different pH buffers (between pH 1.2 and 7.5) and the QC media by the recommended test method.

(b) For extended-release tablets with an osmotic pump release mechanism, the dissolution profile comparison ($f_2 \geq 50$) under one recommended test condition is sufficient for a biowaiver based on dose-proportionality of formulation.

(c) For extended-release, beaded capsules where different strengths have been achieved solely by means of adjusting the number of beads containing the API, a dissolution profile comparison ($f_2 \geq 50$) under one recommended test condition is sufficient for a biowaiver based on dose-proportionality of formulation.

10.3.3 Dissolution profile comparison for biowaivers based on dose-proportionality of formulations

As for biowaivers based on the BCS, a model independent mathematical approach (e.g. f_2 test) can be used for comparing the dissolution profiles of two products. The dissolution profile of the two products (reference strength[3] and additional strength) should be measured under the same test conditions.

The dissolution sampling times for both reference strength and additional strength profiles should be the same. For example:

- for immediate-release products 5, 10, 15, 20, 30, 45 and 60 minutes;
- for 12-hour extended-release products 1, 2, 4, 6, 8 and 12 hours;
- for 24-hour extended-release products 1, 2, 4, 6, 8, 16 and 24 hours.

For the application of the f_2 value see Appendix 1.

10.4 In vitro equivalence testing for non-oral dosage forms

In the case of intravenous micellar solutions with the same qualitative and quantitative composition of the surfactant, but significant changes to other excipients, an in vitro comparison might avoid the need for in vivo studies if a similar micellar system and API release from the micelle after dilution of the FPP or API administration into the blood system is ensured (*24*).

Locally-applied, locally-acting products in the form of aqueous suspensions containing the same API(s) in the same molar concentration and essentially the same excipients in comparable concentrations might be waived from the demonstration of equivalence by means of local availability, pharmacodynamic or clinical studies if in vitro characterization is able to ensure a similar crystallographic structure and particle size distribution as well as any other in vitro test specific for each dosage form, e.g. dissolution. The methodological details for the techniques mentioned below are not covered in these guidelines. Additional information regarding these techniques should be sought from guidelines produced by SRAs or from state-of-the-art literature.

[3] The reference strength is the strength of the FPP that was compared to the comparator product in an in vivo equivalence study.

(a) Suspensions for nebulization with the same qualitative and quantitative composition as the comparator product might be waived from in vivo studies if the particles in the suspensions are shown to have the same crystallographic structure and particle size distribution as those from the comparator product, as well as comparability in any other appropriate in vitro test, e.g. dissolution. In addition, the nebulized droplets should exhibit a similar aerodynamic particle size distribution to that of the comparator product.

(b) Suspensions for nebulization with the different qualitative and quantitative composition might be granted a waiver if, in addition to the requirements defined above under (a), the difference in excipient composition does not alter the nebulizer efficiency (e.g. by the presence or absence of a different surfactant or preservative) and the aerodynamic particle size distribution (e.g. altering product hygroscopicity by the presence of a different amount of salt as isotonic agent). To this end the appropriate state-of-the-art in vitro test should be conducted to ensure product equivalence. Any difference in excipients should be critically reviewed because certain excipients that are considered irrelevant in other dosage forms (e.g. preservative, substance to adjust tonicity or thickening agent) may affect safety and/or efficacy of the product.

(c) Nasal drops where the API is in suspension with the same qualitative and quantitative composition as the comparator product might be waived from in vivo studies if the particles in suspension are shown to have the same crystallographic structure and similar particle size distribution to that of the comparator product, as well as comparability in any other appropriate in vitro test, e.g. dissolution.

(d) Nasal drops where the API is in suspension, with qualitative or quantitative differences in excipient composition with respect to the comparator product, might be waived from in vivo studies if, in addition to the requirements defined above under (c), the difference in excipient composition does not affect efficacy and safety (e.g. a different preservative may affect the safety profile due to greater irritation of the nasal passages and a different viscosity or thixotropy may affect the residence time in the site of action). Therefore any difference in excipients should be critically reviewed.

(e) Nasal sprays in solution with the same qualitative and quantitative composition in excipients can be granted waivers based on a battery of in vitro tests as defined by SRAs (*18*, *25*).

(f) Nasal sprays in solution with qualitative and quantitative differences in the excipient composition might be waived if, in addition to showing similarity in the battery of in vitro tests referenced under (e), differences in excipients are critically reviewed as described above under (d).

(g) Nasal sprays in suspension with the same qualitative and quantitative composition in excipients might be waived if, in addition to the battery of in vitro tests referenced above under (e), the particles in suspension are shown to have the same crystallographic structure and similar particle size distribution, as well as comparability in any other appropriate in vitro test, e.g. dissolution.

(h) Nasal sprays in suspension with qualitative and quantitative differences in excipient composition might be waived if, in addition to the battery of in vitro tests referenced above under (e) and (g), differences in excipients are critically reviewed as described above under (d).

(i) In the case of pressurized metered dose inhalers in solution or suspension, in vivo studies might be waived if similarity is shown in a battery of in vitro tests as described in specific guidelines produced by SRAs (*26*). A waiver of in vivo studies for a dry powder inhaler (DPI) is not considered feasible unless the device for the DPI is identical to the comparator.

(j) For pharmaceutically-equivalent topical gel products, equivalence can be demonstrated by means of in vitro membrane diffusion studies when the products contain essentially the same excipients in comparable concentrations and the API(s) in the product are in solution (*27*).

(k) Otic and ophthalmic suspensions with the same qualitative and quantitative composition in excipients might be granted a waiver if the particles in suspension are shown to have the same crystallographic structure and similar particle size distribution, as well as comparability in any other appropriate in vitro test, e.g. dissolution.

(l) Products acting locally in the GI tract containing highly soluble APIs (as defined by the BCS) in immediate-release dosage forms might be waived from in vivo equivalence studies based on the same dissolution requirements as are applied for the BCS-based biowaiver.

10.5 In vitro equivalence testing for scale-up and post-approval changes

Although these guidelines refer primarily to registration requirements for multisource pharmaceutical products, it should be noted that under certain conditions, following permissible changes to formulation or manufacturing after FPP approval, in vitro dissolution testing may also be suitable to confirm similarity of product quality and performance characteristics. More information on when dissolution testing may be used to support product variations is provided in WHO guidance on variations in pharmaceutical products.

References

1. Agreement on Trade-Related Aspects of Intellectual Property Rights. Marrakesh Agreement Establishing the World Trade Organization, 1994, Annex 1 C.
2. HHS/FDA Guidance for industry: bioavailability and bioequivalence studies for orally administered medicine products – general considerations. Rockville (MD): Department of Health and Human Services, US Food and Drug Administration; 2003 (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070124.pdf, accessed 20 February 2015).
3. Guidelines for registration of fixed-dose combination medicinal products. 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): 94–142.
4. Guidelines for good clinical practice for trials on pharmaceutical products. In: WHO Expert Committee on the Selection and use of Essential Medicines: sixth report. Geneva: World Health Organization; 1995: Annex 3 (WHO Technical Report Series, No. 850):97–137.
5. Handbook. Good laboratory practice (GLP). Quality practices for regulated non- clinical research and development, second edition. Geneva: World Health Organization, on behalf of the Special Programme for Research and Training in Tropical Diseases; 2009.
6. Guidelines for organizations performing in vivo bioequivalence studies. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: Fortieth report. Geneva: World Health Organization; 2006: Annex 9 (WHO Technical Report Series, No. 937).
7. Julious SA. Sample sizes for clinical trials with normal data. Stat Med. 2004;23(12):1921–86.
8. Revision/update of the guidance on the selection of comparator pharmaceutical products for equivalence assessment of interchangeable multisource (generic) products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-ninth report. Geneva: World Health Organization; 2015: Annex 8 (WHO Technical Report Series, No. 992).
9. Midha KK, Rawson MJ, Hubbard JW. Commentary: the role of metabolites in bioequivalence. Pharm Res. 2004;21(8):1331–44.
10. Schuirmann DJ. A comparison of the two one-sided tests procedure and the power approach for assessing the equivalence of average bioavailability J Pharmacokinet Biopharm. 1987; 15(6):657–80.
11. Westlake WJ. Bioavailability and bioequivalence of pharmaceutical formulations. In: Peace KE, editor. Biopharmaceutical statistics for drug development. New York: Marcel Dekker; 1988:329–52.

12. Pocock SJ. Group sequential methods in the design and analysis of clinical trials. Biometrika. 1977;64(2):191–99.

13. ICH E3, Structure and content of clinical study reports. Geneva: International Conference on Harmonisation (ICH) Secretariat/IFPMA; 1995.

14. Blume HH, Midha KK. Bio-International 92, Conference on bioavailability, bioequivalence and pharmacokinetic studies. J Pharm Sci. 1993;82(11):1186–9.

15. Tothfalusi L, Endrenyi L, Midha KK, Rawson MJ, Hubbard JW. Evaluation of bioequivalence of highly variable drugs and drug products. Pharm Res. 2001;18(6):728–33.

16. Tothfalusi L, Endrenyi L, Midha KK. Scaling or wider bioequivalence limits for highly variable drugs and for the special case of C(max). Int J Clin Pharmacol Ther. 2003;41(5):217–25.

17. Tothfalusi L, Endrenyi L. Limits for scaled average bioequivalence of highly variable drugs and drug products. Pharm Res. 2003;20(3):382–9.

18. Yusuf S, Wittes J, Friedman L. Overview of results of randomized clinical trials in heart disease. II. Unstable angina, heart failure, primary prevention with aspirin, and risk factor modification. JAMA. 1988;260(15):2259–63.

19. The Studies of Left Ventricular Dysfunction (SOLVD) Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med. 1991;325:293–302. DOI: 10.1056/NEJM199108013250501.

20. The International Pharmacopoeia. Geneva: World Health Organization (www.who.int/medicines/publications/pharmacopoeia/, accessed 5 January 2015).

21. Amidon GL, Lennernäs H, Shah VP, Crison JR. A theoretical basis for a biopharmaceutic drug classification: The correlation of in vitro drug product dissolution and in vivo bioavailability. Pharm Res. 1995;12:413–20.

22. Yu LX, Amidon GL, Polli JE, Zhao H, Mehta MU, Conner DP, et al. Biopharmaceutics Classification System: The scientific basis for biowaiver extensions. Pharm Res. 2002;19:921–5.

23. WHO guidelines on variations to a prequalified product. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-seventh report. Geneva: World Health Organization; 2013 (WHO Technical Report Series, No. 981): 154.

24. Guideline on the investigation of bioequivalence, London: Committee for Medicinal Products for Human Use (CHMP), European Medicines Agency; 2010 (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/01/WC500070039.pdf, accessed 5 January 2015).

25. European Medicines Agency – Compilation of individual product specific guidance on demonstration of bioequivalence. London: European Medicines Agency; 2014 (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/12/WC500179395.pdf, accessed 20 February 2015).

26. HHS/FDA Draft guidance for industry, bioavailability and bioequivalence studies for nasal aerosols and nasal sprays for local action. Rockville (MD): US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER); 2003.

27. HHS/FDA Guidance for industry, nonsterile semisolid dosage forms scale-up and postapproval changes: chemistry, manufacturing, and controls; in vitro release testing and in vivo bioequivalence documentation. Rockville (MD): US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER); 1997.

Further reading

Committee for Medicinal Products for Human Use/European Medicines Agency Guideline on the requirements for clinical documentation for orally inhaled products (OIP) including the requirements for demonstration of therapeutic equivalence between two inhaled products for use in the treatment of asthma and chronic obstructive pulmonary disease (COPD). (CPMP/EWP/4151/00 rev 1). London: CHMP/EMA; 2009 (http://www.ema.europa.eu, accessed 5 January 2015).

European Medicines Agency. Reflection paper on guidance for laboratories that perform the analysis or evaluation of clinical trial samples. London: EMA; 2010 (EMA/INS/GCP/532137/2010). Fares HM, Zats JL. Measurement of drug release from topical gels using two types of apparatus. Pharm Tech. 1995;52–8.

International Conference on Harmonisation. ICHE6. Good clinical practice: consolidated guidance, Geneva: ICH; 1996 (http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.htm).

Moore JW, Flanner HH. Mathematical comparison of curves with an emphasis on in vitro dissolution profiles. Pharm Tech. 1996;20:64–74.

Shah VP, Tsong Y, Sathe P, Liu JP. In vitro dissolution profile comparison – statistics and analysis of the similarity factor, f2. Pharm Res. 1998;15:889–96.

WHO. General guidance on variations to multisource pharmaceutical products. (QAS/14.575).

WHO. 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, 2007).

WHO. Good clinical laboratory practice (GCLP). Geneva: World Health Organization, on behalf of the Special Programme for Research and Training in Tropical Diseases; 2009.

Appendix 1

Recommendations for conducting and assessing comparative dissolution profiles

The dissolution measurements of the two finished pharmaceutical product (FPPs (e.g. test and comparator or two different strengths) should be made under the same test conditions. A minimum of three time-points (zero excluded) should be included, the time-points for both reference (comparator) and test product being the same. The sampling intervals should be short for a scientifically sound comparison of the profiles (e.g. 5, 10, 15, 20, 30, 45 and 60 minutes for an immediate-release dosage form). The 15-minute time-point is critical to determine whether a product is very rapidly dissolving and to determine whether f_2 must be calculated. For extended-release FPPs the time-points should be set to cover the entire duration of expected release, e.g. in addition to earlier time-points: samples at 1, 2, 3, 5 and 8 hours should be collected for a 12-hour release and additional test intervals would be necessary for longer duration of release.

Studies should be performed in at least three media covering the physiological range, including pH 1.2 hydrochloric acid, pH 4.5 buffer and pH 6.8 buffer. Ph.Int. buffers are recommended; other pharmacopoeial buffers with the same pH and buffer capacity are also accepted. Water may be considered as an additional medium, especially when the API is unstable in the buffered media to the extent that the data are unusable.

If both the test and reference (comparator) products show more than 85% dissolution in 15 minutes the profiles are considered similar (no calculations required). Otherwise:

- similarity of the resulting comparative dissolution profiles should be calculated using the following equation that defines a similarity factor (f_2)

  $$f_2 = 50 \text{ LOG } \{[1+1/n \sum^{n}_{t=1} (R_t - T_t)^2]^{-0.5} \times 100\}$$

  where R_t and T_t are the mean per cent API dissolved in reference (comparator) and test product, respectively, at each time-point. An f_2 value between 50 and 100 suggests that the two dissolution profiles are similar;
- a maximum of one time-point should be considered after 85% dissolution of the reference (comparator) product has been reached;

- in the case where 85% dissolution cannot be reached owing to poor solubility of the API or the release mechanism of the dosage form, the dissolution should be conducted until an asymptote (plateau) has been reached;
- at least 12 units should be used for determination of each profile. Mean dissolution values can be used to estimate the similarity factor, f_2. To use mean data the percentage coefficient of variation at time-points up to 10 minutes should be not more than 20% and at other time-points should be not more than 10%;
- when delayed-release products (e.g. enteric coated) are being compared, the recommended conditions are acid medium (pH 1.2) for 2 hours and buffer pH 6.8 medium;
- when comparing extended-release beaded capsules, where different strengths have been achieved solely by means of adjusting the number of beads containing the API, one condition (normally the release condition) will suffice;
- surfactants should be avoided in comparative dissolution testing.

A statement that the API is not soluble in any of the media is not sufficient, and profiles in the absence of surfactant should be provided. The rationale for the choice and concentration of surfactant should be provided. The concentration of the surfactant should be such that the discriminatory power of the test will not be compromised.

Annex 8

Guidance on the selection of comparator pharmaceutical products for equivalence assessment of interchangeable multisource (generic) products

1. Introduction

In recent years the need for the regulation and assurance of quality of medicines has continued to increase. Large numbers of multisource (generic) medicines are being produced by many different companies and in different countries; this may result in different products. On a global level there is thus a need to address not only the quality, safety and efficacy of multisource products that are exported and imported, but also their possible interchangeability.

In light of the various approaches in scientific and regulatory environments, the feasibility of developing a system of international comparator products was considered in the past. This initiative led to the recommendations published in 2002 entitled, *Guidance on the selection of comparator pharmaceutical products for equivalence assessment of interchangeable multisource (generic) products* (*1*). Since the guidance was published, the World Health Organization (WHO) Model List of Essential Medicines (EML) has been revised several times and many of the products originally listed are no longer marketed and/or available as indicated in the list, which means that the list of international comparators recommended by the WHO Expert Committee on Preparations for Pharmaceutical Specifications needs updating.

In view of the complexity of the list of comparators it was decided to prepare two new, separate, guidance documents: one on the selection of comparator products, including the general guidance on how to select comparator products, and the second one comprising the international list of comparator products. The aim was to facilitate the updating and maintenance process.

2. Background

The *Guidelines on registration requirements to establish interchangeability for multisource (generic) pharmaceutical products* (*2*) are designed to provide recommendations to national regulatory authorities and manufacturers on the requirements for approval of multisource (generic) pharmaceutical products in their respective countries. The guidance provides appropriate in vivo and in vitro requirements to assure interchangeability of the multisource product.

Multisource pharmaceutical products need to conform to the same appropriate standards of quality, efficacy and safety as those applicable to the innovator's product. In addition, reasonable assurance should be provided that the multisource product is therapeutically equivalent and interchangeable with the comparator product. For some classes of products including, for example, parenteral formulations of highly water-soluble compounds, interchangeability is adequately assured by implementation of good manufacturing practices (GMP) and provision of evidence of conformity with relevant pharmacopoeial specifications.

This guidance document provides an update of the previously published list (*1*) and the respective chapter on selection of comparator products (*3*, *4*). The information could also be used for medicine procurement purposes.

The historical development of comparator product criteria is summarized in Table A8.1.

Table A8.1
Historical development of comparator product criteria

Year	Development	Description
Pre-1996	International Conference of Drug Regulatory Authorities (ICDRA) (1991 and 1994) recommended development of global standards and requirements for interchangeability of multisource products; WHO initiated the process	No agreement on the criteria for selecting a list of international comparator products or any list of such products exists. The comparator product chosen is either the most widely used (leading) product on the market or the product that was first introduced in that market. For this reason, among others, significant differences could exist between the comparator products used in different countries
1996	The question of choice of reference product was raised	*Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability* (WHO Technical Report Series, No. 863), Annex 9, including Appendix 7 on "Choice of reference product"
2002	WHO issued the first list of *International comparator products for equivalence assessment of interchangeable multisource (generic) products*	*Guidance on the selection of comparator pharmaceutical products for equivalence assessment of interchangeable multisource (generic) products* (WHO Technical Report Series, No. 902), Annex 11
2006	"In order of preference" principle in comparator product selection was clarified	*Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability* (WHO Technical Report Series, No. 937), Annex 7

3. General principles

The comparator product is defined as a pharmaceutical product with which the multisource product is intended to be interchangeable in clinical practice.

As a general principle, multisource products should comply with the same standards of quality, safety and efficacy as are applicable to the corresponding comparator product. In addition, quality attributes of a multisource product should be tested against the comparator product with which it should be interchangeable.

The selection of the comparator pharmaceutical product is usually made at the national or regional level by the national or regional regulatory authority.

The innovator product is usually the most logical comparator product because its quality, safety and efficacy should have been well assessed in pre- and post-marketing studies and, in addition, the data on its safety and efficacy are usually linked to a pharmaceutical product with defined specifications for quality and performance. However, these products may not always be easy to obtain or may no longer be available on the market. The comparator product chosen is therefore often the most widely used product (market leader) or the product that was first introduced in that market. For this reason, among others, significant differences may exist between the comparator products used in different countries.

In principle, a national regulatory authority has several options for selection of a comparator product. These are listed below in order of preference:

1. the innovator product for which quality, safety and efficacy has been established if this product has been granted a national marketing authorization (*nationally authorized innovator*);
2. national market leader product for which a national marketing authorization has been granted;
3. the WHO-recommended comparator product included in the International list of comparator products (*1*) or, if different and if it exists for the active pharmaceutical ingredient in question, the one suggested within the context of the Prequalification Team;
4. an innovator product approved by a stringent regulatory authority, i.e. a country associated to The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH);
5. a product that has been granted approval in an ICH-associated country;
6. in the case that no innovator or comparator product can be identified according to the above, the choice of the comparator

should be made carefully and should be comprehensively justified by the applicant. In this case, the most important selection criteria in order of preference are:

- prequalification by WHO,
- extensive documented use in clinical trials reported in peer-reviewed scientific journals,
- a long and unproblematic period of post-market surveillance.

Additionally, these comparators should conform to all appropriate compendial quality standards.

It is important to note that a product that has been approved based on comparison with a comparator product that has no national marketing authorization in the country which approved the multisource product, including the study for interchangeability, may or may not be interchangeable with currently marketed domestic products.

The choice of comparator product should be justified by the applicant. The country of origin of the comparator product should be reported together with the product's lot number and expiry date. Consultation with the relevant regulatory authority before purchase of the comparator product is strongly recommended.

Information specifically related to the selection of comparator products for use in studies to be conducted for submission to the WHO Prequalification Team – Medicines is available on the WHO website (www.who.int/prequal) and in the WHO comparator document (*1*).

References

1. Guidance on the selection of comparator pharmaceutical products for equivalence assessment of interchangeable multisource (generic) products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: thirty-sixth report. Geneva: World Health Organization; 2002: Annex 11 (WHO Technical Report Series, No. 902).
2. Guidelines on registration requirements to establish interchangeability for multisource (generic) pharmaceutical products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-ninth report. Geneva: World Health Organization; 2014: Annex 7 (WHO Technical Report Series, No. 992).
3. Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fortieth report. Geneva: World Health Organization; 2006: Annex 7 (WHO Technical Report Series, No. 937).
4. Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. Revision. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-ninth report. Geneva: World Health Organization; 2014: Annex 7 (WHO Technical Report Series, No. 992).

Annex 9

Good review practices: guidelines for national and regional regulatory authorities[1]

Background

The good review practices (GRevP) guidelines for regulatory authorities emanate from a partnership between the Asia-Pacific Economic Cooperation (APEC) Regulatory Harmonization Steering Committee (RHSC) and the World Health Organization (WHO). This is the first set of guidelines of its kind globally and addresses an important gap identified at the 2012 International Conference of Drug Regulatory Authorities (ICDRA). Although the RHSC does not directly produce guidelines, contributing to WHO guidelines is in line with the RHSC's principle of working with appropriate partners to achieve common objectives.

In June 2013 the RHSC convened an expert working group with WHO representation to develop a draft GRevP document, intended to cover both medicines and medical devices, for submission to WHO in early 2014. The draft document subsequently underwent the required WHO consultation process with a view to its further development into WHO guidelines for adoption by the Expert Committee on Specifications for Pharmaceutical Preparations and the Expert Committee on Biological Standardization. This led to these new GRevP guidelines for regulatory authorities adopted by the WHO Expert Committee on Specifications for Pharmaceutical Preparations at its forty-ninth meeting.

[1] Asia-Pacific Economic Cooperation (APEC) Regulatory Harmonization Steering Committee (RHSC) good review practices (GRevP) with the participation of Working Group Members representing the regulatory authorities (RAs) from the economies of Australia, Canada, Taipei (China), Japan, Republic of Korea, Saudi Arabia, Singapore, United States of America; and representatives of the Centre for Innovation in Regulatory Science (CIRS); and the Food and Drug Administration Alumni Association International (FDAAA).

1. Introduction

1.1 Document objective

The objective of this document is to provide high-level guidance on the principles and processes of good review practice (GRevP) for use across a range of regulatory authority (RA) maturities. It is not intended to provide detailed instruction on how to conduct a scientific review.

This document is envisioned as one building block in a set of tools and is sufficiently expandable to accommodate additional annexes or ancillary documents in the future.

1.2 Context

RAs are increasingly seeking ways to improve their performance and ensure the quality of their regulatory systems. GRevPs are an integral part of overall good regulatory practices and focus on the medical product review aspect of regulatory work. Review is a highly complex, multidisciplinary assessment of the medical product applications to ensure that they meet the scientific and evidentiary standards for safety, efficacy[2] and quality. It forms the scientific foundation for regulatory decisions.

The extent to which an RA can achieve timeliness of the review (i.e. completion within a specified time frame), as well as predictability, consistency, transparency, clarity, efficiency and high quality, can have a significant impact on public health (for example, in relation to patients' access to important medical products, and costs to both government and applicants). Implementation of GRevPs helps to achieve these outcomes by ensuring that those involved in the review process have the critical thinking skills and tools needed to optimize scientifically sound, evidence-based decisions. It also facilitates progress towards regulatory convergence through the exchange of review reports and the enhancement of mutual understanding among RAs.

Several RAs have introduced ways of monitoring and improving their review process through structured approaches or by moving towards stepwise implementation of GRevPs. RAs should consider review models and best practices within the context of available resources and legal requirements. The GRevP principles and elements described in this document can be adapted to meet the continuous needs for improvement of a diverse range of RAs.

[2] Although effectiveness is the term often used for medical devices, efficacy is used throughout this document.

1.3 Definition of good review practices

GRevPs are documented best practices for any aspect related to the process, format, content and management of a medical product review. The objective of GRevPs is to help achieve timeliness, predictability, consistency, transparency, clarity, efficiency and high quality in both the content and management of reviews. This is done through the development of review tools (for example, standard operating procedures (SOPs) and templates) and reviewer learning activities (for example, training courses, mentoring, orientation packages and discussion sessions). To promote continuous improvement, all aspects of GRevPs should be continuously evaluated and updated.

1.4 Scope

This document applies to the review of safety, efficacy and quality data in medical product applications filed with RAs for marketing authorization.

Although this document was written to provide guidance on pharmaceutical products and biologicals and higher-risk medical devices used in humans, the concepts may be applied to other types of medical products. Similarly, the concepts could also be applied to the entire product life cycle from investigational testing to new product applications, updates or variations to existing marketing authorizations and maintenance of the product.

2. Glossary

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

applicant. The person or company who submits an application for marketing authorization of a new medical product, an update to an existing marketing authorization or a variation to an existing marketing authorization.

application. The information provided by the applicant to the RA for evidence-based review and marketing authorization decision.

good regulatory practices (GRP). Reference definition in WHO GRP guidelines (currently under development)

good review practices (GRevP). Documented best practices for any aspect related to the process, format, content and management of a medical product review.

marketing authorization. Also referred to as product licence or registration certificate. A legal document issued by the competent medicines RA that authorizes the marketing or free distribution of a medical product in the respective country after evaluation of safety, efficacy and quality. In terms of quality it establishes inter alia the detailed composition and formulation of the medical product and the quality requirements for the product and its ingredients.

It also includes details of the packaging, labelling, storage conditions, shelf-life and approved conditions of use.

principles (of a good review). The important GRevP elements for RAs to implement in order to achieve successful review outcomes.

project management (for the review process). The planning, organization and resources to achieve a complete and high quality review of an application within a specified time frame.

quality management (QM). The coordinated activities that direct and control an organization with regard to quality.

quality management (QM) system. An appropriate infrastructure, encompassing the organizational structure, procedures, processes and resources and systematic actions necessary to ensure adequate confidence that a product or service will satisfy given requirements for quality.

regulatory authority (RA). The agency responsible for the registration of and other regulatory activities concerning medical products.

regulatory convergence. The process whereby regulatory requirements, approaches and systems become more similar or aligned over time as a result of the adoption of internationally recognized technical guidance, standards and best practices.

review. A highly complex, multidisciplinary assessment of medical product applications to assess whether they meet scientific and evidentiary standards for safety, efficacy and quality. It forms the scientific foundation for regulatory decisions. The first stage of the review process, validation (sometimes referred to as screening), occurs before the scientific review with the aim of ensuring completeness of the application in order to subsequently facilitate the scientific review.

review strategy. The approach or plan of action that a reviewer or review team uses to review a medical product application.

standard operating procedure (SOP). An authorized written procedure giving instructions for performing operations (both general and specific).

transparency. Defining policies and procedures in writing and publishing the written documentation, and giving reasons for decisions to the public.

3. Principles of a good review

As noted in the definition of GRevP, the objective of GRevPs is to help achieve successful review outcomes. The principles of a good review describe the GRevP elements that are important for RAs to implement in order to achieve successful review outcomes. Listed in alphabetical order in Box A9.1, the 10 key principles of a good review are provided as a general guide for RAs. Although not prescriptive in nature, they can serve as a solid GRevP foundation upon which RAs can continue to build.

Box A9.1
10 key principles of a good review

Balanced
A good review is objective and unbiased.

Considers context
A good review considers the data and the conclusions of the applicant in the context of the proposed conditions of use and storage, and may include perspectives from patients, health-care professionals and other RAs' analyses and decisions.

Evidence-based
A good review is evidence-based and reflects both the scientific and regulatory state of the art. It integrates legislative, regulatory and policy frameworks with emerging science.

Identifies signals
A good review comprehensively highlights potential areas of concern identified by the applicant and the reviewers.

Investigates and solves problems
A good review provides both the applicant's and the reviewers' in-depth analyses and findings of key scientific data and uses problem-solving, regulatory flexibility, risk-based analyses and synthesis skills to devise and recommend solutions and alternatives where needed.

Makes linkages
A good review provides integrated analysis across all aspects of the application: preclinical; nonclinical; clinical; chemistry/biocompatibility; manufacturing; and risk management plan. It includes timely communication and consultation with applicants, internal stakeholders and, as needed, with external stakeholders who have expertise relevant to the various aspects of the application.

Thorough
A good review reflects adequate follow-through of all the issues by the reviewers.

Utilizes critical analyses
A good review assesses the scientific integrity, relevance and completeness of the data and proposed labelling, as well as the interpretation thereof, presented in the application.

Well-documented
A good review provides a well-written and thorough report of the evidence-based findings and conclusions provided by the applicant in the dossier, and the reviewers' assessment of the conclusions and rationale for reaching a decision. It contains clear, succinct recommendations that can stand up to scrutiny by all the parties involved and could be leveraged by others.

Well-managed
A good review applies project and quality management processes, including clearly defined steps with specific activities and targets.

4. Managing the review

RAs actively manage the process of reviewing medical product applications in order to maximize both the potential for a positive public health impact and the effective and efficient use of review resources. RAs should clearly define the separate steps in the process, each with specific activities and targets.

The principles of project management and quality management are critical to well-functioning RAs. The practices of planning and monitoring review activities coupled with timely, informative communications within the RA and clearly-defined work instructions for the reviewers, can maximize the efficiency and effectiveness of the review.

4.1 Project management

Project management for the review process refers to the planning, organizing and resourcing necessary to achieve a complete and high-quality review of an application within a specified time frame.

Techniques to monitor the progress of applications under review will be specific to each RA. For example, an individual reviewer can use a simple table or spreadsheet, or a project manager may use computer software to monitor many applications at one time. Data should be periodically collected and interpreted to assess the effectiveness of the review strategy (see section 7) for completing reviews within the specified time frame.

The technique most suitable for the RA will be one that enables:

- interpretation of the data to show the progress of one application as well as that of many applications under review at any one time;
- interpretation of the data to help in decision-making with respect to balancing workload against resources;
- monitoring that can be performed and/or interpreted by the relevant people.

As the conditions, resources and workload for the RA evolve, the techniques and complexity of project management should also be adapted.

4.2 Quality management

Quality management (QM) is defined as the coordinated activities that direct and control an organization with regard to quality. A QM system refers to the appropriate infrastructure, encompassing the organizational structure, procedures, processes and resources, and systematic actions necessary to ensure adequate confidence that a product or service will satisfy given requirements for quality.

In an RA, QM includes standardized procedures to ensure that GRevPs are in place, regularly monitored and subject to continuous improvement. Beyond standardized processes and procedures that provide consistency and predictability, QM has the ultimate goal of supporting robust regulatory decisions and actions.

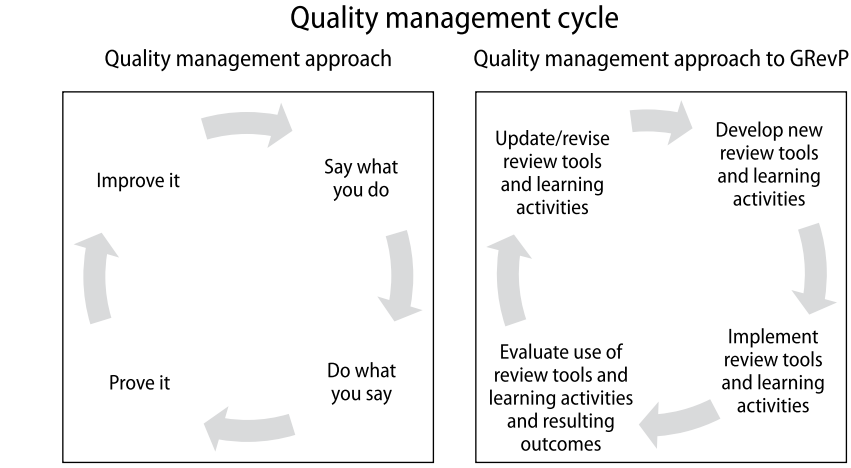
An RA's QM system will be influenced by a number of factors including size and resources of the RA, competencies, its particular objectives, the processes it employs, and its organizational structure. However, even RAs with limited resources can institute the key elements of QM. Successful QM implementation requires the commitment of senior management but is ultimately the responsibility of everyone in the organization.

The quality cycle is made up of four key components:

- say what you do
- do what you say
- prove it
- improve it.

This cycle ensures that GRevPs are not just esoteric guidelines (say what you do) but become embedded in the daily practice of an agency (do what you say). Quality management is also important as it can help an agency review its practice (prove it) and evolve where necessary, either in response to evolving regulatory science or through the adoption of a new review process and procedures (improve it) (Figure A9.1).

Figure A9.1
Quality management cycle



Source: Based on United States of America Food and Drug Administration figure.

4.2.1 Say what you do

- Provide key documents, such as SOPs and assessment templates.
- Define processes for decision-making, such as decision frameworks, time frames for completion and communication of reviews, use of external experts, public meetings and peer-review.

4.2.2 Do what you say

- Implement processes defined in key documents and adhere to specified time frames.
- Offer professional development, mentoring and regular on-the-job training.
- Record and collect key documents, such as minutes of meetings and teleconferences, memoranda, letters and reports.

4.2.3 Prove it

- Ensure that review procedures and templates are being consistently interpreted and applied through the assessment of various inputs, such as internal and external feedback and periodic evaluation of practices by internal and external experts.
- Assess public health impacts of regulatory decisions, such as through a lessons-learned session that could include assessing the impact on disease, the health-care system and any unintended consequences.

4.2.4 Improve it

- Review documentation and decision-making processes regularly.
- Consider introducing improvements to the review and decision-making process, such as: internal assessment of a review; peer review; internal quality audits; self-assessments; analyses of feedback from stakeholders; post-approval analysis of the decision in collaboration with other authorities; the public and applicants; and analysis of impact on public health.
- Implement new and improved work practices, the latest evaluation techniques, and scientific and technological advancements.

Implementing QM is an iterative process that incorporates lessons learned with regard to improved processes and decision-making.

4.3 Standard operating procedures

Creating and adopting a set of SOPs enables the RA to:

- outline the workflow processes that facilitate project management when multiple reviewers assess different parts of the same application and when there are multiple applications to review;
- handle and review product applications in a consistent manner;
- facilitate staff training.

SOPs are authorized written procedures giving instructions for performing operations (both general and specific). They describe procedures (or processes) in a step-by-step manner. They may be detailed or brief, but should describe the overall procedure from start to finish. SOPs should be written clearly to provide both instruction and consistency related to the work being performed.

SOPs may be structured to contain additional tools that will assist in performing the procedure. Alternatively, companion documents can be created to give more detailed instruction and structure in support of an SOP. These companion documents (for example, guidelines for reviewers, templates and checklists) can describe in detail how a particular procedure is performed or give advice on handling a specific situation when performing the procedure.

Templates and checklists present information in a structured manner to facilitate understanding of the information submitted for review. Templates prompt the user to provide specific information, while checklists prompt the user to ensure either that information has been provided or that a particular task has been completed. Templates and checklists have the added benefit of training reviewers and review teams on how to provide information in a structured, consistent manner.

While SOPs have often been kept internal within an RA, making templates and checklists available to applicants can be beneficial in ensuring mutual understanding of the information to be submitted for review. SOPs can be further complemented by guidelines for applicants, in order to promote transparency and guide applicants on how to submit high-quality marketing authorization applications. Guidelines for applicants can be made available using a step-wise approach, usually involving informing applicants of the guidelines before making them publicly accessible.

SOPs, guidelines, templates and checklists will require updating (or in some cases even cancellation) as technological advances occur or scientific and regulatory thinking evolves. This evolution could be related to influences including scientific progress, international harmonization of guidelines, changes in review strategy, available resources, increased volume of applications, collaborative work-sharing and national laws and regulations, among others.

4.4 Review process stages

Two key stages in the process of reviewing medical product applications are validation[3] and scientific review. The validation stage occurs first, with the aim of ensuring completeness of the application in order to facilitate the subsequent scientific review.

Validation involves an examination of the application to ensure that it is well-organized and that all the required forms and relevant documents have been submitted. Identifying missing information in the application prior to scientific review enables the RA to avoid spending time and review resources on an application that does not allow critical analysis, signal identification or regulatory decision-making. Scientific review will be discussed further in section 7.

It is essential that applicants are made aware of the RA's expectations at both stages, including the target time frames, guidelines, requirements, templates and checklists. This results in a more predictable and clear process for applicants. In turn the RA benefits when applicants submit complete applications at the outset.

5. Communications

Good communication is critical and has many advantages for RAs, applicants and the public. It can improve the efficiency of the development and review process, allowing patients faster access to important medical products. It can also improve the quality of the review by providing access to additional expertise.

Communications can take many active forms, from providing information on RAs' websites to engaging with the international community on RA projects. In turn, these active forms of RA communications can be used to the advantage of others, including other RAs.

5.1 Intra-agency

Product reviews are conducted in a collaborative environment. They often require expertise from and coordination with different organizational units within the RA, such as pre- and postmarketing scientific disciplines, pharmacovigilance, inspection and others.

Therefore, good communication will improve efficiency. Open, clear, constructive and timely communications regarding the progress of the review, review findings, differing data interpretations and discussion of possible solutions and actions within the RA are desirable. In addition to establishing

[3] Although screening is a term that is also sometimes used, validation is used throughout this document.

meetings, forums and other vehicles for exchange of ideas among reviewers, a checklist of personnel or departments involved on specific issues or actions may be helpful. Information management systems should be process-centric rather than organizational structure-centric to ensure appropriate and efficient information flow.

5.2 Interagency

RA to RA communications have become more frequent and in many cases normative. As a means of peer collaboration and cooperation, interagency communications can facilitate greater regulatory convergence. This, in turn, can increase the efficiency and quality of medical product development and RA review processes and improve patient access. Types of interagency communication include:

- accessing information from other RAs' public websites, such as guidelines, application decisions and product recalls;
- using information from other RAs, such as review reports and certificates of pharmaceutical product;
- actively sharing information between RAs, such as nonclinical, clinical and inspection findings during an application review;
- actively working with other RAs, for example, on joint reviews of applications and development of new guidelines.

Interagency communication may evolve from sharing and awareness of information, to consideration of findings from one RA by another in its decision-making, to using and relying on those findings to make the best use of resources.

Information-sharing arrangements and procedures, such as memoranda of understanding, confidentiality arrangements, consent from the applicant, redaction and non-disclosure of specific information, as well as other arrangements and actions, have been used to ensure confidentiality of commercial data, trade secrets and personal information.

5.3 With applicants

Public availability of RA guidelines, notices, questions and answers and presentations, as well as finalized RA review reports and decision summaries (redacted as needed), provide insight into the RA's current thinking and expectations. These communications allow applicants to provide better quality applications.

Communication between the RA and individual applicants on specific applications before, during and after the review process is also important as it can:

- foster efficient medical product development through the provision of scientific advice;
- increase applicants' understanding of evolving regulatory expectations in a changing medical and scientific environment;
- increase the RA's understanding of challenges and trade-offs with various requirements;
- foster applicants' compliance with requirements (although it is also important for RAs to be open to proposals from applicants for alternative approaches that address the same requirements);
- inform applicants about the progress and status of the review of their applications.

Procedures allowing applicants and the RA to engage with each other can facilitate the development, review and availability of medical products. Topics for dialogue can relate to product development requirements (including feedback on guideline development and implementation), as well as issues identified during the application review or postmarketing.

5.4 With external experts

Expertise in the scientific assessment of the safety, efficacy and quality of medical products is not limited to applicants and RAs. Academic institutions, industry associations, patient organizations and medical and scientific organizations all have extensive expertise that may be useful to the review.

Asking for the input of external experts into RA decision-making improves public confidence, provides additional perspectives for the RA to consider and provides expertise that otherwise may be lacking. RAs have used advisory panels, both in public and closed sessions, to ensure that expertise and health-care contexts are addressed. RAs may also use a system whereby external experts conduct the review of all or part(s) of the application. Ensuring both confidentiality and absence of conflict of interest is important and can be achieved through transparent processes for management of confidential information and screening for potential conflicts.

5.5 With the public

Communication with the public about the mission and accomplishments of the RA can foster greater public awareness, understanding of and confidence in the RA. Transparency refers to defining policies and procedures in writing, publishing the written documentation, and giving reasons for decisions to the public. For the RA, transparency initiatives usually involve web-based information about how it is organized and operates, its decision-making processes and criteria,

and its actions, such as application approvals and product recalls. Additionally, there may be mechanisms whereby the public can provide input on medical needs, efficacy expectations and risk tolerances, such as through public meetings and RA advisory boards. Providing the public with the opportunity to comment permits enhanced content and feasibility of proposed guidelines and regulations. Use of plain language will ensure RA communications are properly understood.

The public may also be consulted on specific applications under review by the RA. There are various mechanisms by which this can be achieved, such as surveys, focus groups, public meetings, workshops and appointment to advisory boards.

6. Review personnel

The quality, timeliness and success of medical product application reviews are dependent on adequate RA review capacity. In addition to having a sufficient number of reviewers, capacity relates to many personnel factors including the knowledge, skills, abilities and attitudes of reviewers. Together, these considerations define the core competencies for personnel involved in the various aspects of managing and conducting reviews.

Reviewers may be RA staff, external experts or both. To ensure the integrity of product reviews and recommendations, reviewers should be free of actual or perceived conflicts of interests. To be free of any conflict of interest means the review decision or recommendation is not likely to be influenced by personal, family, financial or professional motives, including those of employers when an external expert is also a consultant to the regulated industry.

6.1 Reviewer expertise, competencies and training

The use of core competencies can contribute to improved application review by encouraging evidence-based, population-focused, ethical decision-making.

Core competency starts with reviewers who are scientifically trained. Reviewers should have professional qualifications, training and expertise in scientific or medical fields that relate to the assessment of medical product safety, efficacy and/or quality. Both practical and theoretical knowledge is desirable in order to achieve a good understanding of the issues likely to be associated with the product under review.

Reviewer competencies depend on the duties and scope of review work. Scientific writing, presentation of data, data analysis, inferential and deductive reasoning, risk-based analyses and problem-solving are important skills for reviewing a medical product application. Review staff should also follow sound ethical practices.

General competencies required to conduct review work include:

- knowledge of statutes, regulations, guidelines and precedents, including international guidelines and precedents, and their applicability;
- knowledge of the process of medical product development from early development phases to postmarketing surveillance and risk management;
- scientific communication skills for written evaluations, public presentations and negotiation and consensus building with applicants and stakeholders.

Reviewers should keep their scientific expertise up to date. Increasingly, regulatory science curricula from universities and international regulatory initiatives and organizations are available. Reviewers should have the opportunity to attend relevant conferences, courses and international meetings. Reviewers should also be encouraged to read scientific journals and to be members of professional societies or relevant organizations.

For on-the-job training, a site visit programme that allows reviewers to visit sites such as laboratories, manufacturing facilities and clinical settings may be considered. In addition, experienced reviewers should be encouraged to mentor and train junior reviewers. The establishment of structured training programmes within RAs to facilitate the professional development of review staff should also be considered, whenever feasible.

6.2 Critical thinking

Critical thinking requires an objective and systematic approach to analysing information and to problem-solving. It relies on the collection of data and evidence-based decision-making instead of generalizing from one's own experience, intuition or trial and error. Decisions should be reproducible and clearly understood by others.

Nevertheless, every regulatory decision involves judgement. Therefore, core competence in public health and bioethics, and the ability to integrate up-to-date scientific knowledge with an understanding of the evidentiary standards for regulatory action (including the flexibility inherent in those standards and regulations), can guide decisions.

Beyond their professional qualifications, reviewers should have the ability to critically appraise the information presented in an application and not just accept it as presented. This skill may often be developed or strengthened during the training process, for instance, by evaluating the responses to questions raised by a senior reviewer so that the questioning process becomes a learning tool.

Discussion among reviewers and external experts on application-specific issues can promote critical regulatory thinking and problem-solving.

Good judgement is required to come to a balanced decision. This involves focusing on the important issues in the application, rather than on data that provide more information, but will not ultimately affect the outcome of an application. Good judgement includes, where applicable, using international harmonized regulatory requirements and adopting regulatory approaches that show flexibility to maximize public health benefits while minimizing adverse, unintended consequences.

Regulatory decision-making or recommendations from reviewers should be based on the best current science. The public health needs of the country and its health-care system provide context for this decision-making. In decisions to grant authorization the benefits must, on balance, outweigh the risks, based on sound scientific evidence. Documentation of scientific rationale for decision-making, taking into account regulatory requirements, provides a record to ensure the integrity of the review process. The decision-making document should address dissenting, evidence-based views and clearly identify the information that was considered. Decision-making by an RA should be independent of influences beyond public health.

7. Conducting the review

Defining and then following an application-specific review strategy that is amended only as needed when new information comes to light, ensures soundness of the review process, the quality of the report and the efficient use of resources.

7.1 Key elements in defining a review strategy

A review strategy is the approach or plan of action that a reviewer or review team uses to review a medical product application. The strategy employed may be shaped by the following.

7.1.1 Public health priority of the medical product application

Each medical product application poses unique and varied scientific questions, challenges and opportunities for the public health of a nation and these, in turn, determine the public health priorities of the application. Given the limitations of resources within RAs, prioritization based on public health needs may be helpful in setting and communicating review time frames, the extent of involvement of management and other RAs, resources assigned to the review team (which helps determine who may review what portions of the application), need for public input and other plans.

7.1.2 Understanding other RAs' action on the application

The use of reviews and decisions reached by other RAs is expected to become increasingly important in making the review process more efficient in the face of pressures on resources. To implement optimal and consistent use of other RAs' reviews and decisions, development of a policy framework and review strategy is critical. Such strategies should consider both the use of publicly available information (for example, decisions, review reports and summaries) and of confidential information obtained directly from applicants or other RAs (for example, review packages which include responses to questions posed by RAs). Clear direction and support from senior management on the use of regulatory outputs from other RAs is also essential. The goal is to consider how to achieve efficiencies and improve the quality of the review through use of other RAs' reviews and/or decisions in appropriate situations. When considering another RA's action, it is important to understand whether there are differences in the product reviewed (for example, formulation or final container presentation) and any differences in the proposed indications or conditions of use in the local population.

GRevPs are important in promoting the use of information from other RAs, by:

- encouraging greater transparency and public availability of non-confidential regulatory information (for example, decisions, review reports and/or summaries and review processes);
- promoting confidence and trust in the regulatory system that produced the review report and the regulatory decision;
- applying the same GRevP principles to the consistent integration of the scientific reviews and decisions of other RAs into the domestic review process.

As previously noted, the implementation of GRevPs also facilitates opportunities for work-sharing between RAs.

7.1.3 Understanding specific intrinsic and extrinsic factors

Whether or not a medical product is authorized by another RA, the review should focus on available information that may be clinically relevant to the population of the country where the product is being authorized. Such information could include: identification of potential differences in genotypes and phenotypes; disease manifestation; and comparison of available alternatives and medical practice in both the study population relevant to the application and the population of another RA that has already rendered a decision on the application under review.

7.1.4 Identification of major scientific questions and their possible resolution

Early identification of complex, precedence-setting or high uncertainty issues in the application is important and can lead to faster and more efficient resolution. Major scientific application-specific questions would be likely to relate to product safety, efficacy or quality. Examples may include:

- identification of possible cases of organ toxicity in a patient population with a high background incidence of the same organ disease;
- use of a new end-point for regulatory approval that may not be a direct measure of clinical benefit;
- use of conditions for stability testing that are not appropriate for the RA's regional climate.

If problems are identified early on, reviewers can formulate a plan to first review the data in the application that are of greatest relevance to these problems, the RA can develop a plan to seek external advice if desirable, or if the application does not permit a conclusion about benefits and risks, the RA can avoid spending time and resources altogether.

Understanding what information is needed to reach an acceptable level of certainty to resolve scientific questions and meet regulatory standards for marketing authorization, versus what information can be collected in the postmarketing period, is an important aspect of regulatory decision-making.

7.2 Applying the review strategy

The way a review is conducted will depend on the resources available. While a multidisciplinary team will provide broader expertise, in some cases an application may be assigned to a single reviewer. In this case, input from external experts and/or the information and decisions of other RAs may be necessary to ensure that scientific and evidentiary standards for safety, efficacy and quality are adequately met.

The review should be evidence-based, taking into account national laws and regulations, regional and international guidelines, and, where applicable, monographs and standards. The reviewer should determine the information necessary to approve the product application and consider whether further information can be obtained in post-approval studies without compromising safety.

The model adopted for review may allow for questions to be asked during the review to supplement or clarify information supplied, until the reviewer is satisfied that enough information has been provided to allow a conclusion to be reached. In other models, the review is completed on the basis of the information submitted, and a list of questions is then sent to the applicant setting a specified time-limit for response, and one further round of assessment of the responses takes place before a decision is made.

There are a number of internal processes that may be implemented to help ensure an efficient, consistent and effective review process. These include:

- periodic meetings to allow consideration of the views of different reviewers;
- peer review, in the context of a co-rapporteur, or a team meeting;
- an internal panel review;
- an external panel review;
- the involvement of senior management.

The review strategy should ultimately enable the reviewer or review team to understand the benefit–risk profile of the medical product, given the indication and context of use. The nature of the benefits and types of risks should be described as part of the review. Benefits and risks can be quantified or qualitatively characterized, and the levels of certainty surrounding the benefits and risks should be stated. The review should address generalizability of the data, the clinical significance of findings and what (if any) additional information may be needed to clarify benefits and risks.

Various methodologies can be used to quantify benefits and risks. The choice depends on circumstances such as complexity of issues and utility to the RA. The acceptability of benefits and risks will depend on public health priorities, presence of available alternative therapies, size and certainty of the treatment effect versus that of the adverse reactions and possible risk mitigation or benefit enhancement that can be implemented (such as conducting responder analyses to identify a population more likely to experience benefits). It is important to note that the benefit–risk profile may vary depending on intrinsic and extrinsic factors that may differ among countries and regions. Moreover, judgement may vary from within and among RAs. Evidence-based and public health-focused decision-making principles may serve to mitigate some of the variation.

The findings and conclusions of the review must be described in a well-documented review report (see section 3). Once the final decision is made it should be conveyed to the applicant. If an RA decides not to grant authorization, a statement of reasons should be provided, which details the documents, information and applicable regulatory requirements taken into account in reaching the decision. An appeal mechanism should be provided to ensure that applicants have an opportunity to present their case to an independent arbiter.

Some RAs may offer to hold a post-action discussion with the applicant to help improve the quality of future applications. The RA may also have mechanisms for communication with the public on the approval of the product and/or action taken in relation to the application. Publication of information on the approval of products increases transparency of regulatory actions.

Bibliography

Guidelines on quality risk management. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-sixth report. Geneva: World Health Organization; 2013: Annex 2 (WHO Technical Report Series, No. 981; http://www.who.int/medicines/areas/quality_safety/quality_assurance/Annex2TRS-981.pdf, accessed 14 December 2014).

Liu L-L et al. Characterizing Good Review Practices: A Survey Report Among Agencies of APEC Member Economies, Therapeutic Innovation & Regulatory Science, November 2013; vol. 47, 6: pp. 678-683. First published on July 19, 2013.

Chen J-SS, Lin H-Y, Gau C-S, Liu L-L. APEC workshop report of good review practice on medical products (manuscript accepted for publication).

The International Pharmacopoeia, fourth edition.
Volume 1: general notices; monographs for pharmaceutical substances (A–O)
Volume 2: monographs for pharmaceutical substances (P–Z); monographs for dosage forms and radiopharmaceutical preparations; methods of analysis; reagents.
2006 (1500 pages), also available on CD-ROM and online
First supplement: general notices; monographs for pharmaceutical substances; monographs for dosage forms; general and specific monographs; methods of analysis; International Chemical Reference Substances; International Infrared Reference Spectra; reagents, test solutions and volumetric solutions.
2008 (309 pages), also available on CD-ROM and online
Second supplement: general notices; monographs for pharmaceutical substances and radiopharmaceuticals; monographs for dosage forms; general and specific monographs; methods of analysis; International Chemical Reference Substances; International Infrared Reference Spectra; reagents, test solutions and volumetric solutions.
Third (2013) and Fourth supplements as above and all supplements focusing on essential medicines including new monographs for antiretrovirals, antimalarials, antituberculosis and paediatric medicines.
2014 (CD-ROM and online)

Basic tests for drugs: pharmaceutical substances, medicinal plant materials and dosage forms
1998 (94 pages)

Basic tests for pharmaceutical dosage forms
1991 (134 pages)

Quality Assurance of Pharmaceuticals: a compendium of guidelines and related materials
Updated, comprehensive edition, 2014 (CD-ROM and online)

WHO Expert Committee on Specifications for Pharmaceutical Preparations
Forty-eighth report.
WHO Technical Report Series, No. 986, 2014 (387 pages)

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

The selection and use of essential medicines
Report of the WHO Expert Committee (the 18th WHO Model List of Essential Medicines and including the 4th WHO Model List of Essential Medicines for Children).
WHO Technical Report Series, No. 985, 2013 (219 pages)

Biological Standardization
Report of the WHO Expert Committee on Biological Standardization
WHO Technical Report Series, No. 987, 2014 (266 pages)

Further information on these and other WHO publications can be obtained from
WHO Press, World Health Organization, 1211 Geneva 27, Switzerland
http://www.who.int/bookorders
tel.: +41 22 791 3264; fax: +41 22 791 4857; email: bookorders@who.int

The Expert Committee on Specifications for Pharmaceutical Preparations works towards clear, independent and practical standards and guidelines for the quality assurance of medicines. Standards are developed by the Committee through worldwide consultation and an international consensus-building process. The following new guidelines were adopted and recommended for use. Revised procedure for the development of monographs and other texts for *The International Pharmacopoeia*; Revised updating mechanism for the section on radiopharmaceuticals in *The International Pharmacopoeia*; Revision of the supplementary guidelines on good manufacturing practices: validation, Appendix 7: non-sterile process validation; General guidance for inspectors on hold-time studies; 16 technical supplements to Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products; Recommendations for quality requirements when plant-derived artemisinin is used as a starting material in the production of antimalarial active pharmaceutical ingredients; Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability: revision; Guidance on the selection of comparator pharmaceutical products for equivalence assessment of interchangeable multisource (generic) products: revision; and Good review practices: guidelines for national and regional regulatory authorities.

9 789241 209922