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WHO Expert Committee on Specifications for Pharmaceutical Preparations • WHO Technical Report Series

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: Development of monographs for *The International Pharmacopoeia*; WHO good manufacturing practices: water for pharmaceutical use; Pharmaceutical development of multisource (generic) pharmaceutical products – points to consider; Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part; Development of paediatric medicines: points to consider in formulation; Recommendations for quality requirements for artemisinin as a starting material in the production of antimalarial active pharmaceutical ingredients.

WHO Expert Committee on Specifications for Pharmaceutical Preparations

Forty-sixth report



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WHO Expert Committee on Specifications for Pharmaceutical Preparations

Forty-fifth report.

WHO Technical Report Series, No. 961, 2011 (428 pages)

International Nonproprietary Names (INN) for pharmaceutical substances

Cumulative List No. 14

2011 (available on CD-ROM only)

The selection and use of essential medicines

Report of the WHO Expert Committee (including the Model List of Essential Medicines for Children).

WHO Technical Report Series, No. 965, 2011 (249 pages)

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WHO Expert Committee on Specifications for Pharmaceutical Preparations

Forty-sixth 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
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Contents

1. Introduction	1
2. General policy	6
2.1 International collaboration	6
2.1.1 Collaboration with international organizations and agencies	6
2.1.2 Pharmacopoeial Discussion Group	7
2.1.3 International Conference on Harmonisation	7
2.1.4 International Conference of Drug Regulatory Authorities	8
2.2 Cross-cutting pharmaceuticals – quality assurance issues	8
2.2.1 Biological standardization	8
2.2.2 Essential medicines	9
2.2.3 Herbal and complementary medicines	9
2.2.4 Working group meeting on substandard/spurious/falsely-labelled/falsified/ counterfeit medical products	10
3. Quality control – specifications and tests	10
3.1 <i>The International Pharmacopoeia</i>	10
3.1.1 Fourth edition update	10
3.1.2 Outreach with stakeholders	11
3.1.3 Annotated work plan	11
3.1.4 Monograph development	12
3.2 Specifications for medicines, including children's medicines	12
3.2.1 Medicines for HIV and related conditions	12
3.2.2 Antimalarial medicines	13
3.2.3 Antituberculosis medicines	14
3.2.4 Anti-infectives	14
3.2.5 Other medicines	15
3.2.6 Other paediatrics	16
3.3 General monographs for dosage forms and associated method texts	16
3.3.1 Pharmacopoeial Discussion Group-harmonized general texts	16
3.3.2 Uniformity of content single-dose preparations	21
3.3.3 General monograph on tablets	23
3.4 Preface, general notices and supplementary information sections of <i>The International Pharmacopoeia</i>	24
4. Quality control – International Reference Materials (International Chemical Reference Substances and Infrared Reference Spectra)	25
4.1 Update on International Chemical Reference Substances	25
4.1.1 Report on activities of the host organization related to International Chemical Reference Substances	25
4.1.2 Frequently asked questions about collaborative trials	26
4.1.3 Annual report on International Chemical Reference Substances 2010	26
4.1.4 Lumefantrine for system suitability testing	27
4.1.5 Bacterial endotoxin	27

5.	Quality control – national laboratories	27
5.1	External Quality Assurance Assessment Scheme	27
6.	Quality assurance – good manufacturing practices	29
6.1	WHO good manufacturing practices: water for pharmaceutical use	29
7.	Quality assurance – new approaches	29
7.1	WHO guidelines on quality risk management	29
8.	Quality assurance – distribution and trade of pharmaceuticals	29
8.1	WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce	29
8.2	Update on Joint FIP/WHO guidelines on good pharmacy practice: standards for quality of pharmacy services	30
9.	Prequalification of priority essential medicines including active pharmaceutical ingredients	30
9.1	Update on the Prequalification of Medicines Programme managed by WHO	30
10.	Prequalification of quality control laboratories	31
10.1	Update on the prequalification of quality control laboratories	31
10.2	Update on the surveys of the quality of medicines	32
11.	Regulatory guidance	32
11.1	Policy on oseltamivir and zanamivir	32
11.2	Assessment criteria for blood regulatory systems	33
11.3	Pharmaceutical development for multisource (generic) pharmaceutical products – points to consider	34
11.4	Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product: quality part	34
11.5	Development of paediatric medicines: points to consider in pharmaceutical formulation	35
11.6	Provision by health-care professionals of patient-specific preparations for children that are not available as authorized products: points to consider	37
11.7	Quality requirements for artemisinin as a starting material in the production of antimalarial active pharmaceutical ingredients	38
11.8	Update on comparator products	39
12.	Nomenclature, terminology and databases	39
12.1	Quality assurance terminology	39
12.2	International Nonproprietary Names for pharmaceutical substances	40
13.	Miscellaneous	41
13.1	Brochures on the Expert Committee and on quality assurance of pharmaceuticals	41
13.2	Sampling procedures for monitoring of market situations	41
13.3	<i>Index of pharmacopoeias</i>	42
13.4	Collaboration with pharmacopoeias	42
14.	Summary and recommendations	43
	Acknowledgements	51

Annex 1	63
Development of monographs for <i>The International Pharmacopoeia</i>	
Annex 2	67
WHO good manufacturing practices: water for pharmaceutical use	
Annex 3	91
Pharmaceutical development of multisource (generic) pharmaceutical products - point to consider	
Annex 4	121
Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part	
Annex 5	197
Development of paediatric medicines: points to consider in formulation	
Annex 6	227
Recommendations for quality requirements for artemisinin as a starting material in the production of antimalarial active pharmaceutical ingredients	

WHO Expert Committee on Specifications for Pharmaceutical Preparations

Geneva, 10–14 October 2011

Members

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

Mr A.C. da Costa Bezerra, Senior Pharmacist, Gerente-General de Inspecao e Controle de Medicamentos e Produtos, Agencia Nacional de Vigilancia Sanitaria – Brazilian Health Surveillance Agency, Brasilia, Brazil

Mr E. Wondemagegnehu Biwota, Addis Ababa, Ethiopia

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

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 (*Co-Chairperson*)

Dr T. Kawanishi, Head, Division of Drugs, National Institute of Health Sciences, Tokyo, Japan (*Rapporteur*)

Professor H.G. Kristensen, Vedbaek, Denmark

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

Ms C. Munyimba-Yeta, Director, Inspectorate and Licensing, Pharmaceutical Regulatory Agency, Lusaka, Zambia

Ms L. Slamet,¹ Deputy for Therapeutic Products, Narcotics, Psychotropic and Addictive Substance Control, National Agency of Drug and Food Control, Jakarta Pusat, Indonesia

Temporary advisers

Mr J.-M. Caudron,¹ Braine-le-Château, Belgium

Dr M. Hinds, Director, Barbados Drug Service, St Michael, Barbados

Dr S. Mills, Ware, Hertfordshire, England

Dr L. Paleshnuik, Val-des-Mont, QC, Canada

Ms M.-L. Rabouhans, Chiswick, London, England

¹ Unable to attend.

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

Dr S. Singh,² Drug Controller General (India), Ministry of Health & Family Welfare, Government of India, New Delhi, India

Professor C. Tuleu, Senior Lecturer in Pharmaceutics, Deputy Director, Centre for Paediatric Pharmacy Research, The School of Pharmacy, University of London, London, England

Dr A. J. van Zyl, Sea Point, South Africa

Ms O. del Rosario Villalva Rojas, Executive Director of Quality Control Laboratories, National Quality Control Center, National Institute of Health, Lima, Peru

Representation from United Nations offices³

United Nations Children's Fund (UNICEF)

Dr H.K. Nielsen, Technical Specialist, Essential Medicines, Medicines and Nutrition Centre, UNICEF Supply Division, Copenhagen, Denmark

Representation from specialized agencies and related organizations⁴

The Global Fund to Fight AIDS, Tuberculosis and Malaria

Ms J. Daviaud, Senior Pharmaceutical QA Technical Officer, Pharmaceutical Procurement Unit, Geneva, Switzerland

World Intellectual Property Organization (WIPO)

Ms M. Kira, Consultant, Non-Governmental Organizations and Industry Relations Section, Department of External Relations, Geneva, Switzerland

World Trade Organization (WTO)

Ms X. Wu, Counsellor, Intellectual Property Division, Geneva, Switzerland

Representation from intergovernmental organizations⁵

Council of Europe

Dr A. Lodi, Head, Laboratory Department, European Directorate for the Quality of Medicines and HealthCare (EDQM), Strasbourg, France

² Unable to attend.

³ Unable to attend: United Nations Development Programme (UNDP), New York, NY, USA.

⁴ Unable to attend: International Atomic Energy Agency (IAEA), Vienna, Austria; United Nations Industrial Development Organization (UNIDO), Vienna, Austria; The World Bank, Washington, DC, USA; World Customs Organization (WCO), Brussels, Belgium.

⁵ Unable to attend: European Union (EU), Brussels, Belgium.

European Medicines Agency (EMA)

Dr P. Kozarewicz, Scientific Administrator, London, England

Representation from nongovernmental organizations⁶

European Chemical Industry Council (CEFIC)/APIC

Dr B. Pimentel, Board Member, APIC, and Global Regulatory Affairs Manager, DSM Nutritional Products, Basel, Switzerland

International Federation of Pharmaceutical Manufacturers and Associations (IFPMA)

Dr G. France, Pfizer, United Kingdom; and Dr R. Horder, Abbott, United Kingdom

International Generic Pharmaceutical Alliance (IGPA)

Mr T. Fujino, Director, International Affairs, Japan Generic Medicines Association (JGA), Tokyo, Japan

International Pharmaceutical Excipients Council (IPEC)

Ms L. Vignoli, IPEC Europe, Brussels, Belgium

World Self-Medication Industry (WSMI)

Dr R. Torano, Pharmacopoeial Technical Expert, GlaxoSmithKline, United Kingdom

Pharmacopoeias⁷

British Pharmacopoeia Commission

Mrs M. Vallender, Acting Group Manager, BP and Laboratory Services, London, England

Pharmacopoeia of the Republic of Korea

Dr Y.H. Choi, Pharmaceutical Standardization Research and Testing Division, Pharmaceuticals and Medical Devices Research Department, National Institute of Food and Drug Safety Evaluation (NIFDS), Korea Food and Drug Administration (KFDA), Cheongwon-gun, Chungbuk, Republic of Korea

United States Pharmacopoeia

Dr K.A. Russo, Vice President, Small Molecules, Documentary Standards Division, Rockville, MD, USA

⁶ Unable to attend: Commonwealth Pharmacists Association (CPA), London, England; International Society for Pharmaceutical Engineering (ISPE), Tampa, Florida, USA; International Pharmaceutical Federation (FIP), The Hague, The Netherlands.

⁷ Unable to attend: Farmacopeia Argentina, Buenos Aires, Argentina; Farmacopéia Brasileira, Belo Horizonte MG, Brazil; Pharmacopoeia of the People's Republic of China, Beijing, People's Republic of China; Indian Pharmacopoeia, New Delhi, India; Japanese Pharmacopoeia, Tokyo, Japan; State Pharmacopoeia of the Russian Federation, Moscow, Russian Federation.

Representation from WHO regional offices⁸

WHO Secretariat

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

Dr L. Rágo, Coordinator, Quality and Safety: Medicines, Essential Medicines and Health Products, WHO, Geneva, Switzerland

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

Mr M. Deats, Quality and Safety: Medicines, Essential Medicines and Health Products, WHO, Geneva, Switzerland

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

Dr H. Schmidt, Quality Assurance Programme, Quality and Safety: Medicines, Essential Medicines and Health Products, WHO, Geneva, Switzerland

Dr Xiaoqiong Zheng, Quality Assurance Programme, Quality and Safety: Medicines, Essential Medicines and Health Products, WHO, Geneva, Switzerland

Dr A. Padilla, Manager, Blood Products and Related Biologicals, Quality and Safety: Medicines, Essential Medicines and Health Products, WHO, Geneva, Switzerland

Dr R. Balocco,⁹ Manager, International Nonproprietary Names Programme, Quality and Safety: Medicines, Essential Medicines and Health Products, WHO, Geneva, Switzerland

Dr S. Croft, Prequalification Programme, Quality and Safety: Medicines, Essential Medicines and Health Products, WHO, Geneva, Switzerland

Dr A. Fake, Prequalification Programme, Quality and Safety: Medicines, Essential Medicines and Health Products, WHO, Geneva, Switzerland

Mr D. Mubangizi,⁹ Prequalification Programme, Quality and Safety: Medicines, Essential Medicines and Health Products, WHO, Geneva, Switzerland

Ms J. Sabartova,⁹ Prequalification Programme, Quality and Safety: Medicines, Essential Medicines and Health Products, WHO, Geneva, Switzerland

⁸ Unable to attend: Regional Office for Africa, Brazzaville, Republic of Congo; Regional Office for the Americas, Pan American Health Organization, Washington, DC, United States of America; 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.

⁹ Unable to attend.

- Dr M. Stahl,¹⁰ Prequalification Programme, Quality and Safety: Medicines, Essential Medicines and Health Products, WHO, Geneva, Switzerland
- Dr Hua Yin,¹⁰ Prequalification Programme, Quality and Safety: Medicines, Essential Medicines and Health Products, WHO, Geneva, Switzerland
- Dr S. Azatyan, Manager, Medicines Regulatory Support Programme, Essential Medicines and Health Products, WHO, Geneva, Switzerland
- Dr G.B. Forte,¹⁰ Coordinator, Medicines Programme Coordination, Essential Medicines and Health Products, WHO, Geneva, Switzerland
- Ms L. Hedman, Medicines Access and Rational Use, Essential Medicines and Health Products, WHO, Geneva, Switzerland
- Dr C. Ondari,¹⁰ Coordinator, Medicines Access and Rational Use, Essential Medicines and Health Products, WHO, Geneva, Switzerland
- Dr K. Weerasuriya, Medicines Access and Rational Use, Essential Medicines and Health Products, WHO, Geneva, Switzerland
- Ms Y. Maruyama, Traditional Medicine, Health Policy, Development and Services, Health Systems and Services, WHO, Geneva, Switzerland
- Dr I. Knezevic, Quality, Safety and Standards, Immunization, Vaccines and Biologicals, Family and Community Health, WHO, Geneva, Switzerland
- Dr J. Shin, Quality, Safety and Standards, Immunization, Vaccines and Biologicals, Family and Community Health, WHO, Geneva, Switzerland
- Dr C.R. Penn, Disease Monitoring, Assessment and Control, Global Influenza Programme, Health Security and the Environment, WHO, Geneva, Switzerland
- Dr V. Reggi, Control of Neglected Tropical Diseases, HIV/AIDS, TB, Malaria and Neglected Tropical Diseases, WHO, Geneva, Switzerland
- Mr D. Bramley (Former Editor, *World Health Processing*), Prangins, Switzerland

¹⁰ Unable to attend.

Declarations of interest

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

Professor S. Bawazir, Mr A.C. da Costa Bezerra, Mr E. Wondemagegnehu Biwota, Professor T.G. Dekker, Dr M. Karga-Hinds, Professor J. Hoogmartens, Professor S. Jin, Dr T. Kawanishi, Dr J.A. Molzon, Ms C. Munyimba-Yeta, Dr L. Paleshnuik, Ms M.-L. Rabouhans, Dr J.-L. Robert and Ms O. del Rosario Villalva Rojas reported no conflict of interest.

Professor H. Kristensen: His wife is a former employee of Novo Nordisk and holds approximately US\$ 20 000 in stocks in this company. The WHO Expert Committee on Specifications for Pharmaceutical Preparations does not consider any of the products manufactured by Novo Nordisk.

Dr S. Mills was an employee of the company GlaxoSmithKline until July 2009. Dr Mills did not participate in any sessions of the Committee during which specific products were considered.

Professor C. Tuleu: The School of Pharmacy of the University of London (now: UCL School of Pharmacy), where Professor Tuleu works, received educational grants to support research projects on paediatric formulation and drug delivery from UNICEF and the company Vidopharm SPRL. In addition, the School of Pharmacy has received grants from Pfizer, the Medicine for Children Research Network and Global Research in Paediatrics to support research fellows in Professor Tuleu's team. Professor Tuleu did not participate in any sessions of the Committee during which specific products were considered.

Dr A.J. van Zyl has provided an expert opinion on WHO GMP to the United States Pharmacopeia (USP). This work focused on the preparation of a checklist to assess compliance with WHO GMP for the USP Prequalification of Medicines.

1. Introduction

The WHO Expert Committee on Specifications for Pharmaceutical Preparations met in Geneva from 10 to 14 October 2011. Dr C.F. Etienne, Assistant Director-General for the Health Systems and Services Cluster opened the meeting and, on behalf of the Director-General of the World Health Organization, welcomed all the participants to the forty-sixth meeting of the Expert Committee. She thanked the members of the Expert Committee for contributing their knowledge and expertise to the work of WHO in the area of quality assurance of medicines as well as with practical laboratory studies.

Dr Etienne briefly described the reform process in WHO, adding that the Member States had expressed the view that the work on norms and standards was fundamental to the work of WHO. The work of the Expert Committee had provided considerable support to the Prequalification Programme of the United Nations to the extent that the work of that programme depended on the Expert Committee.

The Expert Committee may have a role to play in dealing with substandard/spurious/falsely-labelled/falsified/counterfeit (SSFFC) medical products, an area on which discussions had increased considerably and the role of WHO in the group was being reviewed.

Dr Etienne acknowledged the elected Chairs, i.e. Professors S.A. Bawazir (Chairperson) and S. Jin (Co-Chairperson), and the Rapporteurs, Dr J.A. Molzon and Dr T. Kawanishi.

She also welcomed the other members of the Committee and the temporary advisers; representatives of the United Nations Children's Fund (UNICEF), the Global Fund to Fight AIDS, Tuberculosis and Malaria, World Intellectual Property Organization (WIPO), World Trade Organization (WTO), Council of Europe/European Directorate for the Quality of Medicines and HealthCare (EDQM), European Chemical Industry Council/Active Pharmaceutical Ingredients Committee, International Federation of Pharmaceutical Manufacturers and Associations, International Generic Pharmaceutical Alliance, International Pharmaceutical Excipients Council and the World Self-Medication Industry; and representatives of the Pharmacopoeias of Great Britain, the Republic of Korea and of the United States of America.

The Coordinator of the Quality Assurance and Safety: Medicines team added his welcome to that of Dr Etienne and said that for the second time the Expert Committee would hold an open session to respond to the interest raised by Member States during the World Health Assembly in the quality of medicines, and especially on prevention and control of SSFFC medical products. The Prequalification Programme was based entirely on the guidelines and standards recommended by the Expert Committee. The work of the Expert Committee was closely linked to other organizations such as United Nations bodies and other

intergovernmental organizations, other international and regional bodies, the Global Fund to Fight HIV/AIDS, Tuberculosis and Malaria, UNICEF, WIPO, the World Bank, manufacturers' associations, national and regional pharmacopoeias, other institutions, and other WHO Expert Committees. He said that the Expert Committee structure had been and will in the future be the "backbone" of the Organization's standard-setting process.

He stated that the international donor community was becoming increasingly aware of the problem of poor quality medicines. Countries with this problem were more open to recognizing it but there was still a long way to go before poor people would have access to good quality medicines. There was a continuing need for a comprehensive set of guidelines and standards in the area of quality assurance as part of the process of strengthening health systems to prevent the occurrence of, and to detect, medicines of compromised quality, including SFFC and substandard medicines.

Open session

The open session, held during the morning of Monday, 10 October 2011, was opened by Dr Etienne, who welcomed representation from permanent representatives to the United Nations Offices, international organizations based in Geneva, and specialized agencies in Switzerland.

She stated that the aim of the open session of the forty-sixth WHO Expert Committee on Specifications for Pharmaceutical Preparations was to provide more information on the Expert Committee, particularly to WHO Member States, in an open and transparent manner.

Poor quality of medicines and SFFC medicines were unfortunately a major threat to public health, putting the health of numerous patients and the trust of these patients in their health systems at risk; thus this issue was of critical importance for WHO. In the medicines area, standard-setting work continued to be a pillar of WHO's activities and priorities in support of WHO Member States.

WHO had been involved in medicines' quality assurance and quality control since 1948. The Expert Committee was created in the very first World Health Assembly. Its work had already begun in 1947, during the transition of health issues previously dealt with under the League of Nations. Thus medicines' quality assurance was one of WHO's oldest programmes.

Strong links existed with other WHO activities, such as support of national medicines regulatory authorities (NMRAs), the Prequalification Programme, the Expert Committee on Biological Standardization, the Expert Committee on Selection and Use of Essential Medicines, Traditional Medicine and specific disease programmes.

The normative activities covered by this Expert Committee not only directly served WHO Member States, but also through implementation by

programmes within WHO and international organizations such as UNICEF and the Global Fund to Fight AIDS, Tuberculosis and Malaria.

Most of the secretariat's activities had in the past been funded from WHO's regular budget. Nowadays more than 80% of the finance was secured through extrabudgetary funding by donors. The Organization took great care to ensure that money did not come from the pharmaceutical industry.

Dr Etienne stated that the work of the Expert Committee was becoming a focus of interest. Its meetings were held annually in response to the increased need for normative work. The work of this Expert Committee was of the highest level of normative work at WHO and the outcome of each meeting was published in the WHO Technical Report Series, and was then presented to the WHO Executive Board. Committee members were invited in a personal capacity and did not represent their respective governments.

The Coordinator of the Quality Assurance and Safety: Medicines team explained that many issues regarding quality assurance would be discussed during the meeting. He suggested that some highlights would be capacity-building, the development and interchangeability of generic pharmaceuticals, paediatric formulations, water for pharmaceutical use, an update on the Prequalification Programme, an update on International Nonproprietary Names (INNs) and a new text on quality risk management. He strongly encouraged members of the Committee to guide WHO on future activities in quality assurance with regard to these and other issues.

The Secretary of the Expert Committee on Specifications for Pharmaceutical Preparations gave an overview of the governance and operational structure of WHO. She said that the main technical work of the Organization was based on the contributions of experts from around the world. In the area of pharmaceuticals WHO works with a range of national quality control laboratories worldwide, with regulatory bodies, international organizations, nongovernmental organizations (NGOs) and international industry associations.

The Secretary described the process for selecting experts, the requirements to be fulfilled, the areas of work in WHO covered by expert committees, and the relationship of the expert committees to the WHO Executive Board and the World Health Assembly. She further explained the wide consultation process used by the Expert Committee and the strict clearance process to be followed before issuing any guidelines or specifications. She also summarized the work of the Secretariat during the past year.

The forty-fifth report of the Expert Committee, which had met in October 2010, had been published and distributed, and its main contents were outlined to members of this Committee.

There was discussion of the relationship between the International Conference of Drug Regulatory Authorities (ICDRA) and the Expert Committee

on Specifications for Pharmaceutical Preparations. WHO had in the past taken actions as a result of recommendations of ICDRA, since this body represents the network of regulatory authorities of WHO Member States.

The International Pharmacopoeia

The World Health Assembly approved *The International Pharmacopoeia* in 1948. Since 1975 *The International Pharmacopoeia* had focused on the WHO Model list of essential medicines. New medicines to be included were proposed by WHO disease control programmes to ensure that they met the needs of Member States. *The International Pharmacopoeia*, which is based on the work and decisions of the Expert Committee, had legal status as soon as a Member State recognized it as official. The consultation procedure for a specification to be entered into *The International Pharmacopoeia* was particularly thorough. Recently *The International Pharmacopoeia* had begun briefing sessions for interested parties and had so far held two such sessions.

The current edition was the fourth, which was issued in 2006, with the first supplement in 2008 and the second in 2011. The second supplement includes a new section on monographs for radiopharmaceuticals. Texts for future publication were accessible online as well as being distributed widely. New trends that impacted on *The International Pharmacopoeia* included a shift towards more sophisticated methods to allow for better control of quality. Earlier methods that were no longer adequate were being reviewed in the light of common analytical practices worldwide.

The advantages of *The International Pharmacopoeia* are that its specifications are validated internationally through an independent process, it is based on input from WHO collaborating centres, it works with manufacturers worldwide, it takes cost of analysis into account, it collaborates with standard-setting organizations, it links to other WHO activities, and it is free for use by WHO Member States.

Other developments

Artemisinin, which is used widely in antimalarial medicines, is derived from the plant *Artemisia annua*, a herb described in Chinese traditional medicine. It was now proposed that a guidance document should be developed on artemisinin starting material.

The work of the WHO External Quality Assurance Assessment Scheme, which advises laboratories when they need to investigate their procedures and review their performance, was described. In addition, it was reported that, in April 2010, EDQM had taken over responsibility for the preparation and storage of WHO International Chemical Reference Substances (ICRS).

Participants in the open session suggested that *The International Pharmacopoeia* should include an explanation of how the pharmacopoeia should

be used, including advice on impurities. It was felt that a distinct and clearly defined section of *The International Pharmacopoeia* containing supplementary information would be very helpful to users.

In response to a question from a participant regarding the future of the International Medical Products Anti-Counterfeit Taskforce (IMPACT), it was stated that in 2010 the World Health Assembly had set up a working group of Member States to review WHO's future activities in the area of SFFFC medicines, including the Organization's involvement in IMPACT. WHO's function as the secretariat of IMPACT had been put on hold pending the outcome of the working group and the subsequent decision by the World Health Assembly.

The Committee members responded to questions raised by the audience. The Chair thanked the Member States' representatives for their attendance and the open session was closed.

The Expert Committee reconvened and was held in accordance with established procedures.

Major publications since October 2010

The forty-fifth report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations (WHO Technical Report Series, No. 961) was presented to the meeting of the WHO Executive Board in May 2011 and had since been made available in both print and electronic formats. Published copies were distributed to the participants at the forty-sixth meeting of the Expert Committee.

The fourth edition of *The International Pharmacopoeia*, including the second supplement, had been issued both on CD-ROM and online.

Two information brochures about the Expert Committee, its procedure and functioning, and one on the technical areas covered, had been prepared and printed. One was translated into all six official languages of WHO.

An updated version of the CD-ROM, including all current WHO quality assurance guidelines adopted by the Expert Committee on Specifications for Pharmaceutical Preparations, would be available in a comprehensive and structured form by the end of 2011.

The Committee wished to thank the secretariat for its efforts in finalizing these publications as they would help to promote the outcome of the work and increase transparency.

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 procurement principles of the Global Fund to Fight AIDS, Tuberculosis and Malaria were outlined for the Expert Committee. The general principles are: best value for money, fairness, integrity and transparency. The Global Fund has procurement guidelines (as published by WHO in 2010) and a quality assurance policy on pharmaceuticals that includes clinical and quality criteria, plus the monitoring of quality. Products are monitored throughout the supply chain; there is systematic random testing and recipients report their test results to the Global Fund. Testing is carried out using the methods of the *British Pharmacopoeia*, *United States Pharmacopoeia* or *International Pharmacopoeia*. Quality control is most difficult at country level.

The challenges of limited access to additional qualified laboratories were described. Difficulty and delay in achieving methods transfer from manufacturers and in obtaining access to reference substances were also noted. However, it was hoped that in the future it would be possible to access additional monographs so as to be able to avoid transfer of manufacturers' methods. The need for clear guidance on how to interpret monographs was raised.

In August 2011 the Global Fund and WHO held a joint meeting on quality assurance of essential medicines which recommended that WHO should continue its work towards common quality requirements for medicines that are not antiviral, antituberculosis and antimalarial (non-ATM) medicines, and should develop a risk categorization of essential medicines. The Global Fund explained its approach to quality assurance of grant-funded medicines, which is particularly thorough for antiretroviral medicines.

The Committee noted the report and expressed its appreciation to the Global Fund.

The Expert Committee recommended that the experience of the Global Fund in this area should be shared with the WHO regions to facilitate future collaboration. It was noted that the proposal for revision of the WHO guidance for national procurement agencies (WHO Technical Report Series, No. 937, Annex 6) may be presented in the future to the Expert Committee.

United Nations Children's Fund

The United Nations Children's Fund (UNICEF) Supply Division procures supplies such as medicines for itself and for partners, including governments, agencies and NGOs. For pharmaceuticals, UNICEF uses several means to assess

potential manufacturers, including the WHO guidance for procurement agencies and a technical questionnaire. The medicines have to be identical to those prequalified by WHO. For those not prequalified by WHO (i.e. non-ATM) other criteria are used, including the United Nations Agency Product Questionnaire and the requirement that the medicines are on the receiving country's national essential medicines list. UNICEF also carries out good manufacturing practices (GMP) inspections and 103 inspections were carried out between 2006 and 2010. Products kept in the UNICEF warehouse are visually inspected with tests on randomly selected samples. The prequalification of medical products is always done in connection with a tendering process.

The Committee noted the report and expressed its appreciation to UNICEF.

2.1.2 Pharmacopoeial Discussion Group

The Pharmacopoeial Discussion Group (PDG), which consists of the *European Pharmacopoeia*, *Japanese Pharmacopoeia* and *United States Pharmacopoeia*, met in June 2011. At present 28 of the 35 General chapters and 41 of the 62 excipient monographs of the current work programme have been harmonized. The General chapter for Microcalorimetry is newly harmonized. Revised General chapters include Bacterial endotoxins and Bulk and tapped density. Excipient sign-offs include revisions to monographs on Benzyl alcohol, Potato starch, Wheat starch, Calcium phosphate dibasic and Calcium phosphate dibasic anhydrous. The last four revisions are the outcome of PDG's review of previously harmonized excipient monographs.

A press release from the PDG was distributed, which stated that the PDG would no longer meet at the same time and place as the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). Thus, the PDG will strengthen its independence, but the intention nevertheless is to strengthen harmonization activities among the three pharmacopoeias. WHO is an observer to this group.

The Expert Committee noted the report.

2.1.3 International Conference on Harmonisation

An update on quality issues was provided to the Expert Committee by the European Union (EU) Quality Lead of the ICH. The concept of "quality by design" was explained and the procedure for developing a product according to this process was outlined. The relationship between risk management, development and a suitable quality management system was highlighted. The ICH quality group carried out six training courses for industry and regulatory staff. A "question and answer" document is available on the ICH web site and a series of "points to consider" documents were produced.

A new draft guideline will address the development and manufacturing of active pharmaceutical ingredients (APIs) including chemical, biotechnological and biological entities.

A further ICH guideline is being drawn up for metal residues, with the aim of providing a global policy for limiting metal impurities in medicines and ingredients.

Following wide consultation, it was decided that the guideline on genotoxic testing and data interpretation for medicines will be revised.

The Expert Committee noted the report.

2.1.4 International Conference of Drug Regulatory Authorities

The 14th International Conference of Drug Regulatory Authorities (ICDRA) was held in Singapore from 30 November to 3 December 2010 and was attended by 345 participants from over 90 agencies in both developing and developed countries. The conference was hosted by the Health Sciences Authority of Singapore in collaboration with the World Health Organization.

The ICDRA conferences have been held since the early 1980s and are intended as a platform for achieving consensus on regulatory matters. Issues discussed at the 2010 conference included quality and safety, with a workshop on this topic which presented experience in implementation of WHO guidelines. The conference also issued recommendations to national authorities for updating requirements for stability studies in line with the recommendations of WHO. Recommendations to WHO included updating its annex on national requirements for stability guidelines for medicines and to encourage further developments in the area of stability testing for vaccines and providing additional tools for thermal testing for vaccines.

The Expert Committee recognized the importance of ICDRA meetings because they bring together regulators from the majority of Member States and recommended the WHO secretariat to pursue its efforts to ensure that the next meeting takes place.

2.2 Cross-cutting pharmaceuticals – quality assurance issues

2.2.1 Biological standardization

The secretary of the Expert Committee on Biological Standardization summarized four cross-cutting issues on that Expert Committee's agenda. One was an assessment tool for regulatory authorities on the quality of blood products, and a second was a proposal to set up a replacement for the international standard on endotoxin, both of which were proposed for discussion by the Expert Committee on Specifications for Pharmaceutical Preparations.

A third cross-cutting issue related to the labelling of vaccines. This issue had originally been raised by the Immunization Practices Advisory Committee

(IPAC) and derived from a concern that the labels attached to vaccines varied enormously. IPAC had requested WHO to devise a standardized format for labels for vaccines. This request would go to the Expert Committee on Biological Standardization. Issues raised related to the format and content of labels, their size, the languages used, the date format, and whether there should be bar coding or another machine-readable system. Also mentioned was the need to improve the readability of labelling.

The fourth cross-cutting issue was a proposed, legally-binding treaty on mercury that was currently being negotiated by the Member States of the United Nations. The United Nations Environment Programme has coordinated the negotiation process. One issue that has arisen is whether the use of mercury in vaccines should be prohibited completely. The substance thiomersal is used as a preservative in the manufacture of vaccines and WHO has evidence of its safety.

The Expert Committee noted that some regulators are already involved in this discussion and encouraged giving further emphasis to the use of these mercury derivatives for medicines.

2.2.2 Essential medicines

It was reported to the Expert Committee that the March 2011 meeting of the Expert Committee on the Selection and Use of Essential Medicines had revised the WHO Model list of essential medicines, and especially the list for children. Although there were some divergent opinions within the Committee regarding guidance about extemporaneous preparations, it had been noted that age-appropriate formulations for children were not available for most medicines. The Expert Committee on Essential Medicines had raised the issue of whether WHO could consider drafting guidelines for the compounding of paediatric medicines.

2.2.3 Herbal and complementary medicines

WHO's work on traditional medicine has been expanding, in part because of the growing interest in herbal and complementary medicine worldwide. Among recently issued guidelines relating to traditional medicine was the updated edition of *Quality control methods for herbal materials* which was discussed by this Expert Committee in 2008. Other guidelines describing different aspects of herbal and traditional medicines had been published, as had three documents aimed at expanding the evidence base on quality, safety and efficacy of herbal medicines. An update was currently under way of guidelines on the conservation of medicinal plants, which is being developed jointly with the International Union for the Conservation of Nature and the World Wildlife Fund, to provide a framework for the conservation and sustainable use of herbal medicines. Furthermore, a second WHO global survey on national policy regarding herbal medicines was under way.

2.2.4 Working group meeting on substandard/spurious/falsely-labelled/falsified/counterfeit medical products

There had been much discussion of the issue of SSFFC medical products at recent meetings of WHO's governing bodies, including the nomenclature and focus for WHO activity. In 2010 the Expert Committee also discussed the issue and decided to leave the terminology for the time being until the concerns of the Member States had been resolved. A working group on SSFFC medical products was set up in 2010 and its meetings are organized by a board composed of Member States, with WHO providing secretarial assistance. The first meeting of the SSFFC working group took place at the beginning of 2011 and the second meeting was due to be held in October 2011. The governing body documents on the working group are available in different languages on the WHO governing bodies' web site.

3. Quality control – specifications and tests

3.1 *The International Pharmacopoeia*

3.1.1 Fourth edition update

The second supplement to the fourth edition of *The International Pharmacopoeia* was issued in July 2011. The fourth edition thus comprised the two main volumes published in 2006, the first supplement published in 2008 and the second supplement. *The International Pharmacopoeia* was now available as a cumulative CD-ROM and freely accessible on the WHO medicines web site (<http://www.who.int/phint>).

The second supplement includes more than 60 new texts as well as about 20 texts that have been revised.

The second supplement comprises the monographs adopted by the Expert Committee at its forty-second, forty-third and forty-fourth meetings in October 2007, 2008 and 2009, respectively, with the addition of two texts adopted in October 2010 (artesanate and oseltamivir phosphate) which were also included in this supplement. Two further texts (amikacin injection and kanamycin injection) were erroneously omitted from the compilation of texts in the second supplement and will be published on the WHO medicines web site as errata to the supplement.

Texts adopted as of October 2010 will be posted on the WHO medicines web site according to the usual procedure, before they are compiled into a forthcoming supplement of *The International Pharmacopoeia*. Finalization work before publication was ongoing for a few remaining texts and it was expected that they would soon be made available.

While most of the texts have been posted on the WHO medicines web site, some of them, such as that for levonorgestrel tablets, required significant changes

which necessitated additional analytical work, as agreed by the Expert Committee. In this case, the text was presented for review at the consultation on specifications for medicines and quality control issues held in July 2011 to validate the changes made. The text was then presented to the Expert Committee (see section 3.2.5).

3.1.2 Outreach with stakeholders

A summary was presented to the Expert Committee on the briefing for stakeholders held in July 2011 to obtain their feedback on *The International Pharmacopoeia*. An earlier briefing had been organized for industry in 2009. The intention of the meetings was to have an informal discussion with manufacturers and to obtain their feedback on *The International Pharmacopoeia*. The July 2011 session was open not only to industry but to all interested parties as a response to many requests from NGOs, Member States and others. Thirty participants attended. The participants were asked to send questions in advance so that detailed responses could be prepared. WHO learned of the interest in having more information available on the web site, such as the draft monographs.

The briefing was also an opportunity for WHO to request samples from manufacturers to support the development of monographs for *The International Pharmacopoeia*. The stakeholders emphasized the importance of these briefings and hoped that they would continue to be held in the future.

3.1.3 Annotated work plan

In October 2010, the Expert Committee had adopted a work plan for monographs to be included in future editions of *The International Pharmacopoeia*. A list of these monographs, updated with their current status (i.e. whether already adopted by the Expert Committee), and with new proposals for developing specifications for active substances and dosage forms, including those for paediatric use, was presented to the Committee. The work plan was updated on the basis of the second supplement of *The International Pharmacopoeia* and the current WHO Model list of essential medicines and with reference to the invitations for expressions of interest of the Prequalification Programme.

The work plan included medicines used in treatment of HIV/AIDS, malaria and tuberculosis treatment, anti-infectives, oral rehydration therapy, and other medicines. The work plan was discussed during the consultation on specifications for medicines and quality control laboratory issues held in July 2011 and, on the advice of the consultation, the work plan had been amended to include not only the individual monographs for products, but also the important general texts or sections intended to be either developed or revised.

The different categories of medicines in the work plan were reviewed. There are monographs on the APIs of most antiretroviral medicines already, and monographs on the new ones are in preparation.

The Expert Committee agreed to adopt the work plan as presented and amended based on discussion.

3.1.4 Monograph development

The monographs in *The International Pharmacopoeia* provide the quality aspects for the medicines in the WHO lists of essential medicines and in WHO treatment guidelines. Therefore, major WHO programmes, such as that on Prequalification of Medicines, and international organizations such as UNICEF and the Global Fund to Fight AIDS, Tuberculosis and Malaria, rely heavily upon the quality specifications of *The International Pharmacopoeia*. A “schedule for the adoption process” outlining the development history of a draft monograph is included in each working document that is circulated for comment. The phases involved in the development of new monographs were discussed by the Expert Committee and the comments already received were outlined.

The process was revised by the Expert Committee in order to appropriately reflect each of the phases involved in developing new monographs.

The Expert Committee adopted the phases which are involved in the development of monographs for *The International Pharmacopoeia* (Annex 1).

3.2 Specifications for medicines, including children’s medicines

3.2.1 Medicines for HIV and related conditions

Antiretrovirals

Ritonavir tablets

The monograph on the ritonavir API had been adopted by the Expert Committee and was included in the second supplement of *The International Pharmacopoeia*. A draft monograph on ritonavir tablets was then proposed. The present draft monograph on tablets had been sent for comments and these had been consolidated by the secretariat. The Expert Committee reviewed the draft monograph and the comments received.

The Expert Committee adopted the monograph on ritonavir tablets subject to inclusion of the agreed changes, based on the comments received and those made during the discussion.

Tenofovir disoproxil fumarate

Work by the collaborating laboratory on the test for optical rotation was ongoing. The investigation was in progress, but the necessity to obtain additional samples had delayed completion of the proposal for discussion.

3.2.2 Antimalarial medicines

Update on artemisinin derivatives

During review of the monograph on artesunate for inclusion in the second supplement, several corrections regarding nomenclature were identified. In consequence, an in-depth review of related WHO publications was carried out and ambiguity regarding the nomenclature was resolved. It was, therefore, proposed to implement the necessary corrections in the relevant texts of *The International Pharmacopoeia*.

In June 2011 a teleconference was organized with the experts involved in the revision of the artemisinin derivatives monographs in order to discuss the approach that should be followed for implementing the corrections identified. Proposals made concerning the different aspects of the monographs to be modified were discussed at the consultation on specifications for medicines and quality control laboratory issues held in July 2011. The monographs concerning artesunate and arteminol were, therefore, presented for discussion by the Expert Committee.

It was noted that both these substances were widely used in artemisinin-based combination therapy and that arteminol was also present as a related substance in the APIs of other artemisinin-derivatives. The Committee emphasized, therefore, that any change made to the monographs for these two substances would need to be implemented in other related monographs.

Artesunate

This monograph on artesunate was initially revised by the Expert Committee in 2009 and again in 2010. Following the correction of the ambiguity regarding the nomenclature, the monograph was presented once more to the Expert Committee for further review.

The Expert Committee adopted the monograph on artesunate subject to inclusion of the agreed changes, based on the comments received and those made during the discussion.

Arteminol

The current monograph was still under review in the context of the general revision of monographs on artemisinin derivatives. Although the revised draft presented to the Expert Committee for review took account of the changes proposed to the monograph with regard to the correction of information related to nomenclature, it was considered that other changes might be required.

The Expert Committee adopted the monograph on arteminol subject to inclusion of the agreed changes, based on the comments received and those made during the discussion.

Mefloquine hydrochloride

Following the adoption of the monograph for mefloquine tablets in October 2010, it was pointed out that the published monograph on mefloquine hydrochloride would need to be reviewed in order to replace the current thin-layer chromatography (TLC) method used for Related substances by a high-performance liquid chromatography (HPLC) method and to revise the limits for impurities.

A first draft of the proposed revision was discussed at the consultation on specifications for medicines and quality control issues held in July 2011 and, in response to the comments made, further analytical work and verifications had been carried out by the collaborating laboratory to which the project was assigned.

The Expert Committee reviewed a revised version of the tests reflecting the changes and approved the text, subject to comments made during the discussion, for submission for wide consultation in line with the usual procedure.

New basic tests for antimalarials

The Expert Committee was informed about the progress made with the basic tests series for antimalarials. These would soon be made available on the web site.

3.2.3 Antituberculosis medicines

Rifampicin

Rifampicin exhibits polymorphism. The polymorph forms I and II, and mixtures of forms I and II, are available on the market. The infrared reference spectrum of Rifampicin RS, published in the first supplement to *The International Pharmacopoeia*, is concordant with form II. It is not intended to place a restriction on the polymorphic form. To this effect the monograph was revised and presented to the Expert Committee with the proposal to add a recrystallization step to the existing infrared (IR) identification method for both the test substance and the reference substance, in case their IR spectra are not concordant. Comments received on the document were reviewed.

The Expert Committee adopted the monograph on rifampicin subject to inclusion of the agreed changes, based on the comments received and those made during the discussion. Moreover, it recommended proceeding with a similar revision of the monographs for tablets and capsules.

3.2.4 Anti-infectives

Pyrantel oral suspension

The Expert Committee reviewed the draft monograph on pyrantel oral suspension and the major comments received. The Expert Committee agreed that the discussion of the monograph should be deferred until a number of issues could be clarified.

Pyrantel chewable tablets

The Expert Committee reviewed the draft monograph on pyrantel chewable tablets and the major comments received. The Expert Committee adopted the monograph on pyrantel chewable tablets subject to inclusion of the agreed changes based on the comments received and those made during the discussion.

Albendazole chewable tablets

The Expert Committee reviewed the draft monograph on albendazole chewable tablets. A first draft of the monograph was received from the collaborating laboratory, subsequently amended by the secretariat and sent for wide consultation in September 2011 according to the usual consultative procedure. The monograph remained open for public comment.

The Expert Committee recommended that further consultation be sought. Furthermore, it was proposed that the API monograph be considered for revision.

3.2.5 Other medicines

Heparins

Following alerts regarding some contaminated heparin injections, discussions were held on detection of impurities in the product, with a view to revising the monographs published in a number of pharmacopoeias. The issue of the revision of the heparins monographs in *The International Pharmacopoeia* had been discussed on several occasions during Expert Committee meetings and consultations, notably in 2008 and 2009.

A new method for the determination of dermatan sulfate and other glycosaminoglycans in heparin was presented to the Expert Committee for possible inclusion in *The International Pharmacopoeia*.

The Expert Committee reviewed this method and approved its inclusion in the monograph, subject to inclusion of the agreed changes. The monograph will be submitted for wide consultation in line with the usual procedure.

Medroxyprogesterone injection

A new monograph on the contraceptive medroxyprogesterone injection was presented to the Expert Committee for review. The monograph had recently been received by the secretariat and had been sent out for comments. The monograph is still open for public comment.

The Expert Committee adopted the monograph on medroxyprogesterone injection subject to inclusion of the agreed changes, based on the comments received and those made during the discussion, and also allowing for further comments by members of the Committee.

Levonorgestrel tablets

The text on levonorgestrel tablets was adopted in 2010, and following the recommendation made by the Expert Committee, specific requirements for the 30 µg tablets had been added with regard to the preparation of test solutions and the dissolution test conditions. As these agreed changes were important, the final text was re-presented to the Expert Committee for final endorsement (see also section 3.3.2).

The proposed modifications were adopted by the Expert Committee.

3.2.6 Other paediatrics

Paediatric retinol oral solution

Draft versions of the monographs on retinol concentrate (oily form), paediatric retinol capsules and paediatric retinol oral solution were discussed at the forty-fifth meeting of the Expert Committee in October 2010. The monograph on retinol concentrate, oily form, was adopted.

The Committee decided to incorporate the dosage form paediatric retinol soft-gel capsules into the monograph on retinol oral solution, considering the soft gelatin shell as a single-unit container and the liquid content as the actual dosage form. Following the meeting held in 2010, the Expert Committee recommended that the monograph on paediatric retinol oral solution should be modified so that its specifications could also be applied to these single-dose units and that the capsule monograph should be withdrawn.

Following the 2010 meeting, revised versions of the monograph on paediatric retinol oral solution were circulated twice according to the usual consultative procedure. The monograph was also discussed at the consultation on specifications for medicines and quality control issues held in July 2011.

The Expert Committee adopted the monograph on paediatric retinol oral solution subject to inclusion of the agreed changes, based on the comments received and those made during the discussion, and subject to the requirement that the monograph on retinol concentrate (oily form) be adapted in line with the changes to that on retinol oral solution.

3.3 General monographs for dosage forms and associated method texts

3.3.1 Pharmacopoeial Discussion Group-harmonized general texts

Following discussion by the Expert Committee on Specifications for Pharmaceutical Preparations at its forty-fifth meeting in 2010, a number of internationally harmonized, PDG-texts had been adapted to the editorial style of *The International Pharmacopoeia* and sent out for wide consultation as per the usual consultative procedure.

A first set of texts with the comments received were initially reviewed at the consultation on specifications for medicines and quality control issues held in July 2011. These texts covered:

- sulfated ash
- test for extractable volume of parenteral preparations
- disintegration test
- test for particulate contamination: subvisible particles
- microbial examination of non-sterile products: acceptance criteria for pharmaceutical preparations and substances for pharmaceutical use
- microbial examination of non-sterile products: tests for specified microorganisms
- microbial examination of non-sterile products: microbial enumeration tests.

A set of additional texts was then prepared in the same way and sent out for wide consultation in August and September 2011:

- sterility test
- tablet friability
- bulk and tapped density of powders
- bacterial endotoxins test.

As a consequence of the inclusion of these internationally harmonized monographs it was pointed out that certain texts in *The International Pharmacopoeia* would also require adaptation, for example, the monograph on parenteral preparations.

The Expert Committee proposed the following maintenance procedure for these texts: when the methods concerned are revised by the PDG and where this will have repercussions for the texts above included in *The International Pharmacopoeia*, the secretariat should consult with selected members of the Expert Committee and then make the required changes to *The International Pharmacopoeia* without the necessity for consulting the full Expert Committee.

For all following general texts, the Expert Committee acknowledged that they were sent out for wide consultation and duly revised, taking into account the comments received. All the texts described and listed were adopted, subject to inclusion of the agreed changes, based on the comments received and those made during the discussion, unless stated otherwise.

Test for sulfated ash

During its meeting in October 2010, the Expert Committee recommended that the current method described in *The International Pharmacopoeia* for the test

of sulfated ash be replaced progressively by the internationally harmonized general test on residue on ignition/sulfated ash test. To this effect the method “2.3 Sulfated ash” was revised and sent for wide consultation in April and August 2011. Both methods would be included in *The International Pharmacopoeia* for an interim period. The internationally harmonized test would be specified in new monographs while, for existing monographs, the current test would be specified until it is replaced during the revision of the monographs in question.

Bulk density and tapped density of powders

This new general method text was proposed for inclusion in the Supplementary information section of *The International Pharmacopoeia*. The text was based on the internationally harmonized test on bulk density and tapped density of powders.

It was intended to revise the Supplementary information section of *The International Pharmacopoeia* (structure and contents). In the proposal being reviewed, a new section on test methods used during pharmaceutical development and/or manufacture of dosage forms was included. The general method for bulk density and tapped density of powders would, therefore, be included in this section and a specific number would be assigned to this method once the proposed format and the methods considered for this section have been adopted.

Tablet friability

In October 2009 the Expert Committee on Specifications for Pharmaceutical Preparations adopted a revision of the general monograph on Tablets where a reference was made under the Manufacture section to a method of friability testing. Based on the internationally harmonized tablet friability test, a general method text was, therefore, proposed for inclusion in the Supplementary information section of *The International Pharmacopoeia*.

Disintegration test

During its meeting in October 2010, the Expert Committee on Specifications for Pharmaceutical Preparations recommended that the current method described in *The International Pharmacopoeia* for the disintegration test for tablets and capsules should be replaced by the internationally harmonized general test.

The revision implies both changes to and additions to dimensions and tolerances in the description of the disintegration apparatus. The possibility for retesting when one or two units fail in the first step of the procedure is introduced, as is the possibility to use automatic detection employing modified discs in cases where the use of discs is prescribed.

Dissolution test

The dissolution test had been reviewed for adaptation for inclusion in *The International Pharmacopoeia*. The Expert Committee judged that the test should be subjected to a thorough review and should be considered by a future Expert Committee.

Test for extractable volume for parenteral preparations

During its meeting in October 2010, the Expert Committee on Specifications for Pharmaceutical Preparations recommended that the current method described in *The International Pharmacopoeia* for the test for extractable volume for parenteral preparations be replaced by the internationally harmonized general test.

Tests for particulate contamination

During its meeting in October 2010, the Expert Committee on Specifications for Pharmaceutical Preparations recommended that the current method described in *The International Pharmacopoeia* for the tests for particulate contamination should be replaced by the internationally harmonized general test, as a revision of method “5.7 Tests for particulate contamination”. The revision includes a distinction between small volume parenterals and large volume parenterals with a limit at 100 ml. The 100 ml preparation is exempted from the pharmacopoeial harmonization and it was proposed to include the 100 ml preparation among the small volume parenterals. As a consequence of the revision of this method, other changes would be made to the headings in chapter 5.7.

Microbial quality of pharmaceutical preparations

This relates to the following headings:

- Microbiological examination of non-sterile products;
- Acceptance criteria for pharmaceutical preparations and substances for pharmaceutical use;
- Microbial enumeration tests;
- Tests for specified microorganisms.

Microbiological examination of non-sterile products had been a subject for harmonization, which has resulted in three texts:

- Microbial enumeration tests;
- Tests for specified microorganisms;
- Acceptance criteria for pharmaceutical preparations and substances for pharmaceutical use.

It was agreed that the texts on microbial enumeration tests and tests for specified microorganisms would be new (3.3.1 and 3.3.2) in the Methods of analysis section. Furthermore, it was agreed to replace the current text on microbial quality (3.3) with the internationally harmonized text on Microbiological examination of non-sterile products: acceptance criteria for pharmaceutical preparations and substances for pharmaceutical use. This text would be provided for information and would, therefore, be moved to the Supplementary information section and renamed as follows: Microbiological quality of non-sterile products: recommended acceptance criteria for pharmaceutical preparations.

Following adoption, the inclusion of methods 3.3.1 and 3.3.2 in *The International Pharmacopoeia* would be reviewed in terms of their applicability within the existing texts of *The International Pharmacopoeia*. Such a review would include excipients and would consider in which monographs of *The International Pharmacopoeia* the methods would be invoked, and would propose limits.

Test for sterility

Following adoption, the current methods “3.2 test for sterility of non-injectable preparations” and that for “3.2.2 sterility testing of antibiotics” will be replaced with the internationally harmonized test for sterility. Testing of surgical materials was not included in the revision.

The revision would result in the need for additional advice concerning the testing of antibiotics within the Supplementary information section of *The International Pharmacopoeia*. Further, it would be necessary to change all references to these monographs.

The clause “unless otherwise prescribed, justified and authorized” is included in the harmonized text. It was felt that the meaning of “justified and authorized” in the context of *The International Pharmacopoeia* needed explanation. It was, therefore, agreed to include the following wording in the General notices of *The International Pharmacopoeia*:

“The expression ‘unless otherwise justified and authorized’ means that the requirements have to be met or instructions to be followed, unless the relevant national or regional authority authorizes an exemption or modification, where justified in a particular case.”

Test for bacterial endotoxins

The proposed revision for inclusion in *The International Pharmacopoeia* contained three method texts in contrast to the current text.

The Expert Committee, therefore, agreed that selected experts would continue to work on the implementation of this new text for existing monographs in *The International Pharmacopoeia*.

3.3.2 Uniformity of content single-dose preparations

A review and explanation of the current pharmacopoeial approach as well as a review of application to published monographs for the general method “5.1 Uniformity of content of single-dose preparations”, was presented to the Expert Committee for consideration.

The Committee discussed the background document, endorsed the explanatory text as summarized below and adopted the proposed revisions of the relevant monographs. It further agreed that, as a basis for a future policy, this background document and explanatory text would be helpful to assist those involved in the development of new and revised monographs. In this respect, the document might also be made available more widely to provide explanatory information to users of *The International Pharmacopoeia* by its inclusion in the Supplementary information section of the pharmacopoeia.

Rationale of the review of method 5.1 and its application to tablets and capsules monographs

At its meeting in October 2010, the Committee discussed the application of uniformity of content testing to monographs in *The International Pharmacopoeia* especially those for tablets and capsules containing two or more APIs, commonly known as fixed-dose combinations (FDCs).

Questions had arisen with respect to the different testing thresholds applied in the WHO Guidelines for registration of fixed-dose combination medicinal products¹ and in the method of analysis 5.1 of *The International Pharmacopoeia*; the threshold in the WHO guidelines being 25 mg/25% whereas that applied in *The International Pharmacopoeia* was 5 mg/5% (see the agreed correction as regards this threshold under Method of analysis 5.1 Uniformity of content of single-dose preparations below).

In light of the discussion by the Committee, a review had been carried out of the test and of its application to all tablets and capsules that were the subject of an individual monograph in *The International Pharmacopoeia*, i.e. both those containing a single API and those that were FDCs.

A review document was discussed at the informal consultation on specifications for medicines and quality control laboratory issues in July 2011. A revised version of this document, reflecting the points raised and the recommendations made during the consultation was presented to the Committee for further discussion.

¹ 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).

Method of analysis

While it had been confirmed by the Expert Committee in 2010 that the technical basis of test 5.1 should not be modified it was, however, recommended at the informal consultation in July 2011 that the text of the method would benefit from editorial improvement. Notably, that an important omission in the method be corrected in including a reference to 5 mg or less in the statement concerning the application threshold. The current text referred only to 5% or less and it was recognized that a threshold expressed in terms of the declared weight of API per tablet was more transparent with respect to individual monographs, than one expressed in terms of the percentage of the tablet weight represented by the API. A threshold of 5 mg was actually already stated in the relevant specific monographs.

The Committee adopted and endorsed the edited text of method 5.1.

Application to tablets and capsules monographs

The Committee adopted and endorsed the general approach of adding, where appropriate:

- *“The use of the average of the uniformity of content results as an option under Assay (Method B) while retaining the current Assay applicable to a mixed sample of 20 tablets/capsules as Method A.”*

It further agreed to the revision proposals for the following individual monographs for tablets and capsules containing either a single or several APIs; these revisions would be made in accordance with normal procedures:

- *a single API*
 - atropine (sulfate) tablets
 - chlorphenamine hydrogen maleate tablets
 - colchicine tablets
 - dexamethasone tablets
 - ergometrine hydrogen maleate tablets
 - glyceryl trinitrate tablets
 - levonorgestrel tablets
 - prednisolone tablets
- *two or more APIs (FDCs)*
 - rifampicin, isoniazid, pyrazinamide and ethambutol hydrochloride tablets
 - sulfadoxine and pyrimethamine tablets.

Note: It was noted that for the monograph on levonorgestrel tablets and that for sulfadoxine and pyrimethamine tablets adopted in October 2010, this approach had already been implemented and endorsed during the finalization of the monographs, prior to their publication on the WHO Medicines web site.

Related WHO quality assurance guidelines

As noted during the review, an important issue was the existence of different thresholds applied in the WHO guidelines on FDCs and in *The International Pharmacopoeia*. After careful consideration of the possible options, the Expert Committee recommended that the WHO guidelines on FDCs, or any other WHO guidelines concerned, should be revised to bring them into line with *The International Pharmacopoeia*.

The Committee, therefore, endorsed the need for revising the following WHO guidelines referring to uniformity of content as a quality control test for finished pharmaceutical products:

- *WHO Guidelines for registration of fixed-dose combination medicinal products*
- *WHO Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product: quality part.*

3.3.3 General monograph on tablets

The general monograph on tablets was adopted by the Expert Committee in 2009 but was not included in the second supplement of *The International Pharmacopoeia* owing to the absence of some texts to be included in the Supplementary information.

Following comments from the WHO Department of Neglected Tropical Diseases (NTD) and from assessors from the WHO Prequalification of Medicines Programme, changes to the general monograph on tablets were proposed. A survey on solid oral forms of albendazole, azithromycin, mebendazole, diethylcarbamazine, ivermectin and praziquantel, which was conducted in six WHO Member States showed that 41 samples out of 72 did not conform with *United States Pharmacopoeia* requirements for dissolution. In the majority of the cases of non-conformity the product was in chewable tablet form. The fact that such a high proportion of samples failed to meet dissolution rate requirements raised concerns about the efficacy of these NTD medicines.

The Expert Committee considered this issue and discussed possibilities for reviewing the existing monograph with a view to making appropriate changes. Several small changes to the document were made and it was agreed to include references in the monograph to the relevant sections of the Supplementary information. With regard to the monograph's definition of chewable tablets, it

was agreed to add text to the effect that “*they are intended to be chewed before being swallowed. However, where indicated on the label, they may be swallowed whole.*” It was also agreed to delete “sublingual” and “buccal” from the heading of “Tablets for use in the mouth”.

It was agreed that the document with the adjusted definition and the editorial changes made by the Expert Committee should be placed on the web site to replace the existing version. The Committee felt that it should undertake a fuller review of the text on chewable tablets in due course.

3.4 Preface, general notices and supplementary information sections of *The International Pharmacopoeia*

Supplementary information section

It was appreciated that the reason for including the Supplementary information section in *The International Pharmacopoeia* was to inform and guide users so as to facilitate the proper use and interpretation of the specifications. It was considered important that users could easily find the relevant guidance. It was agreed that, as this section of *The International Pharmacopoeia* was expanding (for example, guidance on Polymorphism and identity tests had been approved in October 2009), it would be advisable to provide a more structured approach to the contents.

It was recommended that the present texts, together with others agreed or proposed for inclusion under Supplementary information, be presented in a structured format with related texts being grouped together. Adoption of a numbering system similar to that used for Methods of analysis would provide a flexible structure that could accommodate new texts being added to the appropriate section. It was agreed that the structured format preliminarily discussed and presented to the Expert Committee was suitable and it was recommended that it be adopted for the next publication.

It was noted that the document included both existing texts and a number of suggestions as to possible future components of the different subsections of a restructured Supplementary information section. Existing texts could be incorporated into the structured format from the start and new components added as and when they were approved.

It was recognized that providing guidance on certain aspects of pharmacopoeial control, such as impurity control and dissolution testing, would be very helpful to users of *The International Pharmacopoeia*, especially in the context of the Prequalification Programme. It was also recognized that providing details of certain test methods used during pharmaceutical development and manufacture of dosage forms was necessary to support the revised general monograph for Tablets.

It was agreed that Supplementary information for those policy topics considered appropriate should be developed in a similar manner to that for the text

on Polymorphism and identity tests adopted in 2009. Whenever a specific draft text was prepared, it would be circulated for comment to members of the WHO Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations, notably those involved in monograph development, discussed at an informal consultation and presented to the Expert Committee. It was noted that some Supplementary information on monograph development could be compiled from material already available, notably on the WHO Medicines web site and/or in reports of the Expert Committee.

The Expert Committee endorsed the recommendations and encouraged the secretariat to further develop relevant texts for consideration.

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 reference substances for use as primary standards in physical and chemical tests described in *The International Pharmacopoeia*. The standards are suitable for their intended use and officially adopted by the WHO Expert Committee on Specifications for Pharmaceutical Preparations. In April 2010 the European Directorate for the Quality of Medicines and HealthCare (EDQM) of the Council of Europe, Strasbourg, France, took over the responsibility for the establishment, preparation, storage and distribution of WHO ICRS from Apoteket AB, previously the WHO Collaborating Centre for Chemical Reference Substances.

Since the meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations in October 2010 the secretariat had invited national control laboratories to participate in collaborative studies to characterize ICRS. The invitation had received a positive response. In addition, the secretariat had established a database with information on all reference substances described in *The International Pharmacopoeia*. Furthermore, a document on frequently asked questions about collaborative trials to characterize ICRS had been prepared and circulated for comments.

The Expert Committee noted the report.

4.1.1 Report on activities of the host organization related to International Chemical Reference Substances

The Expert Committee received a report from EDQM on progress with regard to the ICRS. A new ICRS, alpha-artemether, would be established in October 2011, and the establishment of beclometasone dipropionate, replacement

batch, was under way. The internal study for a further ICRS, azobenzene, replacement batch, had been completed and a collaborative study was due to begin in October 2011.

While not within the scope of the WHO–EDQM cooperation agreement, the EDQM laboratory had exceptionally performed a study to support the development of *The International Pharmacopoeia* monograph for artemisinin. The study subjects were the correction/response factor artemisinin and the verification of a liquid chromatography (LC) method.

It was reported that the ICRS database included 215 ICRS. They had been ranked according to their demand and this ranking was being used to assign priority in monitoring. A monitoring programme had been established and was currently monitoring 23 ICRS. Of the 15 monitored to date, no deficiencies had been detected. In terms of quality control, eight batches have been subjected to quality control for identification.

The Expert Committee noted the report.

4.1.2 Frequently asked questions about collaborative trials

Reference standards to be used for assay determinations are examined in collaborative trials. The results obtained are used to assign a content or other analytical values to the standards. WHO had invited national quality control laboratories to join in trials to characterize ICRS, and a document that had been prepared to inform candidates about these studies was presented to the Expert Committee for information.

The overall goal of this project was to establish a worldwide distribution of ICRS to assist low- and middle-income countries to test for the quality of essential medicines described in *The International Pharmacopoeia* and used, for example, in the treatment of HIV/AIDS, tuberculosis and malaria. The Expert Committee noted the document.

4.1.3 Annual report on International Chemical Reference Substances 2010

Based on an umbrella agreement signed between WHO and EDQM in March 2010, and after having received the physical stock of existing ICRS from Apoteket, EDQM restarted the distribution of ICRS in May 2010.

Coordination meetings between WHO and EDQM took place in April and September 2010 to agree upon the details of the ICRS establishment workflow and to prioritize the work for the establishment of new ICRS.

In 2010 the total number of ICRS distributed by EDQM was 957. The five most frequently requested substances were, in order of demand: artesunate, vanillin, artemimol, artemether and lumefantrine.

The Expert Committee noted the report and thanked EDQM for its contribution and work in support of WHO Member States.

4.1.4 Lumefantrine for system suitability testing

The report of the EDQM on Lumefantrine for system suitability testing, the first ICRS to be developed by EDQM, was submitted to the Expert Committee. This substance was adopted by the Expert Committee as an International Chemical Reference Substance.

4.1.5 Bacterial endotoxin

A request to develop a replacement for the existing standard on bacterial endotoxin had been submitted to the Expert Committee by the WHO team for Quality, Safety and Standards.

Based on earlier agreement that the only reliable approach to maintaining harmonization of the endotoxin unit for pyrogen testing is the establishment of a shared, harmonized reference material, the establishment of a new material becomes necessary once one of the regional stocks is nearing depletion. This was the case for the EDQM material, necessitating the establishment of a new joint material. It was, therefore, proposed to establish the 3rd International Standard for bacterial endotoxin through an international collaborative study.

Since *The International Pharmacopoeia* includes the general test using this standard the Expert Committee considered that it would be important to maintain the continuity of the International Standard. The proposal was consequently endorsed by the Expert Committee.

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 quality control management systems in chemical control laboratories. It uses inter-laboratory comparisons to determine 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.

Analytical laboratories are required by the WHO good practices for pharmaceutical quality control laboratories and by other regulations, such as ISO/IEC 17025,² to participate in proficiency tests. WHO regularly organizes proficiency studies using physicochemical methods described in *The International Pharmacopoeia* (including methods used in pharmaceutical technology such as dissolution testing).

Up to 60 quality control laboratories from all six WHO regions usually participate in this Scheme.

² ISO/IEC 17025:2005. *General requirements for the competence of testing and calibration laboratories*. Geneva, International Organization for Standardization, 2005.

So far, EQAAS offers proficiency tests which enable participating laboratories to demonstrate their competence by analysing a common test sample. Results are evaluated and participants are judged according to their individual deviation from the true value.

Examples of three tests were described – namely on the water content of amodiaquine hydrochloride by Karl Fischer titration, dissolution tests of artemether and lumefantrine tablets, and assessment of the density and pH measurement of abacavir oral solution (still in progress at the time of the meeting). Three further tests are scheduled to take place in 2012 including an assay by HPLC of amodiaquine and artesunate tablets, a dissolution test of rifampicin capsules, and assay by titration of chloroquine sulfate oral suspension.

The Expert Committee raised concerns about the results of some studies which showed considerable variability between laboratories and indicated the need for training in some laboratories.

It was proposed to extend EQAAS in the future and to encourage participants not only to analyse a common test sample but also, if appropriate, to include commercial medicines drawn from their regional or national markets in the study. Participating laboratories would be given the necessary information to enable them to perform a proficiency test and a market surveillance study concurrently. The plan would be for study participants to receive in advance the protocols and all other details so that they would also be able to collect medicines with a similar composition from their local or regional markets. All samples – the market surveillance samples as well as the proficiency sample(s) – would be analysed in one series under repeatable conditions.

During the consultation on specifications for medicines and quality control laboratory issues in July 2011, national control laboratories expressed appreciation of the proposal to extend the programme.

Members of the Expert Committee noted that the extension of the Scheme could bring certain advantages, namely that:

- WHO could assist national authorities to identify and monitor products of low quality;
- WHO would learn more about the global applicability of methods of *The International Pharmacopoeia* and study results might support revision of relevant monographs and/or general chapters and methods;
- participants could more easily and confidently verify that the performance of the method applied is suitable by referring to their test result for the common sample (provided that it is satisfactory).

The Expert Committee approved the proposed extension of the scheme. It was pointed out that the studies for the extended scheme should be selected with care.

6. Quality assurance – good manufacturing practices

6.1 WHO good manufacturing practices: water for pharmaceutical use

A draft document on water for pharmaceutical use was presented to the Expert Committee for discussion. The document was intended to supplement the general guidelines on good manufacturing practices (GMP) for pharmaceutical products published by WHO in 2003. The text of the document presented was discussed by the Expert Committee in 2009 when the Committee was requested to bring the document into line with pharmaceutical water systems. The revision had been under way since and all comments received had been discussed at informal consultations. The Expert Committee reviewed the document together with the major comments received during the latest circulation phase.

The Expert Committee adopted the document subject to inclusion of the agreed changes, based on the comments received and those made during the discussion (Annex 2).

7. Quality assurance – new approaches

7.1 WHO guidelines on quality risk management

It was reported that a restructured text of the quality risk management document, incorporating all changes proposed during consultations and discussions to date, was in preparation and would be sent to members of the WHO Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations, and would go through the usual wide circulation process in due course. This new guidance is intended to replace the current WHO guidelines on hazard analysis and critical control points to cover new trends. The Expert Committee agreed to defer its discussion of this topic until the most recent version of the document was available.

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 on the quality of pharmaceutical products moving in international commerce is a voluntary agreement between WHO Member States. Dating from 1969 the Scheme has attracted both controversy and support and there have been many discussions about its value. In 2008 the Expert Committee asked for the Scheme to be reviewed in light of the changing situation.

Two question and answer documents on the Scheme had been prepared by the secretariat and approved by the Expert Committee for publication on the WHO Medicines web site. Moreover, in 2010, a circular letter was prepared asking Member States to comment on the recommendations included in the report of the previous Expert Committee and to submit comments and suggestions about the Scheme. Only 12 responses out of 194 Member States were received, examples of which were presented to the Committee. The conclusion was drawn that in spite of some limitations, Member States acknowledged the value of the WHO Certification Scheme.

In 2003 the Expert Committee proposed an extension of the Scheme to include starting materials in addition to finished products, and Poland joined this extended scheme. The WHO Medicines web site will in future have a special section dedicated to the Scheme, anticipating that more countries would join.

The Expert Committee noted the report and stressed the importance of the WHO Certification Scheme for APIs and requested follow-up to make sure that appropriate staff received the communication.

8.2 Update on Joint FIP/WHO guidelines on good pharmacy practice: standards for quality of pharmacy services

The Expert Committee was informed that the good pharmacy practices (GPP) adopted during its forty-fifth meeting had received much attention and had been translated into several languages. It was an important topic on the agenda of the ninety-ninth International Pharmaceutical Federation (FIP) meeting in 2011. The GPP text was endorsed by the FIP Council meeting for implementation by the national pharmaceutical associations of FIP.

The Expert Committee took note of this news.

9. Prequalification of priority essential medicines including active pharmaceutical ingredients

9.1 Update on the Prequalification of Medicines Programme managed by WHO

The Acting Manager of the WHO Prequalification of Medicines Programme reported that, since the 2010 meeting of the Expert Committee, 35 products had been prequalified. These included the new tenofovir/lamivudine + nevirapine combination; amikacin injection; a generic reproductive health product (ethinylestradiol/levonorgestrel); and an artesunate powder for injection. The Programme had also initiated prequalification of APIs during the year and had already prequalified five APIs. The Prequalification Programme had also begun assisting in an external review for the United Nations Population Fund

of reproductive health products. The Programme had continued to work closely with the Global Fund to Fight HIV/AIDS, Tuberculosis and Malaria.

The number of applications for products to be prequalified in 2011 was 54 (as at 10 October 2011), and of these 35 had been accepted. Twenty-one applications for APIs had been received, two of which had been prequalified and 19 were under assessment. As for the prequalification of control laboratories, five laboratories had been prequalified since October 2010. There are now six prequalified control laboratories in all WHO regions.

In addition, a retrospective study of generic product dossiers had been conducted. The results showed a number of deficiencies and indicated the need for capacity building for a number of manufacturers of generic products. An external assessment of the WHO Prequalification of Medicines Programme had been conducted and the results were generally positive.

Training in capacity building for NMRAs was increasing. In 2010 the WHO Prequalification of Medicines Programme organized 16 workshops and was involved in a further five. In 2011 the Programme organized 10 workshops and was involved in a further seven. However the challenge was to ensure that training was translated into improved implementation of the best practices.

Prequalification is highly dependent on the support from national regulators who are assisting WHO in this programme.

It was reported that donor funds were declining and that technical expertise was increasingly difficult to obtain. As in many other areas, the WHO Prequalification of Medicines Programme had been trying to do more with less funds.

The Expert Committee considered that the presentation had highlighted the importance of the WHO Prequalification of Medicines Programme, which was having an influence in a number of areas, such as strengthening capacity at local level and making medicines accessible to those who need them most.

10. Prequalification of quality control laboratories

10.1 Update on the prequalification of quality control laboratories

The prequalification procedure for quality control laboratories was originally established in 2004 for Africa only and has since expanded globally. Any quality control laboratory (whether public or private) may participate in the programme. Participation is voluntary and many laboratories have asked to participate. Most of the interested laboratories have been in the African region (the first to be focused on in the expression of interest), where 22 laboratories have expressed interest and so far six have been prequalified. Six laboratories had also been prequalified in Europe. The programme involves initial inspections and pre-audits to assess capacity, followed by a strong capacity-building component involving training.

10.2 Update on the surveys of the quality of medicines

A survey on the quality of antimalarials in Africa was carried out in cooperation with NMRAs in Cameroon, Ethiopia, Ghana, Kenya, Nigeria and the United Republic of Tanzania. A total of 935 samples was collected at all distribution levels and screened, with 306 of them being tested in a laboratory according to either *The International Pharmacopoeia* or the *United States Pharmacopoeia*. There was a 28.5% failure rate overall; two countries showed a 63% and 58% failure rate, respectively. The failure rate for prequalified products was 4% and that for non-prequalified products was 40%. The survey also revealed that some products tested were not registered in the country concerned and some samples contained no active ingredients.

A further study of TB medicines in the newly independent states showed much less deviation from acceptable standards, and none of the WHO-prequalified products failed. However, the study found that several medicines raised quality concerns. This led to a further study which showed that, for example, rifampicin capsules showed problems in assay, probably as a result of stability problems. An additional study of isoniazid/rifampicin tablets revealed a high rate of failure when tested according to *The International Pharmacopoeia* but samples passed when tested with *British Pharmacopoeia* methods.

The Expert Committee noted the outcome of the study and recommended that feedback should be provided to the respective pharmacopoeias.

11. Regulatory guidance

11.1 Policy on oseltamivir and zanamivir

A draft document on the shelf-life expiry of oseltamivir was reviewed by the Expert Committee. The issue had arisen since, during the recent H1N1 pandemic, much of the stock of oseltamivir was assigned a shelf-life of five years; it also had a five-year expiry date on the package label. Recently, however, some regulators had extended the shelf-life from five to seven years and some special measures were put in place to enable this extension. Much of the stockpile was manufactured five or six years ago and questions had now been received from Member States as to what they should do with the material.

The issue was presented to the Expert Committee with a view to obtaining guidance on the retention or disposal of expired stocks of oseltamivir capsules and zanamivir for finished products for which the shelf-life had been extended from five to seven years by a number of national and regional regulatory authorities.

WHO would not normally recommend use of medicines after their expiration since the manufacturer would have tested the product as being within specifications during that period. However, it was noted that the document acknowledged that countries were reluctant to destroy stockpiled medicines since

the scale and severity of a future pandemic could not be predicted and demand may exceed stockpile and manufacturing capacity. The document drafted for discussion included advice that, where a national authority elected to extend shelf-life, this should be considered only for stocks that had been stored under controlled conditions in accordance with manufacturers' recommendations, and such stocks should be used only in emergencies and where no alternative stocks or alternative medicines were available.

The Expert Committee recommended that such action should be under the sole responsibility of each national authority, taking into consideration the following points, to ensure that there was no negative impact on the patients.

- The manufacturer should be consulted for evidence to support extending the shelf-life.
- The products are maintained under storage conditions which comply with the label requirements.
- The national regulatory authority may wish to follow up with its own testing.

11.2 Assessment criteria for blood regulatory systems

The inherent risks of blood and the difficulty of providing adequate, timely and equitable access to safe blood products require an organized national or regional blood regulatory system in which a competent blood products regulatory authority ensures that appropriate standards are met for production of such products and that safety is monitored. In 2010 the World Health Assembly urged Member States to update their national regulations on donor assessment and deferral: the collection, testing, processing, storage, transportation and use of blood products, and operation of regulatory authorities in order to “ensure that regulatory control in the area of quality and safety of blood products across the entire transfusion chain meets internationally recognized standards”.

At the 13th meeting of ICDRA in 2008 it was recommended that WHO should take steps to further develop and strengthen national and regional blood regulatory authorities, and provide harmonized assessment criteria for blood regulatory systems.

To achieve the aim of an international best practice national blood regulatory framework, the WHO Blood Regulators Network (BRN) had identified a set of integrated general and specific regulatory functions applicable from the time of the collection of source material through to the quality control of the final product, not only covering blood products but also associated substances and medical devices such as *in vitro* diagnostics. The secretariat had subsequently developed a document on assessment criteria for national blood regulatory systems which was presented to the Expert Committee for discussion. The set of functions identified by the BRN was used to develop an assessment tool for regulatory authorities.

Following drafting of the original document at a BRN meeting in 2008, Health Canada and Swissmedic had carried out self-assessment exercises on the basis of the draft and further self-assessment was carried out in Argentina, Brazil and Indonesia. In 2010 the document was introduced to ICDRA at a BRN workshop.

The Expert Committee took note of the assessment tool presented.

11.3 **Pharmaceutical development for multisource (generic) pharmaceutical products – points to consider**

The development of the document on pharmaceutical development for multisource (generic) pharmaceutical products had been originally endorsed by the Expert Committee in 2007 and, following the collation of comments, was discussed by a WHO expert working group in 2008. The draft was subsequently revised, taking into account the comments received and those made by the working group, and the revised draft was submitted to the Expert Committee in 2008. All comments were incorporated and the Expert Committee discussed the guidelines again in 2009. The draft was further discussed both at the WHO consultation on paediatrics and generics guidelines in 2010 and by the Expert Committee that same year. During 2011 the draft was discussed once more at the WHO consultation on paediatrics and generics guidelines and mailed globally for comments before being resubmitted to the Expert Committee.

The document provides guidance on the contents of a pharmaceutical development plan for multisource pharmaceutical products including both pre-development activities and the development period, for both the applicants for marketing authorizations and NMRAs. The guidance focuses on the development of multisource finished pharmaceutical products (FPPs) which are intended to be bioequivalent to the relevant comparator product. Multisource FPPs are usually required to be therapeutically equivalent to the comparator product. It aims to provide a structured approach for industry, following the ICH common technical document format for developing high quality, multisource FPPs.

The Expert Committee reviewed the document and the comments received and made a number of changes to the text. The Committee adopted the document on pharmaceutical development of multisource (generic) pharmaceutical products – points to consider subject to inclusion of the agreed changes, based on the comments received and those made during the discussion (Annex 3).

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

These guidelines, which relate to submission of documentation in an application for the evaluation of a product for prequalification, were drafted in June 2010 and discussed within the WHO Prequalification of Medicines Programme assessment

group. Following further comments and review, the draft was first presented to the Expert Committee in October 2010. In early 2011 the text was once more reviewed in connection with the draft working document on *Points to consider for the development of multisource (generic) medicines*. Further discussion took place during the informal consultation on development of paediatric and generic medicines in May 2011. A further round of comments ensued, and the draft was also discussed by a small subgroup in September 2011 before being presented to the Expert Committee in October.

During the development of the guidelines, some 26 manufacturers who participate in the WHO Prequalification of Medicines Programme also contributed and were involved in the consultation process which led to the first draft of the document. The document was also open for public comment on the WHO Medicines web site, and was presented at workshops organized by the WHO Prequalification of Medicines Programme. The concept behind the guidelines had been implemented since September 2010 with regard to submission to the prequalification process.

The Expert Committee reviewed the document and the comments received. There was concern about the title of the document and it was requested that the document be adapted to make it clear that the general principles outlined were also applicable to the general process of application for prequalification.

The members of the Expert Committee agreed to change the title of the guidelines to read: *Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part*.

The Expert Committee adopted the guidelines, subject to inclusion of the agreed changes, based on the comments received and those made during the discussion (Annex 4). Furthermore, the Expert Committee proposed that a new general document be considered.

11.5 **Development of paediatric medicines: points to consider in pharmaceutical formulation**

Safe and effective pharmacotherapy in paediatric patients requires the timely development of medicines and information on their proper use to suit the age, physiological condition and body size of the child. Formulations developed specifically for children are often needed. The use of unlicensed and off-label medicines in children is widespread. Their effects on children have not been properly studied and age-appropriate formulations are generally not available.

Pharmacists, parents or caregivers are often faced with the need to manipulate an adult medicine in a way that is not described in the summary of product characteristics. This manipulation can be simple (e.g. breaking tablets

that do not have a score line with a tablet splitter) or complex (e.g. using tablets as a source for an API to prepare a suspension). Pharmacists may also be faced with the need to compound a medicine on the basis of the API.

This process itself can increase the potential for errors in dosage accuracy and in general can increase the variability of the product. Such handling may be potentially hazardous for the patient as it may affect the stability, bioavailability and accuracy of dosing of an FPP, in particular for controlled-release preparations. The use of such manipulated medicines may expose children to overdosing and unintended side-effects or underdosing without the expected efficacy. Moreover, excipients that are safe for adults may not necessarily be so for children.

In December 2007, WHO launched its initiative “Make medicines child size” in order to raise awareness and accelerate action in response to the need for improved availability and access to child-specific medicines. Among actions to support the “Make medicines child size” initiative was the *Development of paediatric medicines: points to consider* guidance on pharmaceutical development of paediatric medicines. The intention is to inform regulatory authorities and manufacturers on issues that require special attention during the pharmaceutical development of paediatric medicines, with a focus on the conditions and needs in developing countries.

At the meeting of the Expert Committee in October 2007, a draft of *Development of paediatric medicines: points to consider* was discussed with a view to contributing to the pharmaceutical part of the document. An extended revision of the part on pharmaceutical development as a stand-alone text was drafted in February 2008 and, following circulation of this document, a great number of comments were received.

In April 2010 a consultation on paediatrics and generics draft guidelines discussed the draft together with an outline of the paediatric guidelines. Another version of the working document was prepared, based on the discussions during that meeting, the feedback and comments received on the previous version, and the report of the 2008 WHO Informal Meeting on Dosage Forms of Medicines for Children. Following wide circulation, comments were again received and the feedback was discussed by the Expert Committee in October 2010. A new revision was then prepared, taking into account new developments, such as efforts being undertaken by regulatory authorities. Following further discussion during an informal consultation in May 2011 the document, as revised after that meeting, was once again distributed widely for comments.

It was noted that, among other things, the points to consider document attempted to take into account convenience, reliability, acceptability, minimum dosing and end-user needs. The issues addressed by the guidelines included paediatric dosage forms, formulation design, different means of administration, inhalation, and packaging and labelling. The Expert Committee adopted the

document subject to inclusion of the agreed changes, based on the comments received and those made during the discussion (Annex 5).

11.6 **Provision by health-care professionals of patient-specific preparations for children that are not available as authorized products: points to consider**

In March 2011 the Expert Committee on the Selection and Use of Essential Medicines reviewed the current development of guidance on the extemporaneous preparation of medicines for children and noted the preliminary draft commissioned by the WHO Department of Essential Medicines and Pharmaceutical Policies (now WHO Department of Essential Medicines and Health Products). The Expert Committee on the Selection and Use of Essential Medicines accepted that there may be situations where extemporaneous preparation of medicines for children was necessary, but members expressed concern about the risks of inappropriate preparations. The Committee also considered the risks of diverting efforts aimed at the development of age-appropriate dosage forms for children and indicated that WHO's endorsement of extemporaneous use should not be seen in any way as indicating a lack of need for commercially available paediatric dosage forms. The Committee raised concerns about potentially conflicting signals arising from a WHO publication that might appear to endorse wider use of manipulation of adult dosage forms for children. Notwithstanding these concerns, the Committee on the Selection and Use of Essential Medicines agreed that the document should be finalized for publication as a time-limited guidance that addresses the current need for advice, including review by the Expert Committee on Specifications for Pharmaceutical Preparations. It was noted that consideration could be given to publication of this guidance document by an organization other than WHO.

The document was discussed during the informal consultation on paediatric and generics guidelines in May 2011 under the auspices of the Expert Committee on Specifications for Pharmaceutical Preparations. The participants suggested modifying the title to avoid reference to "extemporaneous" and also suggested aligning the title of this document with other similar guidance texts currently under development as "points to consider".

The document makes it clear that children should have access to authorized, ready-to-administer, age-appropriate preparations of medicines and nothing in the document should detract from this objective. However, the document recognized that such preparations will not always be available and a safe and effective alternative must be sought. In the context of neonatal and paediatric pharmacy practice, the technique of compounding is used by pharmacists to produce medicines from ingredients when no commercially available, authorized, age-appropriate dosage form exists. Compared to the use of authorized medicines there are significant risks; quality, safety and efficacy can

rarely all be assured and there have been many errors reported in the preparation of such medicines.

The Committee noted that a paediatric medicines regulators' network exists.³

The Expert Committee expressed appreciation of the document as a source of general guidance. Furthermore, the Committee advised that the document could be further developed jointly by WHO and FIP as practice guidance for compounding.

11.7 **Quality requirements for artemisinin as a starting material in the production of antimalarial active pharmaceutical ingredients**

On various occasions, including at workshops organized by WHO and the Medicines for Malaria Venture, issues relating to quality control specifications applicable to active substances used not only by themselves, but also as starting materials for other active substances, have been discussed. The main challenge identified was that often, when used as starting materials for derivatives, for example when artemisinin is used in the manufacture of artemisinin-derived APIs, these substances were dealt with by some national authorities applying the same control requirements as when they are used directly for manufacturing of FPPs.

Quality control specifications applicable to APIs are often used not only for the active substance itself but also to control the quality of starting materials for the production of other active substances. An example is artemisinin which is an important API and also serves as a starting material for the production of artemisinin-derived antimalarials.

Some national authorities require the same quality standard (i.e. they apply the same limits) for an API and for a starting material. However, it is sufficient for a starting material to have a quality that guarantees that the final product meets the relevant pharmacopoeial standard. Demanding that a starting material meets a quality standard that is too exacting is likely to increase the price and to reduce access to the related FPPs.

On the basis of a request from the international community, a guidance document on *Quality requirements for artemisinin as a starting material in the production of antimalarial active pharmaceutical ingredients* was prepared to clarify the need for different quality levels for artemisinin. The document includes a specification for artemisinin used as a starting material, which was based on proposals made by the manufacturers.

³ Regulatory support: Paediatric Medicines Regulatory Network. *WHO Drug Information*, 2011, 25:240–241.

The first working document was circulated in March–April 2010 and comments received were first discussed during an informal consultation. A revised version was circulated and the further comments received were discussed at the meeting of the Expert Committee in October 2010. As the assignment of the impurities in the test for related substances in the first revision was tentative and based on the available scientific publications, the Expert Committee members recognized the need to clarify the impurity profile before the document could be completed.

The task of elucidating the impurity pattern was carried out by EDQM. The retention times of artemisitene and 9-epi artemisinin were identified and a correction factor for artemisitene was determined. It was revealed that the impurity assignment published in the first revision was incorrect. On the basis of this information, a second revision was prepared and circulated for comments in August 2011.

The Expert Committee reviewed the second revision of the quality requirements and considered the comments received.

The Expert Committee adopted the document on *Recommendations for quality requirements for artemisinin as a starting material in the production of antimalarial active pharmaceutical ingredients* subject to inclusion of the agreed changes, based on the comments received and those made during the discussion (Annex 6).

11.8 Update on comparator products

It was reported to the Expert Committee that the secretariat was working on the update of the list of comparator products and the assistance of the members of the Committee was requested in order that the list might be published on the web site as soon as possible to replace the version adopted in 2002.

12. Nomenclature, terminology and databases

12.1 Quality assurance terminology

Quality assurance database

The WHO quality assurance terminology database was established in August 2005. The entries in this database are taken from the glossary definitions in WHO guidelines pertaining to quality assurance activities. The objectives of the database are to foster the understanding of quality assurance-related activities, promote harmonization in quality assurance terminology globally, and to avoid misunderstandings that may result from the different terms used in various publications and their interpretations. The publications used as a source of information to create the WHO quality assurance terminology database are the quality assurance guidelines adopted by the Expert Committee on Specifications for Pharmaceutical Preparations.

The WHO quality assurance terminology database has been updated to include all definitions published in glossaries of guidelines from the Expert Committee meeting reports since the Committee was established in 1947. The database currently includes terms and their definitions from a total of 52 guidelines. The number of terms and their definitions is 528; however, the number of entries of terms is more than 800 because many of the terms have been defined differently in various publications or may have differing definitions according to their context. The database clearly indicates in which publication(s) a particular term was defined.

The terminology database is intended to be a simple tool for editing and retrieving terminology records and should be updated and enlarged periodically.

The Expert Committee much appreciated this work carried out by the secretariat and decided to set up a group of experts to continue the work on the preferred terminology.

Definition of API

In many WHO guidelines the definition for an active pharmaceutical ingredient (API) (singular) is found in the Glossary (for instance it appears three times in the WHO Technical Report Series, No. 961). The definition currently used is:

“active pharmaceutical ingredient (API)

Any substance or combination of substances used in a finished pharmaceutical product (FPP), intended to furnish pharmacological activity or to otherwise have direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease, or to have direct effect in restoring, correcting or modifying physiological functions in human beings.”

This definition may imply that commercially available premixes of APIs (such as the popular amoxicillin + clavulanic acid premix) can be regarded as an API, although this would normally be considered to be incorrect. Once an API is mixed with another API, or with an excipient, it is usually no longer considered an API. Thus the current definition may lead to misinterpretation.

The Expert Committee decided to defer this matter to the group of experts mentioned above who would continue the work on the quality assurance terminology.

12.2 International Nonproprietary Names for pharmaceutical substances

The International Nonproprietary Names (INN) team presented the current status of the INN list. Some 61 names were currently in preparation. Six new stems and two new pre-stems were published recently.

Of 92 INN requests in the past year, 44 were for biologicals. A revised naming policy for biologicals had been adopted and would be published in *Bioreview* in 2011. According to this policy, additional Arabic numbers might be used to distinguish subspecies which differ significantly.

The INN team had also worked on establishing definitions of the different INNs. This meant attempting to obtain further information from the companies concerned, but this task had been complicated by the fact that some companies no longer existed or had been incorporated into other companies. An internal document on these definitions had been prepared.

Applications for new INNs could now be made through an online interface, which enables more data to be collected than is possible in print form. There is an online application form which, when filled in, is transferred to the user by a secure transfer (in an encrypted file as used in e-banking). Once stored on the server, the data are also encrypted, and the server is protected by the usual WHO firewall and security systems. The aim was to create a global INN data hub to which access would be very restricted and secure. Any use of the data not in line with the rules of the INN application process would lead to refusal of access. Beta-testing was due to take place later in 2011.

The Expert Committee took note of the INN report.

13. Miscellaneous

13.1 Brochures on the Expert Committee and on quality assurance of pharmaceuticals

The new brochure on the Expert Committee on Specifications for Pharmaceutical Preparations summarizes how the Expert Committee works and provides detailed information on the process of the Committee. The second information brochure on quality assurance of pharmaceuticals summarizes the main areas covered by the Expert Committee in the past three years.

In addition, a CD-ROM had been prepared, including all current guidelines and guidance texts adopted by the Expert Committee and which are also available on the WHO web site in a structured manner according to their subjects, e.g. production, distribution, and so on. A new updated CD-ROM would be issued in due course with the recommendations from the 2011 meeting.

The Expert Committee expressed its appreciation to the Secretary for the content and design of the brochures developed and the CD-ROM on medicines quality assurance.

13.2 Sampling procedures for monitoring of market situations

The development of sampling procedures for monitoring of market situations had been initiated in response to multiple requests from colleagues carrying out studies. Following a wide enquiry a great deal of material had been received from many countries. The outcome and draft procedures resulting from the evaluation of the material received would be presented to the next Expert Committee meeting.

There was also a presentation on a new project within this area of work, particularly focusing on the SSFFC products. There was a deficiency of hard data on this issue and the project aimed to establish a global monitoring and surveillance system and disseminate data, to collate best practice and establish a minimum reporting standard on SSFFC products, to assist regulatory authorities to identify SSFFC products, to establish where the risks were greatest, and to encourage collaboration between regulatory authorities on this issue. This is a four-year project in five phases and is being carried out by the team for Quality Assurance and Safety: Medicines in WHO in close collaboration with the regional offices and countries.

The Expert Committee expressed its appreciation for the project and gave its endorsement. The Committee considered that the idea of having a watch list of products that were frequently falsified would be very helpful to NMRAs.

13.3 *Index of pharmacopoeias*

This index, including all pharmacopoeias around the world, was first prepared in 2001 and has been regularly updated. In accordance with the recommendations made by the Expert Committee at its forty-fifth meeting, the *Index of Pharmacopoeias* had been revised. Africa has one pharmacopoeia (this is the African Pharmacopoeia and not a national pharmacopoeia), the Americas four, the Western Pacific has five, and Europe has 30. Of these, five national pharmacopoeias offer free online access, as does *The International Pharmacopoeia* of WHO. The index contains all contact information for the pharmacopoeias.

The Expert Committee took note of the report and advised the Secretary to complete and update the missing information in the index as notified by the respective pharmacopoeias.

13.4 *Collaboration with pharmacopoeias*

WHO was working on closer collaboration with a view to exchanging information with other pharmacopoeias and achieving further harmonization. A meeting was held in July 2011 with a number of representatives from secretariats of national pharmacopoeias. FIP would provide an opportunity for a meeting of pharmacopoeia representatives with other stakeholders in 2012, and WHO would offer to organize a private meeting for pharmacopoeia representatives only, to discuss common issues and concerns following up on discussions that had started during a side-meeting held at the 10th ICDRA meeting in Hong Kong Special Administrative Region of the People's Republic of China in 2002.

The Expert Committee took note of this initiative and expressed its support for an international meeting of world pharmacopoeias organized by WHO.

14. Summary and recommendations

The Expert Committee on Specifications for Pharmaceutical Preparations provides recommendations and tools to assure the quality of medicines from their development phase to their final distribution to the patients. It advises the Director-General of the World Health Organization in the area of quality assurance of medicines.

The international guidelines, specifications and nomenclature developed under the aegis of this Committee serve all Member States, international organizations, United Nations agencies, regional and interregional harmonization efforts, and underpin important initiatives, including the prequalification of medicines, the Roll Back Malaria Programme, Stop TB, essential medicines and medicines for children.

The advice and recommendations provided by this Expert Committee are intended to help national and regional authorities and procurement agencies, as well as major international bodies and institutions, such as the Global Fund to Fight AIDS, Tuberculosis and Malaria, and international organizations such as the United Nations Children's Fund (UNICEF) to combat circulation of substandard medicines and to work towards access to good-quality medicines.

Since the inception of this WHO Expert Committee in 1948, its members have worked towards making available clear, independent and practical recommendations, written and physical standards, as well as international guidelines for good-quality medicines. Standards in the area of quality assurance for medicines are developed by the Committee through a wide global consultation process building on consensus to reach internationally recognized and up-to-date standards. Detailed recommendations can be found under each relevant section in the report.

The topics are related to various programmes and activities within WHO. There are joint activities, specifically in collaboration with the WHO Expert Committees on Biological Standardization, and on the Selection and Use of Essential Medicines and its Subcommittee on Medicines for Children. In addition, the Committee serves to develop specific additional guidance and specifications as needed for the various medicines recommended by WHO programmes.

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

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

The following new guidelines were adopted and recommended for use:

- Development of monographs for *The International Pharmacopoeia* (Annex 1)
- WHO good manufacturing practices: water for pharmaceutical use (Annex 2)
- Pharmaceutical development of multisource (generic) pharmaceutical products – points to consider (Annex 3)
- Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part (Annex 4)
- Development of paediatric medicines: points to consider in formulation (Annex 5)
- Recommendations for quality requirements for artemisinin as a starting material in the production of antimalarial active pharmaceutical ingredients (Annex 6)

For inclusion in *The International Pharmacopoeia*

The following monographs were adopted:

- *For antiretroviral medicines*
 - ritonavir tablets
- *For antimalarial medicines*
 - artesunate
 - artemimol
- *For antituberculosis medicines*
 - rifampicin (API)

- rifampicin tablets
- rifampicin capsules
- *For anti-infectives*
 - pyrantel chewable tablets
- *For other medicines*
 - levonorgestrel tablets
 - medroxyprogesterone injection
 - paediatric retinol oral solution
 - retinol concentrate (oily form)
- *For harmonized general texts (based on PDG texts)*
 - test for sulfated ash
 - test for bacterial endotoxins
 - test for sterility
 - tablet friability
 - disintegration test for tablets and capsules
 - bulk density and tapped density of powders
 - test for extractable volume for parenteral preparations
 - microbiological examination of non-sterile products: microbial enumeration tests
 - microbiological examination of non-sterile products: tests for specified microorganisms
 - microbial quality of pharmaceutical preparations
 - test for particulate contamination

General policy topics and general revision issues for:

- uniformity of content for single-dose preparations
- supplementary information section

The Committee adopted the following new ICRS:

- Lumefantrine for system suitability

The following monograph was released for the wide consultation process:

- *For antimalarial medicines*
 - mefloquine hydrochloride

Regulatory guidance

Extension of shelf-life

The Expert Committee recommended that each national authority, if opting to extend the shelf-life of oseltamivir and zanamivir, should take into consideration the following points to ensure that there was no negative impact on the patients:

- The manufacturer should be consulted for evidence in support of extended shelf-life.
- The products are maintained under storage conditions in compliance with the label requirements.
- The national regulatory authority may wish to follow up with its own testing.

Recommendations in the quality assurance-related areas

The following recommendations were made in the various quality assurance-related areas. Progress on the suggested actions should be reported to the Expert Committee on Specifications for Pharmaceutical Preparations at its next meeting.

Collaboration with and among pharmacopoeias

- The Expert Committee expressed support for WHO's initiative to work more closely with other pharmacopoeias. It also endorsed the proposed international meeting bringing together representatives of all the world's pharmacopoeias to enable them to discuss common issues and concerns.

The International Pharmacopoeia

- Continue development of specifications for medicines, general methods and texts and general supplementary information in accordance with the work plan and as decided at the forty-sixth meeting.
- Continue the efforts at international collaboration in relation to the revision and inclusion of specific monographs and general methods.
- Continue the preparatory work for a subsequent supplement to *The International Pharmacopoeia*, or towards a fifth edition, especially in electronic form (CD-ROM and online).

International Chemical Reference Substances (ICRS)

- Continue to promote the use of ICRS through various activities, including a promotional offer to national authorities.
- Continue the efforts to further enhance the development of new ICRS.

External Quality Assurance Assessment Scheme (EQAAS)

- Continue the EQAAS for pharmaceutical quality control laboratories, Phase 5, test series 4 onwards.
- Further prepare the extension of the Scheme starting with Phase 6 to encourage participants to include commercial medicines drawn from their local and regional markets in the studies, when the test protocol allows doing so.

Good manufacturing practices (GMP) and manufacture

- Follow up on the revision process for GMP for biologicals undertaken under the aegis of the Expert Committee on Biological Standardization.
- Continue the consultation process on the quality risk management principles with a view to updating the WHO guidelines on hazard analysis and critical control points to cover new trends.

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

- Continue efforts towards a possible review of the WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce.
- Develop a special WHO web site for the WHO Certification Scheme for APIs.

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

- A new general document is to be prepared based on the specific guidance developed for the WHO Prequalification Programme (see Annex 4).

Provision by health-care professionals of patient-specific preparations for children that are not available as authorized products: points to consider

- Further explore development of these “points to consider” jointly with the International Pharmaceutical Federation (FIP) as practice guidance for compounding.

Update on comparator products

- Provide an update of the list of comparator products on the web site, following review by the members of the Expert Committee, to replace the version from 2002.

Sampling procedures for monitoring of market situations

- Continue development of sampling procedures based on the numerous examples obtained from many countries as feedback to the secretariat’s communications.

Quality assurance terminology

- Continue the work on the preferred terms included in the current quality assurance terminology database based on the analysis prepared by the secretariat, with a group of experts, including the definition for an API, on which consultation had already started.

Index of pharmacopoeias

- Consult with the secretariat representatives of the individual world pharmacopoeias included in the *Index of pharmacopoeias* in order to complete and validate the information therein and update the current version on the web site accordingly.

WHO databases

- Maintain the International Nonproprietary Names (INN) database and continue to make it available on the web site.
- Maintain the Quality Assurance database and continue to make it available on the web site.

Summary of additional recommendations from the closed session of the Expert Committee

1. *Drafting of the Expert Committee report*

The Expert Committee appreciated the additional assistance, provided to the rapporteurs by a professional editor during this meeting to speed up and facilitate the report-writing process. Additional practical advice on the future drafting process was given, for example, to enable a review of the draft report by the Expert Committee members each day.

2. *New proceeding*

The Expert Committee suggested providing e-links to the various documents on the agenda to replace the paper versions of these documents at future meetings. It was also suggested that all presentations be given on the first day to assist in the smooth running of the meeting agenda and to discuss related topics later during the Committee meeting under each agenda item. Moreover, the Expert Committee members suggested providing time slots every day to facilitate the creation of specific subgroups to discuss pending issues during each day of the meeting.

3. *Financial situation analysis*

The Expert Committee noted that, from the presentations of the various related programmes during the meeting, it had become apparent that some WHO programmes seemed to have considerably more staff and financial resources than the Quality Assurance of Medicines Programme in QSM. This would result in a certain imbalance in comparison with the work of the Quality Assurance of Medicines Programme. As WHO resources seemed to be decreasing within the Organization and affecting this programme and its related activities even more, the Expert Committee wished the following to appear as a note in the report concerning current achievements:

- since 2003 the meetings of the WHO Expert Committee on Specifications for Pharmaceutical Preparations have been held on an annual basis;
- the total number of guidelines which have been produced is 70;
- the staff currently working in the Quality Assurance of Medicines Programme is two-and-a-half professionals, one secondment and two general-service assistants.

The Expert Committee wishes to express its recognition of the hard work undertaken and the increasing workload faced by the secretariat, which aims to cope with the frequency of meetings and new trends, in order to respond to the international demands and those of the WHO-associated programmes to provide timely advice and guidance as an up-to-date service to WHO Member States and United Nations programmes. The Expert Committee members strongly recommend the Director-General to provide this programme with adequate resources in the future to carry out this important function of providing independent international standards and guidelines in the area of quality assurance of medicines.

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Anti-Counterfeiting Medicines Programme, WHO, Geneva, Switzerland; Blood Products and Related Biologicals Programme, WHO, Geneva, Switzerland; Global Malaria Programme, WHO, Geneva, Switzerland; HIV/AIDS Programme, WHO, Geneva, Switzerland; International Medical Products Anti-Counterfeiting Taskforce (IMPACT), WHO, Geneva, Switzerland; Medicine Access and Rational Use Team, WHO, Geneva, Switzerland; Medicines Regulatory Support Programme, WHO, Geneva, Switzerland; Office of the Legal Counsel, WHO,

Geneva, Switzerland; Prequalification Programme, WHO, Geneva, Switzerland; Quality and Safety: Medicines Team, WHO, Geneva, Switzerland; Quality, Safety and Standards Team, WHO, Geneva, Switzerland; Traditional Medicine Team, 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.

Mrs T. Abdul Sattar, Acting Director General, Directorate General of Pharmaceutical Affairs and Drug Control, Ministry of Health, Muscat, Oman; 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, University of Ghana, Legon, Ghana; Ms R. Ahmad, Centre for Product Registration, National Pharmaceutical Control Bureau, Ministry of Health, Petaling Jaya, Malaysia; Mrs S. Ahmed Jaffar, Directorate General of Pharmaceutical Affairs and Drug Control, Ministry of Health, Muscat, Oman; Dr A. Akkermans, the Netherlands; AMGEN Inc., Engineering, West Greenwich, RI, USA; Dr R. Andrews, Medicines and Healthcare products Regulatory Agency, London, England; Dr C. Anquez Traxler, European Self-Medication Industry, Brussels, Belgium; Dr H. Arentsen, Regulatory Intelligence and Policy Specialist, Regulatory Development Strategy, H. Lundbeck A/S, Copenhagen-Valby, Denmark; Astellas Pharma Europe BV, Leiderdorp, The Netherlands; Dr C. Athlan, Quality Reviewer, Swissmedic, Berne, Switzerland; Dr A. Ba, Directeur, Qualité et Développement, Centrale Humanitaire Medico-Pharmaceutique, Clermont-Ferrand, France; 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, Vice-President for Drug Affairs, Saudi Food and Drug Authority, and Head of Drug Sector, Riyadh, Saudi Arabia; 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; Dr L. Besançon, Manager, Scientific and Professional Affairs, International Pharmaceutical Federation, The Hague, The 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 L. Bigger, ex-Regulatory and Scientific Affairs, International Federation of Pharmaceutical Manufacturers Associations, Geneva, Switzerland; Dr J. Bishop III, Review Management Staff, Office of the Director, Center for Biologics Evaluation and Research/FDA, Rockville, 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. Bourdeau, Méréville, France; Professor R. Boudet-Dalbin, Paris, France; Dr S.K. Branch, Acting Group Manager, Special Populations Group, Medicines and Healthcare products Regulatory Agency, London, England; Dr E. Brendel, Bayer HealthCare, Elberfeld, Germany; Dr M. Brits, Deputy 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; 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 A. Castro, Regulatory Affairs Director and Senior Pharmacist, Roche Servicios, Heredia, Costa Rica; Dr D. Catsoulacos, Scientific Administrator, Manufacturing and Quality Compliance, Compliance and Inspection, European Medicines Agency, London, England; Mr Paulo Cenizo, Southern African Pharmaceutical Regulatory Affairs Association (SAPRAA), Randburg, South Africa; Mr Xuanhao Chan, ex-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 and Cigarette Testing Laboratory, Pharmaceutical Division, Applied Sciences Group, Health Sciences Authority, Singapore; Dr Xu Chen, Director, Division of Drug Distribution Supervision, State Food and Drug Administration, Beijing, People's Republic of China; Professor Y. Cherrah, Directeur, Faculté de Médecine et Pharmacie, Rabat, Morocco; Dr Y.H. Choi, Scientific Officer, Korea Food and Drug Administration, Cheongwon-gun, Chungbuk, Republic of Korea; 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, Kolkata, India; Dr J. Daviaud, Senior Pharmaceutical QA Officer, Pharmaceutical Procurement Unit, Global Fund to Fight AIDS, Tuberculosis and Malaria, Geneva, Switzerland; Dr V. Davoust, Quality & Regulatory Policy, Global CMC, WW Pharmaceutical Sciences, Pfizer Global Research & Development, Paris, France; Professor T. Dekker, Research Institute for Industrial Pharmacy, North-West University, Potchefstroom, South Africa; Dr L. De-Moor, GlaxoSmithKline, Belgium; Dr J. DiLoreto, Executive Director, Bulk Pharmaceuticals Task Force, Washington, DC, USA; Dr V. Divecha, Cipla, India; Professor J.B. Dressman, Professor of Pharmaceutical Technology, 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 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; Dr A. Falodun, Department of Pharmaceutical Chemistry, Faculty of Pharmacy, University of Benin, Benin City, Nigeria; 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; Dr A. Flueckiger, Head, Corporate Health Protection, Corporate Safety, Health and Environmental Protection, F. Hoffmann-La Roche, Basel, Switzerland; Dr G.L. France, Vice-President, Quality Strategy, Pfizer Limited and Vice-Chair, IFPMA/RPTS, Maidenhead, England; Dr N.C. Franklin, Wuppertal, Germany; Mr T. Fujino, Director, International Affairs, Japan Generic Medicines Association, Tokyo, Japan; Dr M. Garvin, Senior Director, Scientific and Regulatory Affairs, Pharmaceutical Research and Manufacturers of America, Washington, DC, USA; Dr F. Giorgi, Research and Development, Analytical Development Manager, Sigma-tau Industrie Farmaceutiche Riunite, Pomezia, Italy; Dr L. Girard, Head, Global Pharmacopoeial Affairs, Novartis Group Quality, Quality Systems and Standards, Basel, Switzerland; Dr N. Goldschmidt, USA; Dr E. Gomez, Ridgefield Park, New Jersey, USA; Ms J. Gouws, Department of Health, Medicines Control Council, Pretoria, South Africa; Dr M. Goverde, QC Expert Microbiology, Novartis Pharma, Basel, Switzerland; Ms R. Govithavatangaphong, Director, Bureau of Drug and Narcotic, 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, New York, NY, USA; Ms N.M. Guerrero-Rivas, Head, Quality Assurance Section, Instituto Especializado de Análisis, Estafeta Universitaria, Panamá, Panama; Guilin Pharmaceutical Company Ltd, Guilin, People's Republic of China; Dr R. Guinet, Agence française de sécurité sanitaire des produits de santé, Saint-Denis, France; Dr G.T. Gunnarsson, Iceland; Professor R. Guy, Professor of Pharmaceutical Sciences, Department of Pharmacy and 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; Dr A. Hawwa, Lecturer in Pharmacy (Medicines in Children), Medical Biology Centre, Queen's University Belfast, Belfast, Northern Ireland; Dr M. Hayes-Bachmeyer, TRIS Management, Technical Regulatory Affairs, Pharmaceuticals Division, F. Hoffmann-la Roche, Basel, Switzerland; Dr G.W. Heddell, Director, Inspection Enforcement and Standards Division, Medicines and Healthcare products Regulatory Agency, London, England; Dr D. Hege-Voelksen, Swissmedic, Berne, Switzerland; Dr M. Helling-Borda, Commugny, Switzerland; Ms J. Hiep, QA Pharmacist and Auditor, Adcock Ingram, Bryanston, South Africa; Ms M. Hirschhorn, Chief, Quality Assurance and Analytical Chemistry, Comisión para el Control de Calidad de Medicamentos, Montevideo, Uruguay; Professor J. Hoogmartens, Professor Emeritus, Laboratorium voor Farmaceutische Analyse, Leuven, Belgium; Dr K. Hoppu, Director, Poison Information Centre, Helsinki University Central Hospital, Helsinki, Finland; Dr R. Horder, Consultant, Abbott, Maidencombe, England; Dr H. Hoseh, Head of Registration Unit, Drug Directorate, Jordan Food and Drug Administration, Jordan; Dr Hou Xiping, TÜV SÜD PSB Chemical & Materials, Singapore; Dr N. Ibrahim, National Pharmaceutical Control Bureau, Ministry of Health, Jalan University, Petaling Jaya, Indonesia; Professor R. Jachowicz, Head, Department of Pharmaceutical Technology and Biopharmaceutics, Jagiellonian University Medical College, Faculty of Pharmacy, Kraków, Poland; Dr R. Jähne, Global Pharma Health Fund e.V., Frankfurt, Germany; Dr M. James, GlaxoSmithKline, Brentford, Middlesex, England; Dr A. Janssen, Manager, Regulatory Affairs, DMV Fonterra Excipients, Friesland Campina Ingredients Innovation, Goch, Germany; Professor Jin Shaohong, 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, France; Mr D. Jünemann, Teaching Assistant; Institut für Pharmazeutische Technologie, Biozentrum, Johann Wolfgang Goethe-Universität, Frankfurt and Main, Germany; Ms A. Junttonen, Senior Pharmaceutical Inspector, National

Agency for Medicines, Helsinki, Finland; 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; Dr T. Kawanishi, Deputy Director General, National Institute of Health Sciences, Tokyo, Japan; Ms H. Kavale, Cipla, Mumbai, India; 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, 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; Professor Kazuko Kimura, Institute of Medicine, Pharmacy and Health Sciences, Kanazawa University, Kanazawa-city, Japan; Ms M. Kira, Consultant, Non-Governmental Organizations and Industry Relations Section, Department of External Relations, World Intellectual Property Organization, Geneva, Switzerland; 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 Scientist, Chemist Laboratory, Therapeutic Goods Administration Laboratories, Woden, ACT, Australia; Professor H.G. Kristensen, Vedbaek, Denmark; Mr A. Kupferman, Industry Pharmacist, Strasbourg, France; Professor S. Læer, Institut für Klinische Pharmazie und Pharmakotherapie, Heinrich-Heine-Universität, Düsseldorf, Germany; Dr J.-M. Legrand, GlaxoSmithKline Biologicals, Wavre, Belgium; 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 Low Min Yong, Director, Pharmaceutical Division, Applied Sciences Group, Health Sciences Authority, Singapore; 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 F. Malik, Pakistan; Reverend J.Y. Martey, Head, Laboratory Services, Quality Control Laboratory, Food and Drugs Board, Accra, Ghana; Dr T. Massa, Vice President, Global Regulatory Sciences – Chemistry, Manufacturing and Control, Bristol-Myers Squibb, USA; Dr B. Matthews, Alcon, Hemel Hempstead, Herts, England; Dr Y. Matthews, Regulatory Operations Executive, GE Healthcare, Amersham, Bucks,

England; Dr J.-L. Mazert, Rueil, France; Dr G. McGurk, Executive Inspector, Irish Medicines Board, Dublin, Ireland; Dr A. Mechkovski, Moscow, Russian Federation; Dr M. Mehmandoust, DEMEB/ DEQPh, Agence française de sécurité sanitaire 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 J.H.McB. Miller, Strasbourg, France; Dr O. Milling, Medicines Inspector, Medicines Control Division, Danish Medicines Agency, Copenhagen, Denmark; Dr S. Mills, Pharmaceutical Consultant, Ware, England; Dr J. Mitchell, GlaxoSmithKline, Belgium; Dr R.H. Mocchetto, Head of INAME Inspectorate, ANMAT, Caba, Argentina; 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, Associate Director for International Programs, Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, MD, USA; Dr I. Moore, Product and Quality Assurance Manager, Croda Europe, Snaith, England; Dr J. Morénas, Assistant Director, Inspection and Companies Department, Agence française de sécurité sanitaire 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 O. Morin, Regulatory and Scientific Affairs, International Federation of Pharmaceutical Manufacturers Associations, Geneva, Switzerland; 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; Dr E. Narciandi, Head, Technology Transfer Department, Center for Genetic Engineering and Biotechnology, La Habana, Cuba; Dr R. Neri, Sanofi, Antony, France; Dr E. Nickličková, Inspector, State Institute for Drug Control, Prague, Czech Republic; Professor A. Nicolas, Head, Laboratories and Controls Directorate, Agence française de sécurité sanitaire des produits de santé, Saint-Denis, France; Dr H.K. Nielsen, Technical Specialist, Essential Medicines, Medicines and Nutrition Centre, UNICEF Supply Division, Copenhagen, Denmark; Dr K. Nodop, Inspections, European Medicines Agency, London, England; Novartis Group, Novartis Campus, Basel, Switzerland; Dr T. Nunn, Clinical Director of Pharmacy, Royal Liverpool Children's NHS Trust and Associate Director, Medicines for Children Research Network, University of Liverpool, Liverpool, England; Dr A. Nystrup, Specialist, DFP QA Logistics and Manufacturing Development, Novo Nordisk, Gentofte, Denmark; Dr A. Ojoo, United Nations Children's Fund, New York, USA; 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 and 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 L. Paleshnuik, Senior Quality Assessor, Val-des-Monts, Canada; Dr Passek, Federal Ministry of Health, Bonn, Germany; Dr D.B. Patel, Secretary-General, Indian Drug Manufacturers' Association, Mumbai, India; Dr T.F. Perrone, North Andover, MA, USA; Dr M. Phadke, Senior Manager, Analytical Research, Ipca Laboratories, Mumbai, India; Dr B. Phillips, Medicines and Healthcare products Regulatory Agency, London, England; Dr B. Pimentel, European Chemical Industry Council, Brussels, Belgium; Dr M. Pokomela, Medicines Evaluation and Research, Department of Health, South Africa; Dr A. Pontén-Engelhardt, Head of Stability Management, Global Quality, Operations, AstraZeneca, Södertälje, Sweden; Ms A. Poompanich, Bangkok, Thailand; Dr R. Prabhu, Regulatory Affairs Department, Cipla, India; Dr R.P. Prasad, Director, Department of Drug Administration, Kathmandu, Nepal; Ms S.J. Putter, Walmer, Port Elizabeth, South Africa; Ms M.-L. Rabouhans, Chiswick, London, England; Dr A. Rajan, Director, Celogen Lifescience and 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; Dr J.-L. Robert, Laboratoire National de Santé, Luxembourg; Dr S. Rönninger, Global Quality Manager, F. Hoffmann-La Roche, Basel, Switzerland; Dr N. Ruangrittinon, Bureau of Drug and Narcotic, Department of Medical Sciences, Ministry of Public Health, Nonthaburi, Thailand; Dr K.A. Russo, Vice President, Small Molecules, United States Pharmacopeia, Rockville, MD, USA; Dr A.P. Sam, Merck, The Netherlands; Dr C. Sánchez, CECMED, La Habana, Cuba; 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 B. Schmauser, Bundesinstitut für Arzneimittel und Medizinprodukte, Bonn, Germany; Dr A. Schuchmann, Brazil; 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 and North Wales LRN, Medicines for Children Research Network, Royal Liverpool Children's NHS Trust, Liverpool, England; Dr R. Shaikh, Pakistan; Dr P.D. Sheth, Vice-President, International

Pharmaceutical Federation, New Delhi, India; Ms R. Shimonovitch, Ministry of Health, Israel; 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.N. Singh, Secretary-cum-Scientific Director, Government of India, Central Indian Pharmacopoeia Laboratory, Ministry of Health and Family Welfare, 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, Director, Drug Control, General Directorate of Drug and Food Control, Jakarta, Indonesia; Mr D. Smith, Principal Scientist, SSI, Guateng, South Africa; Dr C. Sokhan, Deputy Director, Department of Drug and Food, Phnom Penh, Cambodia; Dr A. Spreitzhofer, AGES PharmMed, Vienna, Austria; Dr K. Srinivas, Trimulgherry, Secunderabad, India; Dr Y. Stewart, Scientific, Technical and Regulatory Affairs, European Federation of Pharmaceutical Industries and Associations, Brussels, Belgium; Dr L. Stoppa, Agenzia Italiana del Farmaco, Rome, Italy; Dr R.W. Stringham, Scientific Director, Clinton Health Access Initiative, Boston, MA, USA; Dr N. Sullivan, Director, Sensapharm, Sunderland, England; Mr Philip Sumner, Pfizer Global Engineering, 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; 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; 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; Associate Professor Trinh Van Lau, Director, National Institute of Drug Quality Control, Hanoi, Viet Nam; Professor Tu Guoshi, National Institutes for Food and Drug Control, Ministry of Public Health, Beijing, People's Republic of China; 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; Ms E. Uramis, La Habana, Cuba; Dr A.R.T. Utami, National Agency for Drugs and Food Control, Jakarta Pusat, Indonesia; Mrs M. Vallender, Acting Group Manager BP and Laboratory Services, British Pharmacopoeia Commission Secretariat, London, England; Mr M. van Bruggen, EU Liaison – Regulatory Intelligence, Hoffmann-La Roche, Basel, Switzerland; Mr F. Vandendriessche, Merck, Sharp and Dohme Europe, Brussels, Belgium; Dr

A.J. van Zyl, Cape Town, South Africa; 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. Viornerly, Agence française de sécurité sanitaire des produits de santé, Saint-Denis, France; Dr L. Virgili, USA; Mr Wang Ju, Deputy Commissioner, Dalian Food and Drug Administration, Dalian, Liaoning, People's Republic of China; Professor Wang Ping, Deputy Director, China Pharmacopoeia Committee, Beijing, People's Republic of China; Dr G. Wang'ang'a, Head, Microbiological and Medical Devices Units, National Quality Control Laboratory, Nairobi, Kenya; Dr A. Ward, Regulatory Affairs, Avidia Vaccines, Billingham, England; Dr D. Waters, Acting Scientific Operations Advisor, Office of Laboratories and Scientific Services, Therapeutic Goods Administration, Australia; Dr W. Watson, Associate Manager, CMC Regulatory Affairs, Gilead Sciences International, Cambridge, England; Dr D.E. Webber, Director-General, World Self-Medication Industry, Ferney-Voltaire, France; Professor W. Wieniawski, Polish Pharmaceutical Society, Warsaw, Poland; Dr S. Wolfgang, US Food and Drug Administration, Silver Spring, MD, USA; Mr E. Wondemagegnehu Biwota, Addis Ababa, Ethiopia; Dr B. Wright, Group Manager, GMP/GDP, North East Region, Medicines Inspectorate, Medicines and Healthcare products Regulatory Agency, York, England; Ms X. Wu, Counsellor, Intellectual Property Division, World Trade Organization, Geneva, Switzerland; Professor Yang Zhong-Yuan, Guangzhou Municipal Institute for Drug Control, Guangzhou, People's Republic of China; Dr Yi Dang, Scientist, US Pharmacopoeia, Rockville, MD, USA; Dr H. Yusufu, National Agency for Food and Drug Administration and Control, Abuja, Nigeria; Dr M. Zahn, Keltern, Germany; Dr Hua Zhang, GMP Department Head, Center for Certification & Evaluation, Shanghai Food and Drug Administration, Shanghai, People's Republic of China; Professor Zhong-Yuan Yang, Member, United States Pharmacopoeia International Health Expert Committee, Rockville, MD, USA; 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.

Annex 1

Development of monographs for *The International Pharmacopoeia*

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.

Provision of monographs in *The International Pharmacopoeia* provides the quality dimension for the medicines (included on the basis of their efficacy and safety) in the World Health Organization (WHO) Model lists of essential medicines and in WHO treatment guidelines.

Major WHO programmes such as the Prequalification of Medicines Programme (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 of *The International Pharmacopoeia*.



Process: phases in the development of new monographs

Note: A “schedule for the adoption process” outlining the development history of a draft monograph is included in each working document that is circulated for comment.

- **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 of Medicines Programme). Establish whether monographs also need to be developed for the active pharmaceutical ingredients (APIs) contained in the pharmaceutical products identified. Update the current work plan on *The International Pharmacopoeia* web site.
- **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 for provision of QC specifications and samples.
- **Phase 4:** Identify and contact QC laboratories for collaboration in the project (the number of laboratories 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 Expert Advisory Panel and specialists, provide drafts on the web site.
- **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 and 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 extensively 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 (ECSP) 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 account of any further comments that may be received due to comment deadlines for recirculated texts (Phase 12 and subsequent) falling shortly after the relevant consultation or ECSP meeting.
- **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* web site.
- **Phase 20:** Make “final texts” available on *The International Pharmacopoeia* web site to provide users, such as prequalification assessors and manufacturers, with the approved specifications in advance of the next publication date.
- **Phase 21:** Include in *The International Pharmacopoeia*.

The “final texts” on *The International Pharmacopoeia* web site for the monographs adopted at the October 2011 meeting, for example, are prefaced with the following wording: “This monograph was adopted at the Forty-sixth meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations in October 2011 for inclusion in *The International Pharmacopoeia*”.

Annex 2

WHO good manufacturing practices: water for pharmaceutical use¹

1. Introduction	68
1.1 Scope of the document	68
1.2 Background to water requirements and uses	68
1.3 Applicable guides	69
2. General principles for pharmaceutical water systems	69
3. Water quality specifications	70
3.1 General	70
3.2 Drinking-water	70
3.3 Bulk purified water	71
3.4 Bulk highly purified water	71
3.5 Bulk water for injections	72
3.6 Other grades of water	72
4. Application of specific types of water to processes and dosage forms	72
5. Water purification systems	73
5.1 General considerations	73
5.2 Production of drinking-water	74
5.3 Production of purified water	76
5.4 Production of highly purified water	77
5.5 Production of water for injection(s)	77
6. Water storage and distribution systems	78
6.1 General	78
6.2 Materials that come into contact with systems for water for pharmaceutical use	78
6.3 System sanitization and bioburden control	80
6.4 Storage vessel requirements	80
6.5 Requirements for water distribution pipework	81
7. Operational considerations	83
7.1 Start-up and commissioning of water systems	83
7.2 Qualification	83
7.3 Continuous system monitoring	85
7.4 Maintenance of water systems	86
7.5 System reviews	86
8. Inspection of water systems	87
Further reading	88

¹ The current document is a revision of WHO good manufacturing practices: water for pharmaceutical use, previously published in WHO Technical Report Series, No. 929, Annex 3, 2005.

1. Introduction

1.1 Scope of the document

1.1.1 The guidance contained in this document is intended to provide information about the available specifications for water for pharmaceutical use (WPU), guidance about which quality of water to use for specific applications, such as the manufacture of active pharmaceutical ingredients (APIs) and dosage forms, and to provide guidance on good manufacturing practices (GMP) regarding the design, installation and operation of pharmaceutical water systems. Although the focus of this document is on water for pharmaceutical applications, the guidelines may also be relevant to other industrial or specific uses where the specifications and practices can be applied.

Note: This document does not cover water for administration to patients in the formulated state or the use of small quantities of water in pharmacies to compound individually prescribed medicines.

1.1.2 The GMP guidance for WPU contained in this document is intended to be supplementary to the general GMP guidelines for pharmaceutical products published by WHO (*WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-seventh report*. Geneva, World Health Organization, 2003 (WHO Technical Report Series, No. 908), Annex 4).

1.1.3 This document refers to available specifications, such as the pharmacopoeias and industry guidance for the use, production, storage and distribution of water in bulk form. In order to avoid confusion it does not attempt to duplicate such material.

1.1.4 The guidance provided in this document can be used in whole or in part as appropriate to the application under consideration.

1.1.5 Where subtle points of difference exist between pharmacopoeial specifications, the manufacturer will be expected to decide which option to choose in accordance with the related marketing authorization submitted to the national medicines regulatory authority.

1.2 Background to water requirements and uses

1.2.1 Water is the most widely used substance, raw material or starting material in the production, processing and formulation of pharmaceutical products. It has unique chemical properties due to its polarity and hydrogen bonds. This means it is able to dissolve, absorb, adsorb or suspend many different compounds. These include contaminants that may represent hazards in themselves or that may be able to react with intended product substances, resulting in hazards to health.

1.2.2 Control of the quality of water throughout the production, storage and distribution processes, including microbiological and chemical quality, is a major concern. Unlike other product and process ingredients, water is usually drawn from a system on demand, and is not subject to testing and batch or lot release before use. Assurance of quality to meet the on-demand expectation is, therefore, essential. Additionally, certain microbiological tests may require periods of incubation and, therefore, the results are likely to lag behind the water use.

1.2.3 Control of the microbiological quality of WPU is a high priority. Some types of microorganism may proliferate in water treatment components and in the storage and distribution systems. It is crucial to minimize microbial contamination by proper design of the system, periodic sanitization and by taking appropriate measures to prevent microbial proliferation.

1.2.4 Different grades of water quality are required depending on the route of administration of the pharmaceutical products. Other sources of guidance about different grades of water can be found in pharmacopoeias and related documents.

1.3 **Applicable guides**

1.3.1 In addition to the specific guidance provided in this document, the Further reading section includes some relevant publications that can serve as additional background material when planning, installing and using systems intended to provide WPU.

2. General principles for pharmaceutical water systems

2.1 Pharmaceutical water production, storage and distribution systems should be designed, installed, commissioned, qualified and maintained to ensure the reliable production of water of an appropriate quality. It is necessary to validate the water production process to ensure the water generated, stored and distributed is not beyond the designed capacity and meets its specifications.

2.2 The capacity of the system should be designed to meet the average and the peak flow demand of the current operation. If necessary, depending on planned future demands, the system should be designed to permit increases in the capacity or designed to permit modification. All systems, regardless of their size and capacity, should have appropriate recirculation and turnover to assure the system is well controlled chemically and microbiologically.

2.3 The use of the systems following initial validation (installation qualification (IQ), operational qualification (OQ) and performance qualification (PQ)) and after any planned and unplanned maintenance or modification work should be approved by the quality assurance (QA) department using change control documentation.

2.4 Water sources and treated water should be monitored regularly for chemical, microbiological and, as appropriate, endotoxin contamination. The performance of water purification, storage and distribution systems should also be monitored. Records of the monitoring results, trend analysis and any actions taken should be maintained.

2.5 Where chemical sanitization of the water systems is part of the biocontamination control programme a validated procedure should be followed to ensure that the sanitizing process has been effective and that the sanitizing agent has been effectively removed.

3. Water quality specifications

3.1 General

3.1.1 The following requirements concern water processed, stored and distributed in bulk form. They do not cover the specification of water formulated for patient administration. Pharmacopoeias include specifications for both bulk and dosage-form types of water.

3.1.2 Pharmacopoeial requirements or guidance for WPU are described in national, regional and international pharmacopoeias and limits for various impurities or classes of impurities are either specified or recommended. Companies wishing to supply multiple markets should set specifications that meet the strictest requirements from each of the relevant pharmacopoeias.

Similarly, requirements or guidance are given in pharmacopoeias on the microbiological quality of water.

3.2 Drinking-water

3.2.1 Drinking-water should be supplied under continuous positive pressure in a plumbing system free of any defects that could lead to contamination of any product.

3.2.2 Drinking-water is unmodified except for limited treatment of the water derived from a natural or stored source. Examples of natural sources include springs, wells, rivers, lakes and the sea. The condition of the source water will dictate the treatment required to render it safe for human consumption (drinking). Typical treatment includes desalinization, softening, removal of specific ions, particle reduction and antimicrobial treatment.

3.2.3 It is common for drinking-water to be derived from a public water supply that may be a combination of more than one of the natural sources listed above. It may also be supplied either from an offsite source, e.g. a municipality, or appropriate quality may be achieved onsite through appropriate processing.

3.2.4 It is also common for public water supply organizations to conduct tests and guarantee that the drinking-water delivered is of drinking quality. This testing is typically performed on water from the water source.

3.2.5 It is the responsibility of the pharmaceutical manufacturer to assure that the source water supplying the purified water (PW) treatment system meets the appropriate drinking-water requirements. There may be situations where the water treatment system is used first to achieve drinking-water quality and subsequently purified water. In these situations the point at which drinking-water quality is achieved should be identified and tested.

3.2.6 Drinking-water quality is covered by the WHO drinking-water guidelines, standards from the International Organization for Standardization (ISO) and other regional and national agencies. Drinking-water should comply with the relevant regulations laid down by the competent authority.

3.2.7 If drinking-water is used directly in certain stages of pharmaceutical manufacture or is the feed-water for the production of higher qualities of WPU, then testing should be carried out periodically by the water user's site to confirm that the quality meets the standards required for drinking-water.

3.3 Bulk purified water

3.3.1 Bulk purified water (BPW) should be prepared from a drinking-water source as a minimum-quality feed-water. It should meet the relevant pharmacopoeial specifications for chemical and microbiological purity with appropriate action and alert limits. It should also be protected from recontamination and microbial proliferation. BPW may be prepared by a combination of reverse osmosis (RO) RO/electro-deionization (EDI) and vapour compression (VC). Alert levels for the water system should be determined from knowledge of the system and are not specified in the pharmacopoeias.

3.4 Bulk highly purified water

3.4.1 Bulk highly purified water (BHPW) should be prepared from drinking-water as a minimum-quality feed-water. BHPW is a unique specification for water found only in the *European Pharmacopoeia*. This grade of water must meet the same quality standard as water for injections (WFI), including the limit for endotoxins, but the water-treatment process used may be different. Current production methods include, for example, double-pass RO coupled with other suitable techniques such as ultrafiltration and deionization.

BHPW may be prepared by a combination of different methods such as RO, ultrafiltration and deionization.

3.4.2 BHPW should also be protected from recontamination and microbial proliferation.

3.4.3 BHPW and WFI have identical microbiological requirements.

3.5 Bulk water for injections

3.5.1 Bulk water for injections (BWFI) should be prepared from drinking-water (usually with further treatment) or purified water as a minimum-quality feed-water. BWFI is not sterile water and is not a final dosage form. It is an intermediate bulk product and suitable to be used as an ingredient during formulation. BWFI is the highest quality of pharmacopoeial WPU.

3.5.2 Certain pharmacopoeias place constraints upon the permitted purification techniques as part of the specification of the BWFI. *The International Pharmacopoeia* and the *European Pharmacopoeia*, for example, allow only distillation as the final purification step.

3.5.3 BWFI should meet the relevant pharmacopoeial specifications for chemical and microbiological purity (including endotoxin) with appropriate action and alert limits.

3.5.4 BWFI should also be protected from recontamination and microbial proliferation.

3.6 Other grades of water

3.6.1 When a specific process requires a special non-pharmacopoeial grade of water, its specification must be documented within the company quality system. As a minimum it must meet the pharmacopoeial requirements relating to the grade of WPU required for the type of dosage form or process step.

4. Application of specific types of water to processes and dosage forms

4.1 Product licensing authorities specify the minimum grade of WPU that must be used during the manufacture of the different dosage forms or for different stages in washing, preparation, synthesis, manufacturing or formulation.

4.2 The grade of water used should take into account the nature and intended use of the intermediate or finished product and the stage in the manufacturing process at which the water is used.

4.3 BHPW can be used in the preparation of products when water of high quality (i.e. very low in microorganisms and endotoxins) is needed, but the

process stage or product requirement does not include the constraint on the production method defined in some of the pharmacopoeial monographs for BWFI.

4.4 BWFI should be used in the manufacture of injectable products for dissolving or diluting substances or preparations during the manufacturing of parenterals, and for manufacture of sterile water for preparation of injections. BWFI should also be used for the final rinse after cleaning of equipment and components that come into contact with injectable products as well as for the final rinse in a washing process in which no subsequent thermal or chemical depyrogenization process is applied.

4.5 When steam comes into contact with an injectable product in its final container or with equipment for preparing injectable products, it should conform to the specification for BWFI when condensed.

5. Water purification systems

5.1 General considerations

5.1.1 The specifications for WPU found in compendia (e.g. pharmacopoeias) do not define the permissible water purification methods apart from for BWFI (refer to section 3.5).

5.1.2 The chosen water purification method or sequence of purification steps must be appropriate to the application in question. The following should be considered when selecting the water treatment method:

- the final water quality specification;
- the quantity of water required by the user;
- the available feed-water quality and the variation over time (seasonal changes);
- the availability of suitable support facilities for system connection (raw water, electricity, heating steam, chilled water, compressed air, sewage system, exhaust air);
- the sanitization strategy;
- the availability of water-treatment equipment on the market;
- the reliability and robustness of the water-treatment equipment in operation;
- the yield or efficiency of the purification system;
- the ability to adequately support and maintain the water purification equipment;

- the continuity of operational usage considering hours/days, days/years and planned downtime;
- the total life-cycle costs (capital and operational including maintenance).

5.1.3 The specifications for water purification equipment, storage and distribution systems should take into account the following:

- the location of the plant room;
- extremes in temperature that the system will encounter;
- the risk of contamination from leachates from contact materials;
- the adverse impact of adsorptive contact materials;
- hygienic or sanitary design, where required;
- corrosion resistance;
- freedom from leakage;
- a system configuration to avoid proliferation of microbiological organisms;
- tolerance to cleaning and sanitizing agents (thermal and/or chemical);
- the sanitization strategy;
- the system capacity and output requirements;
- the provision of all necessary instruments, test and sampling points to allow all the relevant critical quality parameters of the complete system to be monitored.

5.1.4 The design, configuration and layout of the water purification equipment, storage and distribution systems should also take into account the following physical considerations:

- ability to collect samples;
- the space available for the installation;
- structural loadings on buildings;
- the provision of adequate access for maintenance;
- the ability to safely handle regeneration and sanitization chemicals.

5.2 Production of drinking-water

5.2.1 Drinking-water is derived from a raw water source such as a well, river or reservoir. There are no prescribed methods for the treatment of raw water to produce drinking-water from a specific raw water source.

5.2.2 Typical processes employed at a user plant or by a water supply authority include:

- desalinization;
- filtration;
- softening;
- disinfection or sanitization (e.g. by sodium hypochlorite (chlorine) injection);
- iron (ferrous) removal;
- precipitation;
- reduction of concentration of specific inorganic and/or organic materials.

5.2.3 The drinking-water quality should be monitored routinely to account for environmental, seasonal or supply changes which have an impact on the source water quality.

5.2.4 Additional testing should be considered if there is any change in the raw-water source, treatment techniques or system configuration.

5.2.5 Trend review may be used to identify changes. If the drinking-water quality changes significantly, but is still within specification, the direct use of this water as a WPU, or as the feed-water to downstream treatment stages, should be reviewed and the result of the review documented.

5.2.6 Where drinking-water is derived from an “in-house” system for the treatment of raw water, the water-treatment steps used and the system configuration should be documented. Changes to the system or to its operation should not be made until a review has been completed and the change approved by the QA department in accordance with change control procedures.

5.2.7 Where drinking-water is stored and distributed by the user, the storage systems must not allow degradation of the water quality before use. After any such storage, testing should be carried out routinely in accordance with a defined method. Where water is stored, the system design and operation should ensure a turnover or recirculation of the stored water sufficient to prevent stagnation.

5.2.8 The drinking-water system is usually considered to be an “indirect impact system” and does not need to be qualified.

5.2.9 Drinking-water purchased in bulk and transported to the user by tanker has additional problems and risks not associated with drinking-water delivered by pipeline. Vendor assessment and authorized certification activities, including confirmation of the acceptability of the delivery vehicle, should be undertaken in a similar way to that used for any other starting material.

5.2.10 Equipment and systems used to produce drinking-water should be able to be drained and sanitized. Storage tanks should be closed with appropriately protected vents, and should allow for visual inspection and for being drained and sanitized. Distribution pipework should be able to be drained or flushed and sanitized.

5.2.11 Special care should be taken to control microbiological contamination of sand filters, carbon beds and water softeners. Once microorganisms have infected a system, the contamination can rapidly form biofilms and spread throughout the system. Techniques for controlling contamination such as back-flushing, chemical and/or thermal sanitization and frequent regeneration should be considered as appropriate.

5.3 Production of purified water

5.3.1 Any appropriate qualified purification technique or sequence of techniques may be used to prepare purified water (PW). PW is commonly produced by ion exchange, RO, ultrafiltration and/or electro-deionization processes and distillation.

5.3.2 The following should be considered when configuring a water purification system or defining user requirement specifications (URS):

- the feed-water quality and its variation over seasons;
- the quantity of water required by the user;
- the required water-quality specification;
- the sequence of purification stages required;
- the energy consumption;
- the extent of pretreatment required to protect the final purification steps;
- performance optimization, including yield and efficiency of unit treatment-process steps;
- appropriately located sampling points designed in such a way as to avoid potential contamination;
- unit process steps should be provided with appropriate instrumentation to measure parameters such as flow, pressure, temperature, conductivity, pH and total organic carbon.

5.3.3 Ambient-temperature systems such as ion exchange, RO and ultrafiltration are especially susceptible to microbiological contamination, particularly when equipment is static during periods of no or low demand for water. It is essential to consider the mechanisms for microbiological control and sanitization.

The method for sanitizing each stage of purification needs to be defined and must include verification of the removal of any agents used. There should be documented evidence of its efficacy.

5.3.4 The following should be considered:

- maintenance of minimum flow through the water generation system is recommended at all times;
- control of temperature in the system by heat exchanger or plant-room cooling to reduce the risk of microbial growth (guidance value < 25 °C);
- provision of ultraviolet disinfection;
- selection of water-treatment components that can periodically be thermally sanitized;
- application of chemical sanitization (including agents such as ozone, hydrogen peroxide and/or peracetic acid);
- thermal sanitization at > 65 °C.

5.4 Production of highly purified water

5.4.1 Highly purified water (HPW) can be produced by double-pass reverse osmosis coupled with ultrafiltration or by any other appropriate qualified purification technique or sequence of techniques.

5.4.2 The guidance provided in section 5.3 for PW is equally applicable to HPW.

5.5 Production of water for injection(s)

5.5.1 Some pharmacopoeias prescribe or limit the permitted final water purification stage in the production of BWFI. Distillation is the preferred technique; it is considered a more robust technique based on phase change, and in some cases, high-temperature operation of the process equipment.

5.5.2 The following should be considered when designing a water purification system and defining URS:

- the feed-water quality;
- the required water quality specification;
- the quantity of water;
- the optimum generator size or generators with variable control to avoid over-frequent start/stop cycling;
- blow-down and dump functions;
- cool-down venting to avoid contamination ingress.

5.5.3 The system configuration guidance provided in section 5.3 for PW is equally applicable to water for injection.

6. Water storage and distribution systems

6.1 This section applies to WPU systems for PW, BHPW and BWFI. The water storage and distribution should work in conjunction with the purification plant to ensure delivery of water of consistent quality to the user points, and to ensure optimum operation of the water purification equipment.

6.1 General

6.1.1 The storage and distribution system should be considered as a key part of the whole system and should be designed to be fully integrated with the water purification components of the system.

6.1.2 Once water has been purified using an appropriate method it can either be used directly or, more frequently, it will be fed into a storage vessel for subsequent distribution to points of use. The following text describes the requirements for storage and distribution systems and point of use (POU).

6.1.3 The storage and distribution system should be configured to prevent microbial proliferation and recontamination of the water (PW, BHPW, BWFI) after treatment. It should be subjected to a combination of online and offline monitoring to ensure that the appropriate water specification is maintained.

6.2 Materials that come into contact with systems for water for pharmaceutical use

6.2.1 This section applies to generation equipment for PW, BHPW and BWFI and the associated storage and distribution systems.

6.2.2 The materials that come into contact with WPU, including pipework, valves and fittings, seals, diaphragms and instruments, should be selected to satisfy the following objectives.

- *Compatibility.* The compatibility and suitability of the materials should encompass the full range of its working temperature and potential chemicals that will come into contact with the system at rest, in operation and during sanitization.
- *Prevention of leaching.* All materials that come into contact with WPU should be non-leaching at the range of working and sanitization temperatures of the system.
- *Corrosion resistance.* PW, BHPW and BWFI are highly corrosive.

To prevent failure of the system and contamination of the water, the materials selected must be appropriate, the method of jointing must be carefully controlled and all fittings and components must be compatible with the pipework

used. Appropriate sanitary specification plastics and stainless-steel materials are acceptable for WPU systems.

When stainless steel is used it should be at least grade 316. In general 316L or a higher grade of stainless steel is used.

The system should be passivated after initial installation or after significant modification. When accelerated passivation is undertaken the system should be thoroughly cleaned first and the passivation process should be undertaken in accordance with a clearly defined documented procedure.

- *Smooth internal finish.* Once water has been purified it is susceptible to microbiological contamination and the system is subject to the formation of biofilms when cold storage and distribution are employed. Smooth internal surfaces help to avoid roughness and crevices within the WPU system. Crevices can be the source of contamination because of possible accumulation of microorganisms and formation of biofilms. Crevices are also frequently sites where corrosion can commence. The internal material finish should have an arithmetical average surface roughness of not greater than 0.8 micrometre (Ra). When stainless steel is used, mechanical and electro-polishing techniques may be employed. Electro-polishing improves the resistance of the stainless-steel material to surface corrosion.
- *Joining.* The selected system materials should be easily joined by welding in a controlled manner. The control of the process should include, as a minimum, qualification of the operator, documentation of the welder set-up, work session test pieces (coupons), logs of all welds and visual inspection of a defined proportion of welds, e.g. 100% hand welds, 10% automatic welds.
- *Design of flanges, unions and valves.* Where flanges, unions or valves are used they should be of a hygienic or sanitary design. Appropriate checks should be carried out to ensure that the correct seals and diaphragms are used and that they are fitted and tightened correctly. Threaded connections should be avoided.
- *Documentation.* All system components should be fully documented and be supported by original or certified copies of material certificates.
- *Materials.* Suitable materials that may be considered for sanitary elements of the system include 316L (low carbon) stainless steel, polypropylene, polyvinylidene-difluoride and perfluoroalkoxy. The choice of material should take into account the intended sanitization method. Other materials such as unplasticized polyvinyl-chloride (uPVC) may be used for treatment equipment designed for less pure water such as ion exchangers and softeners.

None of the materials that come into contact with WPU should contain chemicals that will be extracted by the water. Plastics should be non-toxic and should be compatible with all chemicals used. They should be manufactured from materials that should at least meet minimum food grade standards. Their chemical and biological characteristics should meet any relevant pharmacopoeia specifications or recommendations.

Precautions should be taken to define operational limits for areas where water circulation is reduced and turbulent flow cannot be achieved. Minimum flow rate and change volumes should be defined.

6.3 System sanitization and bioburden control

6.3.1 Water treatment equipment, storage and distribution systems used for BPW, BHPW and BWFI should be provided with features to control the proliferation of microbiological organisms during normal use, as well as techniques for sanitizing the system after intervention for maintenance or modification. The techniques employed should be considered during the design of the system and should take into account the interdependency between the materials and the sanitization techniques.

6.3.2 Systems that operate and are maintained at elevated temperatures (e.g. > 65) are generally less susceptible to microbiological contamination than systems that are maintained at lower temperatures. When lower temperatures are required due to the water treatment processes employed or the temperature requirements for the water in use, special precautions should be taken to prevent the ingress and proliferation of microbiological contaminants (see section 6.4.3 for guidance).

6.4 Storage vessel requirements

6.4.1 General

6.4.1.1 The water storage vessel used in a system serves a number of important functions. The design and size of the vessel should take into consideration the following.

6.4.2 Capacity

6.4.2.1 The capacity of the storage vessel should be determined on the basis of the following requirements:

- It is necessary to provide a buffer capacity between the steady-state generation rate of the water-treatment equipment and the potentially variable simultaneous demand from user points.
- The water-treatment equipment should be able to operate continuously for significant periods to avoid the inefficiencies and

equipment stress that occur when the equipment cycles on and off too frequently.

- The capacity should be sufficient to provide short-term reserve capacity in the event of failure of the water-treatment equipment or inability to produce water due to a sanitization or regeneration cycle. When determining the size of such reserve capacity, consideration should be given to providing sufficient water to complete a process batch, work session, tank turnover by recirculation to minimize stagnation, or other logical period of demand.

6.4.3 Contamination control considerations

6.4.3.1 The following should be taken into account for the efficient control of contamination:

- The headspace in the storage vessel is an area of risk where water droplets and air can come into contact at temperatures that encourage the proliferation of microbiological organisms. The use of spray-ball or distributor devices should be considered in these systems to wet the surfaces during normal operation, chemical and/or thermal sanitization.
- Nozzles within the storage vessels should be configured to avoid dead zones where microbiological contamination might be harboured.
- Vent filters are fitted to storage vessels to allow the internal level of liquid to fluctuate. The filters should be bacteria-retentive, hydrophobic and should ideally be configured to allow in situ testing of integrity. Offline testing is also acceptable. The use of heated vent filters should be considered for continuous hot storage or systems using periodic heat sanitization to prevent condensation within the filter matrix that might lead to filter blockage and to microbial growth that could contaminate the storage vessels.
- Where pressure-relief valves and bursting discs are provided on storage vessels to protect them from under- and over-pressurization, these devices should be of a sanitary design. Bursting discs should be provided with external rupture indicators to ensure that loss of system integrity is detected.

6.5 Requirements for water distribution pipework

6.5.1 General

6.5.1.1 The distribution of BPW, BHPW and BWFI should be accomplished using a continuously circulating pipework loop. Proliferation of contaminants within

the storage tank and distribution loop should be controlled. Good justification for using a non-recirculating one-way system should be provided.

6.5.1.2 Filtration should not usually be used in distribution loops or at take off-user points to control biocontamination. Such filters are likely to conceal system contamination.

6.5.2 Temperature control and heat exchangers

6.5.2.1 Where heat exchangers are employed to heat or cool WPU within a system, precautions should be taken to prevent the heating or cooling utility from contaminating the water. The more secure types of heat exchangers of the double tube plate or double plate and frame or tube and shell configuration should be considered. Where these types are not used, an alternative approach whereby the utility is maintained and monitored at a lower pressure than the WPU may be considered. The latter approach is not usually adopted in BWFI systems.

6.5.2.2 Where heat exchangers are used they should be arranged in continually circulating loops or subloops of the system to avoid unacceptable static water in systems.

6.5.2.3 When the temperature is reduced for processing purposes the reduction should occur for the minimum necessary time. The cooling cycles and their duration should be proven satisfactory during the qualification of the system.

6.5.3 Circulation pumps

6.5.3.1 Circulation pumps should be of a sanitary design with appropriate seals that prevent contamination of the system. Where stand-by pumps are provided, they should be configured or managed to avoid dead zones trapped within the system.

Consideration should be given to preventing contamination in systems where parallel pump systems are used, especially if there is stagnant water when one of the pumps is not being used.

6.5.4 Biocontamination control techniques

6.5.4.1 Water purification systems should be sanitized using chemical or thermal sanitization procedures as appropriate (production and distribution). The procedure and conditions used (such as times and temperatures) should be suitable.

6.5.4.2 The following control techniques may be used alone or more commonly in combination:

- maintenance of continuous turbulent flow circulation within water distribution systems reduces the propensity for the formation of biofilms;

- the system design should ensure the shortest possible length of pipework;
- for ambient temperature systems, pipework should be isolated from adjacent hot pipes;
- deadlegs in the pipework should be minimized through appropriate design, and as a guide should not significantly exceed three times the branch diameter as measured from the ID pipe wall to centre line of the point-of-use valve where significant stagnation potential exists;
- pressure gauges should be separated from the system by membranes;
- hygienic pattern diaphragm valves should be used;
- pipework for steam-sanitized systems should be sloped and fully drainable;
- the growth of microorganisms can be inhibited by:
 - ultraviolet radiation sources in pipework;
 - maintaining the system heated (greater than 65 °C);
 - sanitizing the system periodically using hot water (guidance temperature > 70 °C);
 - sanitizing the system periodically using superheated hot water or clean steam;
 - routine chemical sanitization using ozone or other suitable chemical agents. When chemical sanitization is used, it is essential to prove that the agent has been removed prior to using the water. Ozone can be effectively removed by using ultraviolet radiation.

7. Operational considerations

7.1 Start-up and commissioning of water systems

7.1.1 Planned, well-defined, successful and well-documented commissioning and qualification is an essential precursor to successful validation of water systems.

7.1.2 The commissioning work should include setting to work, system set-up, controls, loop tuning and recording of all system performance parameters. If it is intended to use or to refer to commissioning data within the validation work then the quality of the commissioning work and associated data and documentation must be commensurate with the validation plan requirements.

7.2 Qualification

7.2.1 WPU, BPW, BHPW and BWFI systems are all considered to be direct impact, quality critical systems that should be qualified. The qualification

should follow the validation convention of design review or design qualification (DQ), IQ, OQ, and PQ.

7.2.2 This guidance does not define the standard requirements for the conventional qualification stages DQ, IQ and OQ, but concentrates on the particular PQ approach that should be used for WPU systems to demonstrate their consistent and reliable performance. A three-phase approach should be used to satisfy the objective of proving the reliability and robustness of the system in service over an extended period.

Tests on the source water must be included within the validation programme and continued as part of the routine monitoring. The source water should meet the requirements for drinking-water and any internal specification.

Phase 1. Sample daily or continuously monitor the incoming feed-water to verify its quality.

A test period of two weeks should be spent monitoring the system intensively. During this period, the system should operate continuously without failure or performance deviation. Usually water is not used for finished pharmaceutical product (FPP) manufacturing during this period. The following activities should be included in the testing approach.

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

Phase 2. A further test period of two weeks should be spent carrying out further intensive monitoring while deploying all the refined SOPs after the satisfactory completion of phase 1. The sampling scheme should be generally the

same as in phase 1. Use of the water for FPP manufacturing purposes during this phase may be acceptable, provided that both commissioning and phase 1 data demonstrate appropriate water quality and the practice is approved by QA. The approach should also:

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

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

- to demonstrate reliable performance over an extended period;
- to ensure that seasonal variations are evaluated.

The sample locations, sampling frequencies and tests should be reduced to the normal routine pattern based on established procedures proven during phases 1 and 2.

7.3 Continuous system monitoring

7.3.1 After completion of phase 3 of the qualification programme for the WPU system, a system review should be undertaken. Following this review a routine monitoring plan should be established based on the results of phase 3.

Monitoring should include a combination of monitoring with online instruments (with appropriately qualified alarm systems) of parameters such as flow, pressure, temperature, conductivity and total organic carbon, and offline sample testing for physical, chemical and microbiological attributes. Offline samples should be taken from points of use or dedicated sample points where points of use cannot be sampled. All water samples should be taken using the same methodology as detailed in production procedures. There should be a suitable flushing and drainage procedure in place.

7.3.2 Tests should be carried out to ensure that the approved pharmacopoeial and company specification has been met.

This may include the microbiological quality of water as appropriate.

Monitoring data should be subject to trend analysis (trending should typically be within 2 sigma). Suitable alert and action levels should be established based on historical reported data.

7.3.3 Any trend towards frequently exceeding alert limits should trigger a thorough investigation of the root cause, followed by appropriate corrective actions.

7.4 Maintenance of water systems

7.4.1 WPU systems should be maintained in accordance with a controlled, documented maintenance programme that takes into account the following:

- defined frequency for system elements;
- the calibration programme;
- SOPs for specific tasks;
- control of approved spares;
- issue of a clear maintenance plan and instructions;
- review and approval of systems for use upon completion of work;
- record and review of problems and faults during maintenance.

7.5 System reviews

7.5.1 WPU (BPW, BHPW and BWFI) systems should be reviewed at appropriate regular intervals. The review team should comprise representatives from engineering, QA, microbiology, operations and maintenance. The review should consider matters such as:

- changes made since the last review;
- system performance;
- reliability;
- quality trends;
- failure events;
- investigations;
- out-of-specifications results from monitoring;
- changes to the installation;
- updated installation documentation;
- log books;
- the status of the current SOP list.

7.5.2 For new systems, or systems that display instability or unreliability, the following should also be reviewed:

- need for investigation;
- corrective actions and preventative actions (CAPA);

- qualification (DQ, factory acceptance test (FAT), IQ, site acceptance test (SAT), OQ, PQ) or equivalent verification documents, and monitoring phases of the system.

8. Inspection of water systems

8.1 WPU (BPW, BHPW and BWFI) systems are likely to be the subject of regulatory inspection from time to time. Users should consider conducting routine audit and self-inspection of established water systems.

8.2 This GMP guidance can be used as the basis of inspection. A tour of the water generation plant and visible pipework (including user points) should be performed to ensure that the system is appropriately designed, installed and maintained (e.g. that there are no leaks and that the system matches the piping and instrumentation diagram or drawing (P&ID).

The following list identifies items and a logical sequence for a WPU system inspection or audit:

- a current drawing of the water system showing all equipment in the system from the inlet to the points of use along with sampling points and their designations;
- approved piping drawings (e.g. orthographic and/or isometric);
- a sampling and monitoring plan with a drawing of all sample points;
- training programme for sample collection and testing;
- the setting of monitoring alert and action levels;
- monitoring results and evaluation of trends;
- inspection of the last annual system review;
- review of any changes made to the system since the last audit and a check that the change control has been implemented;
- review of deviations recorded and their investigation;
- general inspection of system for status and condition;
- review of maintenance, failure and repair logs;
- checking calibration and standardization of critical instruments.

8.3 For an established system that is demonstrably under control this scope of review should prove adequate.

Further reading

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US Pharmacopeia: Published annually; see <http://www.usp.org/>.

Annex 3

Pharmaceutical development of multisource (generic) finished pharmaceutical products – points to consider

1. Introduction	92
1.1 General principles	92
1.2 Scope	92
2. Predevelopment activities	93
2.1 Desk research	93
2.1.1 Quality risk management	93
2.2 Additional considerations	94
2.2.1 Selection and characterization of comparator finished pharmaceutical product(s)	94
2.2.2 Benchmarking for formulation experiments and stability studies	95
2.2.3 Formulation selection experiments	95
2.2.4 Bioequivalence and dissolution studies	96
3. Pharmaceutical development	96
3.1 Components of the finished pharmaceutical product	98
3.1.1 Active pharmaceutical ingredient	98
3.1.2 Excipients	99
3.2 Finished pharmaceutical product	100
3.2.1 Formulation development	100
3.2.2 Overages	102
3.2.3 Physicochemical and biological properties	103
3.3 Manufacturing process development	103
3.4 Container-closure system	104
3.5 Microbiological attributes	107
3.6 Compatibility	108
4. Glossary	109
References	113
Appendix 1	115
Examples of presenting quality attributes of active pharmaceutical ingredients	115
Appendix 2	118
Information on development batches	118

1. Introduction

The aim of pharmaceutical development is to design a quality product and its manufacturing process to consistently deliver the intended performance of the product. The information and knowledge gained from pharmaceutical development studies provide scientific understanding to support the establishment of specifications and manufacturing controls.

This document focuses on the development of multisource finished pharmaceutical products (FPPs) which are intended to be bioequivalent to the relevant comparator product. Multisource FPPs should¹ accordingly be therapeutically equivalent to the comparator product.

This document provides a structured approach for industry following the International Conference on Harmonisation (ICH) common technical document (CTD) format, for developing high-quality, multisource FPPs. The ICH-CTD structure for pharmaceutical development information allows for a logical, progressive description of the development process.

The document is also intended to provide assessors and inspectors with a good understanding of best practices in the development of multisource FPPs and their manufacturing processes.

Manufacturers who have chosen a more systematic approach to product development would follow the development within the broader context of quality assurance principles, including the use of quality risk management and pharmaceutical quality systems.

This document is designed to be used in conjunction with other WHO guidelines and guidance documents (1).

1.1 General principles

The pharmaceutical development studies and the manufacture of primary batches are essential elements for the science and risk-based approach to establish the critical quality attributes (CQAs) of the FPP and the critical process parameters (CPPs) of the manufacturing process.

1.2 Scope

This document addresses the pharmaceutical development of multisource FPPs containing existing active pharmaceutical ingredients (APIs) of synthetic or semi-synthetic origin. For the purposes of this document an existing API is one that has been previously authorized through a finished product by a stringent regulatory authority (SRA) or, for the purposes of a national medicines regulatory authority

¹ For the purpose of this document the term “should” is generally to be interpreted as “is recommended” or “is usually required”.

(NMRA), that has been authorized by that NMRA or for which a monograph exists in the pharmacopoeia(s) recognized by that NMRA. APIs of biological or biotechnological origin are not covered here.

This document provides guidance on the contents of a pharmaceutical development plan for multisource pharmaceutical products for both the applicants for marketing authorizations and NMRAs.

Pharmaceutical development issues depend on the API(s), the excipients, the dosage form, the manufacturing process and the container-closure system.

2. Predevelopment activities

2.1 Desk research

Desk research includes all relevant documentation being collected and evaluated prior to initiation of any laboratory activities. This documentation may include information such as is found in:

- WHO, European Medicines Agency (EMA) and United States Food and Drug Administration (US-FDA) web sites that contain regulatory information, for example, the qualitative composition, mode of administration and the primary packing materials of the innovator and multisource FPPs;
- compendial monographs, scientific literature, patents, technical information typically found in the applicant's (open) part of the API master file (APIMF), technical information on excipients and prior company knowledge.

2.1.1 Quality risk management

An essential part of desk research entails the identification of possible risks prior to the development of a multisource product.

An important consideration when selecting the API manufacturer is the fact that the FPP manufacturer is responsible for the control of the API and as such must have a comprehensive understanding of the API. Analysis of the applicant's part of the APIMF (or drug master file) is, therefore, important.

Poor solubility in aqueous medium is an important quality risk factor for APIs administered in the solid state as there is a high risk that inter-batch variability in physical properties may translate into significant differences in the *in vivo* performance.

It is recommended that polymorphism, pseudo-polymorphism and the implications of variability in particle size be routinely considered. Variability in any of these key physical properties is likely to be of particular significance for APIs that have low solubility according to the biopharmaceutics classification

system (BCS). The requirement for routine control of polymorphic form and particle size should be considered in accordance with advice in Decision Trees 3 and 4 of ICH Q6A (2). When controls are necessary they should be established based on the results obtained for the API lot(s) used in the biostudies.

For example, *The International Pharmacopoeia* (Ph. Int.) (3) restricts the polymorphic form of mebendazole API to form C and furthermore states that the formulation, manufacturing process and product packaging of chewable mebendazole tablets are designed and controlled so as to minimize the conversion of the polymorphic form of mebendazole from C to A.

The initial risk assessment of potential CQAs and CPPs of a multisource product should be based on desk research and the applicant's own experience with the manufacture of the dosage form.

Literature, preferably peer-reviewed, may contain risk information essential for predevelopment. For example, the presence of meso-ethambutol hydrochloride in commercial ethambutol hydrochloride API material has been demonstrated in the literature (4), although some pharmacopoeial monographs do not clearly reveal the presence of this impurity. Recently a specific test was included in the *European Pharmacopoeia* (Ph. Eur.) (5) for control of this impurity.

The least risky strategy for multisource product development is to use the same qualitative and, where possible, quantitative formula as that of the comparator FPP – so long as this does not lead to the possibility of patent infringement – in order to minimize the risks related to compatibility, stability and bioequivalence.

Accompanying reconstitution diluents should also be included in the development strategy where appropriate. This topic is discussed further in section 3.

2.2 Additional considerations

2.2.1 Selection and characterization of comparator finished pharmaceutical product(s)

In many countries the NMRA provides a list of comparator products. Alternatively, references are available from WHO (Prequalification of Medicines Programme), and in international lists of comparator products. Note that for a dossier to be submitted to the Prequalification of Medicines Programme the comparator must be selected from the published lists. Guidance regarding Prequalification of Medicines Programme comparator products is available under Guidance on bioequivalence studies on the Prequalification of Medicines Programme web site (apps.who.int/prequal/).

In the case of fixed-dose combination (FDC) FPPs, there will be instances when a combination of APIs is recommended for clinical use but an innovator FDC FPP containing these APIs, whose approval was based on clinical trial data, will not be available as a comparator product. FDCs approved based on data

such as bioequivalence data are not typically used as comparators, as the original safety and efficacy data are linked to the monocomponent products and not the FDC FPP. For FDC FPPs, the development strategy should take into account the formulas of the individual component comparator FPPs. If the innovator FDC exists this should be the target product for the FDC multisource product development – even if the individual comparator tablets could also be used in the bioequivalence study (see also WHO *Guidelines for registration of fixed-dose combination medicinal products* (6)).

The comparator product batch may be selected by dissolution profile testing (see WHO's *Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability* (7)). Ideally a batch which shows intermediate dissolution under the most discriminative condition (where the difference in dissolution between the fastest and slowest batches studied is the largest) should be selected as the reference product for pharmaceutical equivalence studies and bioequivalence studies.

2.2.2 Benchmarking for formulation experiments and stability studies

The comparator sample should be thoroughly examined for parameters such as physical properties, shelf-life, including in-use stability information, storage instructions and details of the container-closure system in comparison to the outcome of the desk research and the requirements for marketing the new multisource product in the intended market.

All the relevant quality attributes of the dosage form should be analysed, e.g. assay, related substances, dissolution rate, pH, preservative concentrations, water content, total mass, mass variation, resistance to crushing, friability and disintegration of tablets.

The information obtained forms the basis for the development of the new multisource FPP.

2.2.3 Formulation selection experiments

Based on the outcome of the desk research and the national requirements for marketing authorization, formulation experiments will be conducted to develop the quality target product profile (QTPP) of the FPP.

Experiments may include determining the qualitative and quantitative composition of the comparator product. The qualitative information on the comparator product may be available in the public domain, e.g. in its summary of product characteristics (SmPC) or package leaflet. Screening different formulations to match the comparator dissolution profile is the best method to select the final formula for scale-up from laboratory to pilot batch.

Selected formulations may be stress-tested to challenge CQAs and to establish tentative acceptance limits for their control.

Any special design features of the pharmaceutical product (e.g. tablet score-line, overfill, or anti-counterfeiting measure) should be identified as such features affect the pharmaceutical product and a rationale for their use should be provided in the product dossier (PD).

2.2.4 Bioequivalence and dissolution studies

Bioequivalence and comparative dissolution studies should be conducted with samples from a batch of the FPP of at least pilot size. The dissolution conditions and acceptance criteria should be derived from the dissolution profiles obtained for the biobatch.

Where an *in vivo* bioequivalence study could be waived, similarity of the formulations may be required, in particular with respect to excipients that may have an influence on the extent and rate of absorption, e.g. sorbitol in liquid formulations or mannitol in solid dosage forms. For instance, when considering a biowaiver for an immediate-release solid oral dosage form containing a BCS class 3 API, the risk of reaching an inappropriate biowaiver decision needs to be critically evaluated, especially when the extent of absorption (f_{abs}) is less than 50%. As part of the risk assessment the excipients used will also need to be scrutinized carefully in terms of both qualitative and quantitative composition – the greater the deviation from the comparator composition, the greater the risk of an inappropriate biowaiver decision.

Inclusion of summaries of all bioequivalence studies (passed and failed) on the final formulation in the PD may be required.

3. Pharmaceutical development

It is recommended to use an internationally harmonized structure when submitting a dossier for obtaining a marketing authorization. This section therefore follows the ICH-CTD structure according to ICH M4 (8).

The text of the M4Q (CTD-Q) guideline (9) is reproduced verbatim in this document in *italic* text, with minor modifications to accommodate WHO terminology and to include certain changes to the text that would be appropriate for multisource pharmaceutical products, notably:

- drug substance is replaced with active pharmaceutical ingredient or API;
- drug product is replaced with finished pharmaceutical product or FPP;
- application is replaced with product dossier or PD;

- combination product is replaced with fixed-dose combination or FDC;
- clinical batches is replaced with comparative bioavailability or biowaiver batches.

Following the *italic* text of the M4Q (CTD-Q) guideline (9), additional guidance by WHO is added in normal type to enable it to be easily distinguishable from the ICH text. This additional text is included to further clarify WHO's expectations and requirements. This approach is intended to facilitate the identification and origin of the text in the document (i.e. whether from ICH or WHO).

In section 3.2.P.2 below, reference may be made to CTD sections that are not discussed in this document. This is done to guide the manufacturer in completing the PD according to national or regional requirements.

3.2.P.2 *The Pharmaceutical development section should contain information on the development studies conducted to establish that the dosage form, the formulation, manufacturing process, container-closure system, microbiological attributes and usage instructions are appropriate for the purpose specified in the product dossier. The studies described here are distinguished from routine control tests conducted according to specifications. Additionally, this section should identify and describe the formulation and process attributes (critical parameters) that can influence batch reproducibility, product performance and FPP quality. Supportive data and results from specific studies or published literature can be included within or attached to the Pharmaceutical development section. Additional supportive data can be referenced to the relevant nonclinical or clinical sections of the product dossier.*

Pharmaceutical development information usually includes, at a minimum:

- the definition of the QTPP as it relates to quality, safety and efficacy, considering, for example, the route of administration, dosage form, bioavailability, strength and stability;
- identification of the potential CQAs of the FPP so as to adequately control product characteristics that could have an impact on quality;
- discussion of the potential CQAs of the API(s), excipients and container-closure system(s) including the selection of the type, grade and amount necessary to deliver the product of the desired quality;
- discussion of the selection criteria for the manufacturing process and the control strategy required to manufacture commercial lots meeting the QTPP in a consistent manner.

These features should be discussed as part of the product development, using the principles of risk management over the entire life-cycle of the product (ICH Q8 (10)). The information gained through the predevelopment activities may already have disclosed some of these features and could form an integral part of pharmaceutical development.

For a discussion of additional pharmaceutical development issues specific to the development of FDCs, reference can be made to WHO Technical Report Series, No. 929, Annex 5, section 6.3.2 (6).

Reference documents for pharmaceutical development include ICH guidelines Q6A, Q8, Q9 and Q10 (2, 10–12).

3.1 Components of the finished pharmaceutical product

3.2.P.2.1 The components of the FPP are the ingredients listed under section 3.2.1.P.1 (Description and composition of the FPP in the PD). The components thus include the API(s) and all the excipients, as well as those excipients that may not be added to every batch (e.g. acid and alkali), those that may be removed during processing (e.g. water for granulation) and any others (e.g. nitrogen or silicone for stoppers).

3.1.1 Active pharmaceutical ingredient

3.2.P.2.1.1 *The compatibility of the API with excipients listed in 3.2.P.1 should be discussed. Additionally, key physicochemical characteristics (e.g. water content, solubility, particle size distribution, polymorphic or solid state form) of the API that can influence the performance of the FPP should be discussed. For FDCs, the compatibility of APIs with each other should be discussed.*

Physicochemical characteristics of the API may influence both the manufacturing capability and the performance of the FPP.

Information on the intrinsic physicochemical properties of the molecule, e.g. solubility, solid-state properties, including polymorphism and habit, melting range, pK_a and hygroscopicity, is needed for the development of the product to allow the manufacturer of the FPP to take full responsibility for the quality and quality control (QC) of the API and the FPP.

Additionally, the manufacturer will need information (either from the API manufacturer, or gathered by another party, or by itself) on potentially critical properties of the API, together with specifications, as applicable, e.g. solubility at 37 °C at relevant physiological pH values to permit BCS classification of the API, partition coefficient (octanol/water) at 37 °C and particle size distribution, which may affect dissolution rate and bioavailability, as well as density, bulk and tapped density, flowability, compressibility, and other factors which may influence processibility. The above-mentioned properties of the API should usually be supported by experimental data (or by information from peer-reviewed literature) and discussed with respect to CQAs and CPPs.

The specifications of the API manufacturer and the retest period or expiry date derived from formal regulatory stability studies should also be available to the manufacturer of the FPP.

Guidance on compatibility studies is provided in Appendix 3 of the WHO *Guidelines for registration of fixed-dose combination medicinal products* (6). In addition to visual examination, chromatography results (assay, purity) are required to demonstrate API-API and API-excipient compatibility. In general, API-excipient compatibility is not required to be established for specific excipients when evidence is provided (e.g. in the SmPC or product leaflet) that the excipients are present in the comparator product.

Stress testing of the API should be designed to include simulation, as far as possible, of the conditions that may be encountered during the manufacturing process of the FPP. An example is provided in Appendix 1.

3.1.2 Excipients

“3.2.P.2.1.2 The choice of excipients listed in 3.2.P.1, their concentration and their characteristics that can influence the FPP performance should be discussed relative to their respective functions.”

When choosing excipients, those with a compendial monograph are generally preferred and may be required in certain jurisdictions. Other resources are available for information on acceptable excipients and their concentrations such as the US-FDA IIG (13) list and the *Handbook of pharmaceutical excipients* (14). Use of excipients at concentrations outside the established ranges is discouraged and generally requires justification. In addition, available guidelines which address particular excipients to be avoided should usually be consulted, for example, azo colourants as listed in EMA guideline CPMP/463/00 (15). Other guidelines such as WHO's *Development of paediatric medicines: points to consider in pharmaceutical development* (16) may provide useful general guidance in this regard.

The characteristics and amounts of excipients that can influence the performance of the pharmaceutical product or its manufacturing capability should usually be discussed relative to the respective function. The ability of functional excipients, e.g. pH-adjusting agents, buffers, stabilizers (such as antioxidants and chelating agents), preservatives and dissolution modifiers (such as surface active agents), to perform throughout the intended shelf-life of the FPP should usually be demonstrated.

Antimicrobial preservatives are discussed in 3.2.P.2.5.

Many excipients such as povidone, microcrystalline cellulose and lactose are by nature multifunctional. The chemically identical excipients may have different grades (physical properties) with different functional characteristics; therefore, conformance to pharmacopoeial specifications does not always

provide sufficient confidence that an excipient will perform according to its intended purpose.

When an excipient is critical for manufacturing capability of the FPP, batch or batch variations should be minimized by including user requirements additional to those specified in the pharmacopoeia, e.g. particle size distribution.

Ranges or alternatives for excipients are normally not accepted unless supported by appropriate process validation data. Where relevant, compatibility study results (e.g. compatibility of a primary or secondary amine API with lactose) should be included to justify the choice of excipients. Specific details should usually be provided in the PD where necessary (e.g. on use of potato or corn starch).

3.2 Finished pharmaceutical product

"3.2.P.2.2"

3.2.1 Formulation development

3.2.P.2.2.1 *A brief summary describing the development of the FPP should be provided, taking into consideration the proposed route of administration and usage. The differences between the comparative bioavailability or biowaiver formulations and the formulation (i.e. composition) described in 3.2.P.1 should be discussed. Results from comparative in vitro studies (e.g. dissolution) or comparative in vivo studies (e.g. bioequivalence) should be discussed when appropriate.*

When preparing the PD for submission, the data requirements of the NMRA regarding formulation development may depend on whether the multisource product has been newly developed by the applicant or manufacturer or whether it is an established multisource product.

The WHO Prequalification of Medicines Programme defines an established multisource product as one that has been marketed by the applicant or manufacturer associated with the dossier for at least five years and for which at least 10 production batches were produced over the previous year or, if less than 10 batches were produced in the previous year, not less than 25 batches were produced in the previous three years. For products that meet the criteria of an established multisource product, all sections of P.2.2.1 of the dossier should usually be completed with the exception of P.2.2.1 (a). In addition, a product quality review should usually be provided in the PD as outlined in Appendix 2 of the WHO Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part (1).

The requirements for bioequivalence studies should be taken into consideration, for example, when formulating multiple strengths and/or when the product(s) may be eligible for a biowaiver. WHO reference documents (e.g.

WHO guidelines on registration requirements to establish interchangeability for multisource (generic) pharmaceutical products (7) can be consulted.

Tablet scoring may be recommended or required in certain jurisdictions or, for example, when scoring is indicated in the WHO invitation for expression of interest, or is specified for an invited FPP in the listing of recommended comparator products, or when division into fractional doses may be necessary according to approved posology.

If the proposed FPP is a functionally scored tablet a study should be undertaken to ensure the uniformity of dose in the tablet fragments. The data provided in the PD should usually include a description of the test method, individual values, mean and relative standard deviation of the results. Uniformity testing (i.e. content uniformity or mass variation, depending on the requirement for the whole tablet) should be performed on each split portion from a minimum of 10 randomly selected whole tablets. As an example the number of units (i.e. the splits) would be 10 halves for bisected tablets (one half of each tablet is retained for the test) or 10 quarters for quadrisectioned tablets (one quarter of each tablet is retained for the test). At least one batch of each strength should be tested. Ideally the study should cover a range of the hardness values. The splitting of the tablets should be performed in a manner that would be representative of that used by the consumer (e.g. manually split by hand). The uniformity test on split portions only needs to be demonstrated once and does not need to be added to the FPP specification(s). The tablet description in the FPP specification and in the product information (e.g. SmPC, labelling or package leaflet) should reflect the presence of a score line.

If a paediatric dose is to be obtained by splitting a tablet, a demonstration of content uniformity of tablet fragments may be required.

For modified-release tablets designed to be divided into equal halves, demonstration of dissolution profile similarity of the tablet halves against the whole tablet may be required.

Where relevant, labelling should state that the score line is only intended to facilitate breaking for ease of swallowing and not to divide the tablet into equal doses. In this case a demonstration of uniformity is unlikely to be required.

In vitro dissolution or drug release

A discussion should usually be included as to how the development of the formulation relates to development of the dissolution method(s) and the generation of the dissolution profile.

The results of studies justifying the choice of in vitro dissolution or drug release conditions (e.g. apparatus, rotation speed and medium) are usually required in the PD. Data should also usually demonstrate whether the method is sensitive to changes in manufacturing processes and/or changes in grades and/

or amounts of critical excipients and particle size where relevant. The dissolution method should be sensitive to any changes in the product that would result in a change in one or more of the pharmacokinetic parameters.

Recommendations for conducting and assessing comparative dissolution profiles can be found in Appendix 1 of the WHO Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part (1).

In the case of rapidly dissolving FPPs containing highly soluble APIs (BCS classes 1 and 3), a single-point dissolution test limit of 80% in 30 minutes or less is considered sufficient as a routine QC test for batch-to-batch uniformity. For slowly dissolving or poorly water-soluble APIs (BCS classes 2 and 4) in immediate-release products, a two-point dissolution range (a dissolution window), one at an early time-point (e.g. Q = 60% in 45 minutes) and the other at a later point (e.g. Q = 80% in 90 minutes), is recommended to characterize the quality of the product. Note that in some cases the later point may be lower than 80% if a plateau is reached.

Modified-release FPPs should have a meaningful *in vitro* release rate (dissolution) test that is used for routine QC. Preferably, this test should possess *in vitro*–*in vivo* correlation. Results demonstrating the effect of pH on the dissolution profile are usually required, if appropriate for the type of dosage form.

For extended-release FPPs the testing conditions should be set to cover the entire period of expected release (e.g. at least three test intervals chosen for a 12-hour release and additional test intervals for longer duration of release). One of the test points should be at the early stage of drug release (e.g. within the first hour) to demonstrate absence of dose dumping. At each test period, upper and lower limits should be set for individual units. Generally the acceptance range at each intermediate test point should not exceed 25% or $\pm 12.5\%$ of the targeted value. Dissolution results are usually required for several lots including those used for pharmacokinetic and bioavailability or biowaiver studies.

The dissolution acceptance limit(s) should also be incorporated into the stability programmes.

Where there are scientific grounds that the defined release characteristics of oral pharmaceutical products may be adversely affected by the presence of alcohol, e.g. for modified-release products containing opiates, 5%, 10% and 20% ethanol should be added to the dissolution medium proposed for routine testing in order to demonstrate that no dose dumping will occur through intake with alcoholic beverages.

3.2.2 Overages

3.2.P.2.2.2 *Any overages in the formulation(s) described in 3.2.P.1 should be justified.*

Justification of an overage to compensate for loss during manufacture

should usually be provided in the PD, including the step(s) where the loss occurs, the reasons for the loss and batch analysis release data (assay results).

Overages for the sole purpose of extending the shelf-life of the FPP are generally not acceptable.

3.2.3 Physicochemical and biological properties

3.2.P.2.2.3 *Parameters relevant to the performance of the FPP, such as pH, ionic strength, dissolution, redispersion, reconstitution, particle size distribution, aggregation, polymorphism, rheological properties, biological activity or potency and/or immunological activity, should be addressed.*

3.3 Manufacturing process development

3.2.P.3.3 *The selection and optimization of the manufacturing process described in 3.2.P.3.3, in particular its critical aspects, should be explained. Where relevant, the method of sterilization should be explained and justified.*

For products that meet the criteria of an established multisource product, in order to fulfil the requirements of section P.2.3, section P.2.3 (b) of the dossier should be completed and a product quality review should usually be submitted as outlined in Appendix 2 of the WHO Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part (1). The guidance below applies to all other products, for which section P.2.3 should be completed in its entirety.

The rationale for choosing the particular pharmaceutical product (e.g. dosage form, delivery system) should be provided in the PD. The scientific rationale for the choice of the manufacturing, filling and packaging processes that can influence quality and performance of the FPP should usually be explained (e.g. wet granulation using high-shear granulator). The results of an API stress study may be included in the rationale. Any developmental work undertaken on protecting the FPP from deterioration (e.g. protection from light or moisture) should also be included.

The manufacturing process of the multisource FPP should be appropriate for the product that is in development. It does not need to be the same as that of the comparator FPP.

Efforts should be primarily directed towards reducing variability in process and product quality. In order to achieve this, all critical sources of variability should be identified and explained and the sources of variability should be minimized and controlled.

Process development studies should provide the basis for process improvement, process validation and any process control requirements. All CPPs should usually be identified, monitored or controlled to ensure that the product is of the desired quality.

For sterile products an appropriate method of sterilization for the pharmaceutical product and primary packaging material should be chosen. Where relevant, justification for the selection of aseptic processing or other sterilization methods over terminal sterilization should be provided in the PD.

Differences between the manufacturing process(es) used to produce comparative bioavailability or biowaiver batches and the process described in 3.2.P.3.3 that can influence the performance of the product should be discussed.

The scientific rationale for the selection, optimization and scale-up of the manufacturing process described in 3.2.P.3.3 should usually be explained, in particular the CPPs (e.g. rate of addition of granulating fluid, massing time, and granulation end-point). A discussion of the CPPs, controls and process robustness with respect to the QTPP and CQA of the product should usually be included (10).

Based on close monitoring of the manufacturing process in the pilot batches, provisional acceptance ranges should be proposed for the CQAs of intermediates and CPPs that impact on downstream processing. Interim acceptance criteria may be approved until enough knowledge is available to finalize CQAs of intermediates and CPPs for production batches.

The manufacturing process used for pilot batches should be the same as the one proposed to be applied to production batches and should provide product of the same quality and meeting the same specifications as that intended for marketing.

3.4 Container-closure system

3.2.P.2.4 The suitability of the container-closure system (described in 3.2.P.7) used for the storage, transportation (shipping) and use of the FPP should be discussed. This discussion should consider, e.g. choice of materials, protection from moisture and light, compatibility of the materials of construction with the dosage form (including sorption to container and leaching) safety of materials of construction and performance (such as reproducibility of the dose delivery from the device when presented as part of the FPP).

The properties of the container-closure systems should be defined by the characteristics of the FPP and the conditions prevailing in the intended market (e.g. climatic zone IVb).

Stability testing of primary batches of the FPP is conducted on samples packaged in the container-closure system selected for marketing in order to confirm compatibility and product stability to support PDs for marketing authorization.

When the container-closure system is a critical factor for FPP stability, batch or supplier variations need to be minimized through tight specifications and extended sampling plans for QC testing.

To facilitate the visual identification of spuriously or falsely-labelled, falsified or counterfeit (SFFC) medicines (including by the public) the description needs to be completely detailed in the product information. Details may include information on the container-closure system, such as “round, white opaque, high-density polyethylene (HDPE) bottles fitted with white opaque, polypropylene continuous thread closures with induction sealing liner”, or “a blister package comprising clear transparent polyvinyl chloride (PVC) film with a backing of aluminium foil coated with heat-seal lacquer”.

Primary packing materials, particularly plastics, should comply with relevant pharmacopoeial and food contact regulations.

Testing requirements to verify the suitability of the container-closure system contact material(s) depend on the dosage form and route of administration and possibly, the manufacturing process. The pharmacopoeias provide standards that are required for packaging materials; examples include the following:

- glass containers (17, 18);
- plastic containers (19, 20);
- rubber/elastomeric closures (21, 22).

Table 1 outlines the general recommendations for the various dosage forms for once-only studies to establish the suitability of the container-closure system contact materials.

Table 1
Studies to establish the suitability of the container-closure system contact materials

	Solid oral products	Oral liquid and topical products	Sterile products (including ophthalmic preparations)
Description of any additional treatments ^a	×	×	× (sterilization and depyrogenation of the components)
Extraction studies	–	×	×
Interaction studies (migration/sorption)	–	×	×
Moisture permeability	× (uptake)	× (usually loss)	× (usually loss)
Light transmission	× ^b	×	×

× Information should usually be submitted.

– Information does not need to be submitted.

^a E.g. coating of tubes, siliconization of rubber stoppers, sulfur treatment of ampoules or vials.

^b Not required if product has been shown to be photostable.

The suitability of the container-closure system used for the storage, transportation (shipping) and use of any intermediate or in-process products (e.g. premixes, bulk FPP) should also be discussed.

Devices

There are certain situations in which pharmaceutical dosage forms are developed in association with specific devices. The device might be critical to enabling delivery of the medicine or it might be included in order to facilitate administration.

Where the device is critical to drug delivery and fully integrated with the product formulation, this product formulation–device combination should be considered as the primary product for the purposes of regulatory submission. Examples of such products include metered dose inhalers (MDIs), dry powder inhalers, intranasal sprays and ready-made intravenous infusions. For these products the data necessary to support a regulatory submission would include:

- physical and chemical stability data for the product formulation–device combination in its primary pack in order to support the claimed shelf-life and storage conditions;
- relevant data on extractables and leachables;
- for multidose products, demonstration of accurate dose delivery over the shelf-life of the product under the registered storage conditions;
- for multidose products with a dose-counting mechanism, stability data to demonstrate reliable performance of that mechanism over the shelf-life of the product under the registered storage conditions;
- specification control and secure sourcing of all device components;
- relevant information on any secondary device associated with the FPP, such as a spacer device sometimes associated with inhaled products such as MDIs and nebulizers. This device enables dose delivery in situations where the patient cannot easily use the primary product to inhale the dose, particularly where administration to children is involved. The device acts as a temporary reservoir for the dose which can then be inhaled more easily by the patient. There will be some variability inherent to a spacer device but, nevertheless, an acceptable accuracy of dose delivery when using this device needs to be demonstrated.

Alternatively, the co-developed device may be intended to facilitate measurement of the prescribed dose prior to administration; this is particularly important for paediatric products where flexibility of dose may also be a requirement. Examples include spoons, cups, syringes or droppers for oral

delivery and droppers for nasal or aural delivery. A device is required to be included with the container-closure system for oral liquids or solids (e.g. solutions, emulsions, suspensions and powders or granules), whenever the package provides for multiple doses.

In accordance with the Ph. Int. (3) general chapter *Liquid preparations for oral use*:

“Each dose from a multidose container is administered by means of a device suitable for measuring the prescribed volume. The device is usually a spoon or a cup for volumes of 5 ml or multiples thereof, or an oral syringe for other volumes or, for oral drops, a suitable dropper.”

In these cases the following data would be required to support a regulatory submission:

- for a device accompanying a multidose container, the results of a study demonstrating the reproducibility of the device (e.g. consistent delivery of the intended volume), generally at the lowest intended dose;
- specifications for the device materials, including specific identification testing of the material which will be in contact with the FPP.

When the intention is to submit a PD in CTD format a sample of the device should usually be provided with Module 1 of the PD.

3.5 Microbiological attributes

3.2.P.2.5 *Where appropriate the microbiological attributes of the dosage form should be discussed, including, for example, the rationale for not performing microbial limits testing for non-sterile products and the selection and effectiveness of preservative systems in products containing antimicrobial preservatives. For sterile products the integrity of the container-closure system to prevent microbial contamination should be addressed.*

Where an antimicrobial preservative is included in the formulation the amount used needs to be justified by submission of results of studies of the product formulated with different concentrations of the preservative(s) to demonstrate the lowest necessary but still effective concentration. The effectiveness of the agent needs to be justified and verified by appropriate studies (e.g. national, regional or international pharmacopoeial general chapters on antimicrobial preservatives) using a batch of the FPP. If the lower limit for the proposed acceptance criterion for the assay of the preservative is less than 90.0%, the effectiveness of the agent has to be established with a batch of the FPP containing a concentration of the antimicrobial preservative corresponding to the lower proposed acceptance criteria.

As outlined in the WHO guidelines on *Stability testing of active pharmaceutical ingredients and finished pharmaceutical products* (23), a single

primary stability batch of the FPP should be tested for effectiveness of the antimicrobial preservative (in addition to preservative content) for the duration of the proposed shelf-life for verification purposes, regardless of whether there is a difference between the release and shelf-life acceptance criteria for preservative content.

3.6 Compatibility

3.2.P.2.6 *The compatibility of the FPP with reconstitution diluent(s) or dosage devices (e.g. precipitation of API in solution, sorption on injection vessels, stability) should be addressed to provide appropriate and supportive information for the labelling.*

Where a device is required for oral liquids or solids (e.g. solutions, emulsions, suspensions and powders or granules for reconstitution), which are intended to be administered immediately after being added to the device, the compatibility studies mentioned in the following paragraphs are not required.

Where sterile, reconstituted products are to be further diluted, compatibility will have to be demonstrated with all diluents over the range of dilution proposed in the labelling. These studies should preferably be conducted on aged samples. Where the labelling does not specify the type of containers, compatibility (with respect to parameters such as appearance, pH, assay, levels of individual and total degradation products, subvisible particulate matter and extractables from the packaging components) should be demonstrated in glass, PVC and polyolefin containers. However, if one or more containers are identified in the labelling, compatibility of admixtures needs to be demonstrated only in the specified containers.

In the case of infusion sets where a product formulation is added to an infusion vehicle in an intravenous administration set (giving set) immediately prior to administration, the following data would be required:

- physical and chemical stability data for the prepared infusion to support the claimed in-use shelf-life and storage conditions;
- compatibility data to support the claimed in-use shelf-life and storage conditions;
- specification control and secure sourcing of all giving set contact materials.

Studies are usually required to cover the duration of storage reported in the labelling (e.g. 24 hours under controlled room temperature and 72 hours under refrigeration). Where the labelling specifies co-administration with other FPPs, compatibility should be demonstrated with respect to the principal FPP as well as the co-administered FPP (i.e. in addition to the other, aforementioned parameters for the mixture, the assay and degradation levels of each co-administered FPP should be reported).

In some cases when a pharmaceutical product is developed for global marketing there may also be a need to consider alternative diluents or liquids for dispersion and/or in-use reconstitution for a product, and compatibility with these diluents or liquids may be required to be established.

4. Glossary

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

active pharmaceutical ingredient

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

comparator product

The comparator product is a pharmaceutical product with which the multisource product is intended to be interchangeable in clinical practice. The comparator product will normally be the innovator product for which efficacy, safety and quality have been established. The selection of the comparator product is usually made at the national level by the medicines regulatory authority. (For the WHO Prequalification of Medicines Programme, the selection of the comparator product is based on the information presented under Guidance on bioequivalence studies available on the Prequalification web site.)

control strategy

A planned set of controls, derived from current product and process understanding that ensures process performance and product quality. The controls can include parameters and attributes related to active pharmaceutical ingredient 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.

critical process parameter (CPP)

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

critical quality attribute (CQA)

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

finished pharmaceutical product (FPP)

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

fixed-dose combination finished pharmaceutical product (FDC-FPP)

A finished pharmaceutical product that contains two or more active pharmaceutical ingredients.

formal experimental design

A structured, organized method for determining the relationship between factors affecting a process and the output of that process. Also known as “design of experiments”.

generic product

See *multisource (generic) pharmaceutical products*.

life-cycle

All phases in the life of a product from the initial development through marketing until the product’s discontinuation.

multisource (generic) pharmaceutical products

Multisource pharmaceutical products are pharmaceutically equivalent or pharmaceutically alternative products that may or may not be therapeutically equivalent. Multisource pharmaceutical products that are therapeutically equivalent are interchangeable.

pharmaceutical alternatives

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

pharmaceutical equivalence

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

pharmaceutical product

Any preparation for human or veterinary use that is intended to modify or explore physiological systems or pathological states for the benefit of the recipient.

pilot-scale batch

A batch of an active pharmaceutical ingredient or finished pharmaceutical product manufactured by a procedure fully representative of and simulating that to be applied to a full production-scale batch. For example, for solid oral dosage forms, a pilot scale is generally, at a minimum, one-tenth that of a full production scale or 100 000 tablets or capsules, whichever is the larger; unless otherwise adequately justified.

primary batch

A batch of an active pharmaceutical ingredient or finished pharmaceutical product used in a stability study, from which stability data are submitted in a registration application for the purpose of establishing a retest period or shelf-life, as the case may be.

process robustness

Ability of a process to tolerate variability of materials and changes of the process and equipment without negative impact on quality.

production batch

A batch of an active pharmaceutical ingredient or finished pharmaceutical product manufactured at production scale by using production equipment in a production facility as specified in the application.

quality

The suitability of either an active pharmaceutical ingredient or a pharmaceutical product for its intended use. This term includes such attributes as the identity, strength and purity.

quality target product profile (QTPP)

A prospective summary of the quality characteristics of a finished pharmaceutical product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the finished pharmaceutical product.

stringent regulatory authority (SRA)

For the purpose of this document, a stringent regulatory authority (SRA) is the medicines regulatory authority in a country which is:

- (a) a member of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) (European Union, Japan and the United States of America); or (b) an ICH Observer, being the European Free Trade Association as represented by SwissMedic and Health Canada (as may be updated from time to time); or (c) a regulatory authority associated with an ICH member through a legally binding, mutual recognition agreement including Australia, Iceland, Liechtenstein and Norway (as may be updated from time to time);
- only in relation to good manufacturing practices inspections: a medicines regulatory authority that is a member of the Pharmaceutical Inspection Co-operation Scheme as specified at <http://www.picscheme.org>.

therapeutic equivalence

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

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Appendix 1

Examples of presenting quality attributes of active pharmaceutical ingredients

Physicochemical characteristics of the active pharmaceutical ingredient (API) that can influence manufacturing capability and the performance of the finished pharmaceutical product (FPP) should be tabulated and discussed, for example, as in the following tables.

pH (of the buffer)	Solubility (mg/ml)
1.2	
4.5	
6.8	
pKa of API	

Method (compendial):

Particle size of API used in relevant laboratory and pilot-scale batches					
Measured data (µm)	Batch number (and use)				Proposed acceptance range (µm)
	<API batch no.> <FPP batch no.> (design)	<API batch no.> <FPP batch no.> (final laboratory)	<API batch no.> <FPP batch no.> (stability)	<API batch no.> <FPP batch no.> (bioequivalence)	
D 10					
D 50					
D 90					

Add rows as needed. Change data range as relevant

Method (compendial):

Apparent density of API used in relevant laboratory and pilot-scale batches					
	<API batch no.> <FPP batch no.> (design)	<API batch no.> <FPP batch no.> (final laboratory)	<API batch no.> <FPP batch no.> (stability)	<API batch no.> <FPP batch no.> (bioequivalence)	Proposed acceptance range (g/ml)
Bulk					
Tapped					

Method (compendial):

Stress Condition	Treatment	Observations
None	Initial values of the API	Assay: S1: <i>Insert as many rows as necessary</i>
		D1: <i>Insert as many rows as necessary</i> Total unspecified: Total impurities:
Temperature	A thin layer of the API is kept at 80 °C for 4 weeks in a Petri dish (open system) with sampling once a week	Assay: S1: D1: Total unspecified: Total impurities:

continues

Stress Condition	Treatment	Observations
Humidity	A thin layer of the API is kept at 40 °C /100% relative humidity for 4 weeks in a Petri dish (open system) with sampling once a fortnight	Assay: S1: D1: Total unspecified: Total impurities:
Oxidation	Oxygen is bubbled slowly through the oxygen-saturated aqueous solution/suspension (under constant mixing) of the API for 24 hours with sampling every 8 hours	Assay: S1: D1: Total unspecified: Total impurities:

S1, S2, etc., are synthesis impurities (as in API specifications).

D1, D2, etc., are degradation products.

Appendix 2

Information on development batches

Table 1
Screening laboratory batches with different proportions of excipients to match comparator dissolution

Composition of formulation development experiments								
Ingredients	Lab01		Lab02		Lab03		Lab04	
	Grams	%	Grams	%	Grams	%	Grams	%
active pharmaceutical ingredient (API) 1								
API 2								
API 3								
Excipient 1								
Excipient 2								
Excipient 3								
Excipient 4								
Excipient 5								
Dissolution, % at pH ...								

Table 2

Example table for developmental multipoint dissolution profiles (hypothetical example – Ph. Int., paddle, 75 rpm, 900 ml)

	Percentage API dissolved	Percentage API dissolved	Percentage API dissolved
Time (min)	pH 1.2 buffer	pH 4.5 buffer	pH 6.8 buffer
5			
10			
15			
20			
30			
45			
60			
90			

Repeat the table as needed, for example, for comparator product and development batch chosen for scale-up.

When comparing dissolution profiles of products, for example, comparator and test products or different strengths of the same product, the dissolution conditions and sampling intervals must be the same.

Graphical presentation and summary evaluation of the results of comparative dissolution studies of the test (samples taken from the bioequivalence batch no. ...) and comparator products:

Annex 4

Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part

1. Introduction	122
1.1 Background	122
1.2 Objectives	122
1.3 Scope	123
1.4 General principles	123
1.5 Guidance on format	124
2. Glossary	125
3. Quality summaries	128
3.1 Module 2.3: Quality overall summary – product dossiers (QOS-PD)	128
3.2 Module 1.4.2: Quality information summary (QIS)	129
4. Module 3: Quality	129
4.1 Table of contents of Module 3	129
4.2 Body of data	129
3.2.S Drug substance (or active pharmaceutical ingredient (API))	129
3.2.P Drug product (or finished pharmaceutical product (FPP))	158
3.2.A Appendices	187
3.2.R Regional information	187
4.3 Literature references	189
References	189
Appendix 1	193
Recommendations for conducting and assessing comparative dissolution profiles	193
Appendix 2	195
Product quality review requirements for <i>established multisource products</i>	195

1. Introduction

1.1 Background

The *Procedure for prequalification of pharmaceutical products* (1) outlines the procedure and considerations for the process undertaken by WHO in providing United Nations agencies with advice on the acceptability, in principle, of pharmaceutical products for procurement by such agencies. It states:

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

As mentioned in WHO Technical Report Series, No. 961 (1), in submitting an expression of interest (EOI) for product evaluation, the applicant should send a product dossier (PD) to the WHO focal point (together with the other data required), in the format specified in the WHO guidance documents on submitting product data and information.

Through the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) process, considerable harmonization has been achieved on the organization for the Quality module of the registration documents with the issuance of the *Common technical document (CTD) – quality (ICH M4Q)* guideline (2). This format, recommended in the M4Q guideline for the quality information of registration applications, has become widely accepted by regulatory authorities both within and beyond the ICH regions.

The current document provides recommendations on the quality information for active pharmaceutical ingredients (APIs) and finished pharmaceutical products (FPPs) that should be submitted to WHO to support PDs.

Alternative approaches to the principles and practices described in this document may be acceptable provided they are supported by adequate scientific justification. It is also important to note that the WHO Prequalification of Medicines Programme may request information or material, or define conditions not specifically described in this guidance, in order to adequately assess the quality of a pharmaceutical product.

1.2 Objectives

These guidelines are intended to:

- assist applicants in the preparation of the *Quality Module* of PDs for multisource products by providing clear general guidance on the format of these dossiers;

- fully adopt the modular format of the *Common technical document – quality (M4Q) (2)* as developed by ICH;
- provide guidance on the technical and other general data requirements.

These measures are intended to promote effective and efficient processes for the development of these PDs by applicants and for the subsequent assessment procedures by WHO.

1.3 Scope

These guidelines apply to PDs for multisource pharmaceutical products containing existing APIs of synthetic or semi-synthetic origin. For the purposes of these guidelines, an existing API is one that has been previously approved through a finished product by a stringent regulatory authority (SRA)¹ or by WHO. Fermentation, biological, biotechnological and herbal APIs are covered by other guidelines.

1.4 General principles

To facilitate the preparation of the PD, these guidelines are organized in accordance with the structure of the ICH *Common technical document – quality (M4Q) guideline (2)*.

The text of the M4Q (CTD-Q) guideline (2) has been restated verbatim in these guidelines in **bold text**, with minor modifications to accommodate WHO terminology and to include certain text that would be appropriate for multisource pharmaceutical products, notably:

- “Drug substance” is replaced with “active pharmaceutical ingredient” or “API”.
- “Drug product” is replaced with “finished pharmaceutical product” or “FPP”.
- “Application” is replaced with “product dossier” or “PD”.
- “Combination product” is replaced with “fixed-dose combination” or “FDC”.
- “Clinical batches” is replaced with “comparative bioavailability” or “biowaiver batches”.

¹ A stringent regulatory authority (SRA): a regulatory authority which is:

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

Additional guidance by WHO, following the **bold** text reproduced from the M4Q (CTD-Q) guideline (2), is printed in plain text to make it easily distinguishable from the ICH text and is included to provide further clarity on WHO's expectations for the content of PDs. This approach is intended to facilitate the identification and origin of the text in these guidelines (i.e. from ICH or from WHO).

The content of these guidelines should be read in conjunction with relevant information described in other existing WHO or ICH reference documents and guidelines. The quality of existing APIs and corresponding multisource products should not be inferior to new APIs and innovator (comparator) FPPs. Therefore, the principles of the ICH guidelines that are referenced throughout this document and in other WHO guidelines may equally apply to existing APIs and multisource products.

Scientific literature may be appropriate to fulfil the requirements for some of the information or parameters outlined in these guidelines (e.g. qualification of specified identified impurities). Furthermore, the requirements outlined in certain sections may not be applicable to the proposed API or FPP. In these situations, either a summary and the full reference to the scientific literature should be provided, or the non-applicability of the requested information should be clearly indicated with an accompanying explanatory note.

1.5 Guidance on format

The recommendations outlined in the WHO general filing guideline *Guidelines on submission of documentation for a multisource (generic) finished product: general format: preparation of product dossiers in common technical document format* (3) should be followed for the format and presentation of the PD.

There may be a number of instances where repetition of sections can be considered appropriate. Whenever a section is repeated, it should be made clear what the section refers to by creating a distinguishing title in parentheses following the M4Q (CTD-Q) guideline heading, e.g. 3.2.S Drug substance (or API) (name, Manufacturer A).

The following are recommendations for the presentation of the information in the Quality module for different scenarios that may be encountered:

- The Open part (non-proprietary information) of each APIMF should always be included *in its entirety* in the PD, as an annex to 3.2.S.
- For an FPP containing more than one API, one complete “3.2.S” section should be provided for one API, *followed by* another complete “3.2.S” section for each of the other APIs.
- For an API from multiple manufacturers, one complete “3.2.S” section should be provided for the API from one manufacturer, *followed by*

another complete “3.2.S” section for the API from each of the other API manufacturers.

- For an FPP with multiple strengths (e.g. 10, 50, 100 mg) one complete “3.2.P” section should be provided with the information for the different strengths provided *within* the subsections. One complete copy of the PD should be provided for each FPP strength.
- For an FPP with multiple container-closure systems (e.g. bottles and unit dose blisters) one complete “3.2.P” section should be provided with the information for the different presentations provided *within* the subsections.
- For multiple FPPs (e.g. tablets and a parenteral product) a separate dossier is required for each FPP.
- For an FPP supplied with reconstitution diluent(s) one complete “3.2.P” section should be provided for the FPP, *followed by* the information on the diluent(s) in a separate part “3.2.P”, as appropriate.
- For a co-blistered FPP one complete “3.2.P” section should be provided for each product.

2. Glossary

The definitions provided below apply to the words and phrases used in these guidelines. Although an effort has been made to use standard definitions as far as possible, they may have different meanings in other contexts and documents. The following definitions are provided to facilitate interpretation of the guidelines.

active pharmaceutical ingredient (API)

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

active pharmaceutical ingredient (API) starting material

A raw material, intermediate, or an API that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API. An API starting material can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement, or produced in-house (ICH Q7). See also *starting materials for synthesis*.

applicant

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

Biopharmaceutics Classification System (BCS) highly soluble

An API for which the highest dose recommended by WHO (if the API appears on the WHO Model list of essential medicines) or highest dose strength available on the market as an oral solid dosage form (if the API does not appear on the WHO Model list of essential medicines) is soluble in 250 ml or less of aqueous media over the pH range of 1.2–6.8 at 37 °C.

commitment batches

Production batches of an API or FPP for which the stability studies are initiated or completed post-approval through a commitment made in a regulatory application.

comparator product

A pharmaceutical product with which the generic 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. For the Prequalification of Medicines Programme, the selection of the comparator product is based on the information presented under Guidance on bioequivalence studies available on the Prequalification web site.

established multisource (generic) product

A multisource product that has been marketed by the applicant or manufacturer associated with the dossier for at least five years and for which at least 10 production batches were produced over the previous year, or, if less than 10 batches were produced in the previous year, not less than 25 batches were produced in the previous three years.

existing API

An API that is not considered a new active substance, which has been previously approved through a finished product by a stringent regulatory authority or by WHO, but requires the filing of a dossier. This would include, for example, new PDs and variations to multisource products.

finished pharmaceutical product (FPP)

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

innovator pharmaceutical product

Generally the pharmaceutical product that was first authorized for marketing (normally as a patented product) on the basis of documentation of efficacy, safety and quality.

manufacturer

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

multisource (generic) pharmaceutical products

Pharmaceutically equivalent or pharmaceutically alternative products that may or may not be therapeutically equivalent. Multisource pharmaceutical products that are therapeutically equivalent are interchangeable.

officially recognized pharmacopoeia (or compendium)

Those pharmacopoeias recognized in the WHO Prequalification of Medicines Programme (i.e. *British Pharmacopoeia* (BP), *European Pharmacopoeia* (Ph.Eur.), *The International Pharmacopoeia* (Ph.Int.), *Japanese Pharmacopoeia* (JP) and *United States Pharmacopoeia* (USP)).

ongoing stability study

The study carried out by the manufacturer on production batches according to a predetermined schedule in order to monitor, confirm and extend the projected retest period (or shelf-life) of the API, or confirm or extend the shelf-life of the FPP.

pilot-scale batch

A batch of an API or FPP manufactured by a procedure fully representative of and simulating that to be applied to a full production-scale batch. For example, for solid oral dosage forms a pilot scale is generally, at a minimum, one-tenth that of a full production scale or 100 000 tablets or capsules, whichever is the larger; unless otherwise adequately justified.

primary batch

A batch of an API or FPP used in a stability study, from which stability data are submitted in a registration application for the purpose of establishing a retest period or shelf-life. For the WHO Prequalification of Medicines Programme, primary batch requirements are outlined in 3.2.S.7.1 and 3.2.P.8.1 for the API and FPP, respectively.

production batch

A batch of an API or FPP manufactured at production scale by using production equipment in a production facility as specified in the application.

starting materials for synthesis

Materials that mark the beginning of the manufacturing process as described in an application or in an API master file (APIMF). A starting material for a synthetic API is a chemical compound of defined molecular structure that contributes to the structure of the API. See also *API starting material*.

3. Quality summaries

3.1 Module 2.3: Quality overall summary – product dossiers (QOS-PD)

The Quality overall summary (QOS) is a summary that follows the scope and the outline of the Body of data in Module 3. The QOS should not include information, data or justification that was not already included in Module 3 or in other parts of the CTD.

The QOS should include sufficient information from each section to provide the Quality assessor with an overview of Module 3. The QOS should also emphasize critical key parameters of the product and provide, for instance, justification in cases where guidelines were not followed. The QOS should include a discussion of key issues that integrates information from sections in the Quality module and supporting information from other Modules (e.g. qualification of impurities via toxicological studies), including cross-referencing to volume and page number in other Modules.

The WHO *Quality overall summary – product dossiers (QOS-PD)* template should be completed for multisource pharmaceutical products containing APIs of synthetic or semi-synthetic origin (see 1.3 Scope for further clarification) and their corresponding FPPs.

All sections and fields in the QOS-PD template that would be applicable should be completed. It is understood that certain sections and fields may not apply and should be indicated as such by reporting “not applicable” in the appropriate area with an accompanying explanatory note.

The use of tables to summarize the information is encouraged where possible. The tables included in the template may need to be expanded or duplicated (e.g. for multiple strengths). These tables are included as illustrative examples of how to summarize information. Other approaches can be used to summarize the information if they fulfil the same purpose.

3.2 Module 1.4.2: Quality information summary (QIS)

The QIS template should be completed to provide a condensed summary of the key quality information for the PD and constitutes part of the submission package. The QIS provides an accurate record of technical data in the PD at the time of prequalification. The QIS is a condensed version of the QOS-PD and represents the final agreed-upon key information on the API and FPP from the PD assessment (including, but not limited to, identification of the manufacturer(s), site addresses, API/FPP specifications, stability conclusions and relevant commitments).

The QIS template is structured according to the numbering and section headings of the ICH M4Q (CTD-Q) guideline to permit the rapid assembly of the QIS by copying the requisite information from the corresponding portions of the QOS-PD filed with the PD. It is acknowledged that the numbering of the sections in the QIS may not be entirely sequential. Those sections not considered necessary for inclusion in the QIS have been removed (e.g. 2.3.S.5 Reference standards or materials) and the remaining sections have retained their original numbering to maintain consistency with the original PD.

The QIS will serve as an official reference document in the course of good manufacturing practices (GMP) inspections, variation assessments and requalification assessments as performed by WHO.

4. Module 3: Quality

4.1 Table of contents of Module 3

A Table of contents for the filed product dossier should be provided.

4.2 Body of data

3.2.5 Drug substance (or active pharmaceutical ingredient, API)

There are four options for submitting the API information to WHO:

- Option 1: confirmation of API prequalification document;
- Option 2: Certificate of Suitability of the *European Pharmacopoeia* (Ph.Eur.) (CEP); or
- Option 3: active pharmaceutical ingredient master file (APIMF) procedure; or
- Option 4: full details in the PD.

The applicant should clearly indicate at the beginning of the API section (in the PD and in the QOS-PD) how the information on the API for each API manufacturer is being submitted. The API information submitted by the applicant or FPP manufacturer should include the following according to the options used.

- *Option 1: Confirmation of API prequalification document.*
 A complete copy of the Confirmation of API prequalification document should be provided in Module 1, together with the duly filled out authorization box in the name of the FPP manufacturer or applicant.
 The applicant should supply the following information in the dossier, with data summarized in the QOS-PD.
 - 3.2.S.1.3 *General properties* – discussions on any additional applicable physicochemical and other relevant API properties that are not controlled by the API manufacturer's specifications, e.g. solubilities and polymorphs according to the guidance in this section.
 - 3.2.S.2 – if the sterility of the FPP is based upon the sterile manufacture of the API then data on the sterilization process together with full validation data should be provided.
 - 3.2.S.3.1 *Elucidation of structure and other characteristics* – studies to identify polymorphs and particle size distribution, where applicable, according to the guidance in this section.
 - 3.2.S.4.1 *Specification* – the specifications of the FPP manufacturer including all tests and limits of the API manufacturer's specifications and any additional tests and acceptance criteria that are not controlled by the API manufacturer's specifications such as polymorphs and/or particle size distribution.
 - 3.2.S.4.2/3.2.S.4.3 *Analytical procedures and validation* – any methods used by the FPP manufacturer in addition to those in the API manufacturer's specifications.
 - 3.2.S.4.4 *Batch analysis* – results from two batches of at least pilot-scale, demonstrating compliance with the FPP manufacturer's API specifications.
 - 3.2.S.5 *Reference standards or materials* – information on the FPP manufacturer's reference standards.
 - 3.2.S.7 *Stability* – data to support the retest period if either the proposed retest period is longer or the proposed storage conditions are at a higher temperature or humidity to that of the prequalified API.

- *Option 2: Certificate of Suitability of the European Pharmacopoeia (CEP)*
 A complete copy of the CEP (including any annexes) should be provided in Module 1. The declaration of access for the CEP should be

duly filled out by the CEP holder on behalf of the FPP manufacturer or applicant to the WHO Prequalification of Medicines Programme who refers to the CEP.

In addition, a written commitment should be included that the applicant will inform WHO in the event that the CEP is withdrawn. It should also be acknowledged by the applicant that withdrawal of the CEP will require additional consideration of the API data requirements to support the PD. The written commitment should accompany the copy of the CEP in Module 1.

Together with the CEP, the applicant should supply the following information in the dossier, with data summarized in the QOS-PD.

- 3.2.S.1.3 *General properties* – discussions on any additional applicable physicochemical and other relevant properties of the API that are not controlled by the CEP and Ph.Eur. monograph, e.g. solubilities and polymorphs according to the guidance in this section.
- 3.2.S.3.1 *Elucidation of structure and other characteristics* – studies to identify polymorphs (except where the CEP specifies a polymorphic form) and particle size distribution, where applicable, according to the guidance in this section.
- 3.2.S.4.1 *Specification* – the specifications of the FPP manufacturer including all tests and limits of the CEP and Ph.Eur. monograph and any additional tests and acceptance criteria that are not controlled in the CEP and Ph.Eur. monograph, such as polymorphs and/or particle size distribution.
- 3.2.S.4.2/3.2.S.4.3 *Analytical procedures and validation* – for any methods used by the FPP manufacturer in addition to those in the CEP and Ph.Eur. monograph.
- 3.2.S.4.4 *Batch analysis* – results from two batches of at least pilot-scale, demonstrating compliance with the FPP manufacturer's API specifications.
- 3.2.S.5 *Reference standards or materials* – information on the FPP manufacturer's reference standards.
- 3.2.S.6 *Container-closure system* – specifications including descriptions and identification of primary packaging components except where the CEP specifies a container-closure system and the applicant declares the intent to use the same container-closure system.
- 3.2.S.7 *Stability* – except where the CEP specifies a retest period that is the same as or longer than that proposed by the applicant, and storage conditions are the same or at a higher temperature and humidity than those proposed by the applicant.

In the case of sterile APIs, data on the process for sterilization of the API including validation data should be included in the PD.

- *Option 3: Active pharmaceutical ingredient master file (APIMF) procedure*

Full details of the chemistry, manufacturing process, quality controls during manufacturing and process validation for the API may be submitted as an APIMF by the API manufacturer as outlined in WHO's *Guidelines on active pharmaceutical ingredient master file procedure* (4).

In such cases, the Open part (non-proprietary information) needs to be included in its entirety in the PD as an annex to 3.2.S. In addition, the applicant or FPP manufacturer should complete the following sections in the PD and QOS-PD in full according to the guidance provided unless otherwise indicated in the respective sections:

General information S.1.1–S.1.3

Manufacture S.2

Manufacturer(s) S.2.1

Description of manufacturing process and process controls S.2.2

Controls of critical steps and intermediates S.2.4

Elucidation of structure and other characteristics S.3.1

Impurities S.3.2

Control of the API S.4.1–S.4.5

Reference standards or materials S.5

Container-closure system S.6

Stability S.7.1–S.7.3

It is the responsibility of the applicant to ensure that the complete APIMF (i.e. both the applicant's Open part and the API manufacturer's Restricted part) is supplied to WHO directly by the API manufacturer and that the applicant has access to the relevant information in the APIMF concerning the current manufacture of the API.

A copy of the letter of access should be provided in the PD Module 1. APIMF holders can use the guidance provided for the option "Full details in the PD" for preparation of the relevant sections of the Open and Restricted parts of their APIMFs. Reference should also be made to the APIMF guidelines in WHO Technical Report Series, No. 948, Annex 4 (4).

- *Option 4: Full details in the PD*
Information on the 3.2.S *Active pharmaceutical ingredient* sections, including full details of chemistry, manufacturing process, quality controls during manufacturing and process validation for the API,

should be submitted in the PD as outlined in the subsequent sections of these guidelines. The QOS-PD should be completed according to section 3.1 of these guidelines.

3.2.S.1 General information (name, manufacturer)

3.2.S.1.1 *Nomenclature (name, manufacturer)*

Information on the nomenclature of the API should be provided. For example:

- (recommended) International Nonproprietary Name (INN);
- compendial name, if relevant;
- chemical name(s);
- company or laboratory code;
- other nonproprietary name(s) (e.g. national name, United States Adopted Name (USAN), British Approved Name (BAN));
- Chemical Abstracts Service (CAS) registry number.

The chemical names listed should be consistent with those appearing in the scientific literature and those appearing on the product labelling information (e.g. in the summary of product characteristics (SmPC) and package leaflet, also known as the patient information leaflet (PIL)). Where several names exist the preferred name should be indicated.

3.2.S.1.2 *Structure (name, manufacturer)*

The structural formula, including relative and absolute stereochemistry, the molecular formula, and the relative molecular mass should be provided.

This information should be consistent with that provided in section 3.2.S.1.1. For APIs existing as salts the molecular mass of the free base or acid should also be provided.

3.2.S.1.3 *General properties (name, manufacturer)*

A list should be provided of physicochemical and other relevant properties of the API.

This information can be used in developing the specifications, in formulating FPPs and in the testing for release and stability purposes.

The physical and chemical properties of the API should be discussed, including the physical description, solubilities in common solvents (e.g. water, alcohols, dichloromethane and acetone), quantitative aqueous pH solubility profile (e.g. pH 1.2–6.8, dose/solubility volume), polymorphism, pH and pKa values, ultraviolet (UV) absorption maxima and molar absorptivity, melting point, refractive index (for a liquid), hygroscopicity and partition coefficient (see

table in the QOS-PD). This list is not intended to be exhaustive but provides an indication as to the type of information that could be included.

Some of the most relevant properties to be considered for APIs are discussed below in greater detail.

Physical description

The physical description should include appearance, colour and physical state. Solid forms should be identified as being crystalline or amorphous (see 3.2.S.3.1 for further information on API solid forms).

Solubilities and quantitative aqueous pH solubility profile

The following should be provided for all options for the submission of API data.

The solubilities in a number of common solvents should be provided (e.g. in water, alcohols, dichloromethane and acetone).

The solubilities over the physiological pH range (pH 1.2–6.8) in several buffered media should be provided in mg/ml. If this information is not readily available (e.g. from literature references), it should be generated in-house.

For solid oral dosage forms, the dose/solubility volume should be provided as determined according to the formula:

$$\text{dose/solubility volume} = \frac{\text{largest dosage strength (mg)}}{\text{the minimum concentration of the drug (mg/ml)*}}$$

* corresponding to the lowest solubility determined over the physiological pH range (pH 1.2–6.8) and temperature ($37 \pm 0.5^\circ\text{C}$).

According to the Biopharmaceutics Classification System (BCS), highly soluble (or highly water soluble) APIs are those with a dose/solubility volume of ≤ 250 ml.

For example, compound A has as its lowest solubility at $37 \pm 0.5^\circ\text{C}$, 1.0 mg/ml at pH 6.8 and is available in 100 mg, 200 mg and 400 mg strengths. This API would not be considered a BCS *highly soluble* API as its dose/solubility volume is greater than 250 ml ($400 \text{ mg}/1.0 \text{ mg/ml} = 400 \text{ ml}$).

Polymorphism

As recommended in ICH's *CTD-Q Questions and answers/location issues* document (5) the following list explains where specific data should be located in the PD:

- The polymorphic form(s) present in the proposed API should be listed in section 3.2.S.1.3.

- The description of manufacturing process and process controls (3.2.S.2.2) should indicate which polymorphic form is manufactured, where relevant.
- The literature references or studies performed to identify the potential polymorphic forms of the API, including the study results, should be provided in section 3.2.S.3.1.
- If a polymorphic form is to be defined or limited (e.g. for APIs that are not *BCS highly soluble* and/or where polymorphism has been identified as an issue), details should be included in 3.2.S.4.1–3.2.S.4.5.

Additional information is included in the referenced sections of these guidelines.

Particle size distribution

As recommended in ICH's *CTD-Q Questions and answers/location issues* document (5), the studies performed to determine the particle size distribution of the API should be provided in section 3.2.S.3.1 (refer to this section of these guidelines for additional information).

Information from the literature

Supportive data and results from specific studies or published literature can be included within or attached to this section.

Reference documents: ICH Q6A (6).

3.2.S.2 Manufacture (name, manufacturer)

3.2.S.2.1 *Manufacturer(s) (name, manufacturer)*

The name, address, and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in manufacturing and testing should be provided.

The facilities involved in the manufacturing, packaging, labelling, testing and storage of the API should be listed. If certain companies are responsible only for specific steps (e.g. milling of the API) this should be clearly indicated.

The list of manufacturers or companies should specify the *actual addresses* of the production or manufacturing site(s) involved (including block(s) and units(s)), rather than the administrative offices. Telephone number(s), fax number(s) and e-mail address(es) should be provided.

A valid manufacturing authorization should be provided for the production of APIs. If available, a certificate of compliance with GMP should be provided in the PD in Module 1.

3.2.S.2.2 Description of manufacturing process and process controls (name, manufacturer)

The description of the API manufacturing process represents the applicant's commitment for the manufacture of the API. Information should be provided to adequately describe the manufacturing process and process controls. For example:

A flow diagram of the synthetic process(es) should be provided that includes molecular formulas, weights, yield ranges, chemical structures of starting materials, intermediates, reagents and API reflecting stereochemistry, and identifies operating conditions and solvents.

A sequential procedural narrative of the manufacturing process should be submitted. The narrative should include, for example, quantities of raw materials, solvents, catalysts and reagents reflecting the representative batch scale for commercial manufacture, identification of critical steps, process controls, equipment and operating conditions (e.g. temperature, pressure, pH, time).

Alternative processes should be explained and described with the same level of detail as the primary process. Reprocessing steps should be identified and justified. Any data to support this justification should be either referenced or filed in 3.2.S.2.5.

Where the APIMF procedure is used, a cross-reference to the Restricted part of the APIMF may be indicated for confidential information. In this case, if detailed information is presented in the Restricted part, the information to be provided for this section of the PD includes a flow chart (including molecular structures and all reagents and solvents) and a brief outline of the manufacturing process, with special emphasis on the final steps, including purification procedures. However, for sterile APIs, full validation data on the sterilization process should be provided in the Open part (in cases where there is no further sterilization of the final product).

The following requirements apply to the fourth option for submission of API information, where full details are provided in the dossier.

As discussed in ICH Q7 (7) and *WHO Technical Report Series*, No. 957, Annex 2 (8), the point at which the *API starting material* is introduced into the manufacturing process is the starting point for the application of GMP requirements. The API starting material itself needs to be proposed and its choice justified by the manufacturer and accepted as such by assessors. The API starting material should be proposed taking into account the complexity of the molecule, the proximity of the API starting material to the final API, the availability of the API starting material as a commercial chemical and the quality controls placed upon the API starting material. This justification should be documented in the dossier and be available for review by WHO GMP inspectors.

In situations where the API starting material is a complex molecule and only a minimal number of synthetic steps from the final API, a further molecule called the starting material for synthesis should be proposed and its choice

justified by the applicant. The starting material for synthesis defines the starting point in the manufacturing process for an API to be described in an application. The applicant should propose and justify which substances should be considered as starting materials for synthesis (see section 3.2.S.2.3 for further guidance). In the case where the precursor to the API is obtained by fermentation, or is of plant or animal origin, such a molecule can be considered the API starting material regardless of complexity.

A one-step synthesis may be accepted in exceptional cases, for example, where the API starting material is covered by a CEP, or where the API starting material is an API accepted through the APIMF or API prequalification procedure within the WHO Prequalification of Medicines Programme, or when the structure of the API is so simple that a one-step synthesis can be justified, e.g. ethambutol or ethionamide.

In addition to the detailed description of the manufacturing process as per ICH M4Q, the recovery of materials, if any, should be described in detail with the step in which they are introduced into the process. Recovery operations should be adequately controlled such that impurity levels do not increase over time. For recovery of solvents, any processing to improve the quality of the recovered solvent should be described. Regarding recycling of filtrates (mother liquors) to obtain second crops, information should be available on maximum holding times of mother liquors and maximum number of times the material can be recycled. Data on impurity levels should be provided to justify recycling of filtrates.

Where there are multiple manufacturing sites being used by one API manufacturer, a comprehensive list in tabular form should be provided comparing the processes at each of the sites and highlighting any differences.

All solvents used in the manufacture (including purification and/or crystallization step(s)) should be clearly identified. Solvents used in the final steps should be of high purity. Use of recovered solvents in the final steps of purification and/or crystallization is not recommended; however their use can be justified on presentation of sufficient data demonstrating that recovered solvents meet appropriate standards as outlined in ICH Q7 (7).

Where polymorphic or amorphous forms have been identified, the form resulting from the synthesis should be stated.

Where particle size is considered a critical attribute (see 3.2.S.3.1 for details) the particle size reduction method(s) (e.g. milling or micronization) should be described.

Justification should be provided for use of alternative manufacturing processes. Alternative processes should be explained with the same level of detail as for the primary process. It should be demonstrated that batches obtained by the alternative processes have the same impurity profile as obtained by the principal process. If the impurity profile obtained is different it should be demonstrated to be acceptable according to the requirements described under S.3.2.

It is acceptable to provide information on pilot-scale manufacture, provided it is representative of production scale and scale-up is reported immediately to WHO according to the requirements of the WHO variation guidelines (9).

3.2.S.2.3 Control of materials (name, manufacturer)

Materials used in the manufacture of the API (e.g. raw materials, starting materials, solvents, reagents, catalysts) should be listed identifying where each material is used in the process. Information on the quality and control of these materials should be provided. Information demonstrating that materials meet standards appropriate for their intended use should be provided, as appropriate (details in 3.2.A.2).

Where the APIMF procedure is used, a cross-reference to the Restricted part of the APIMF is considered sufficient for this section.

The following requirements apply to the fourth option for submission of API information, where full details are provided in the dossier.

The API starting material should be fully characterized and suitable specifications proposed and justified, including, at a minimum, control for identity, assay, impurity content and any other critical attribute of the material. For each API starting material, the name and address of the manufacturing site(s) of the manufacturer(s) should be indicated. A brief description of the preparation of the API starting material should be provided for each manufacturer, including the solvents, catalysts and reagents used. A single set of specifications should be proposed for the starting material that applies to material from all sources. Any future changes to the API starting material manufacturers, mode of preparation or specifications should be notified.

As indicated in section 3.2.S.2 there are occasions where a starting material for synthesis may also need to be defined. In general, the starting material for synthesis described in the PD should:

- be a synthetic precursor of one or more synthesis steps prior to the final API intermediate. Acids, bases, salts, esters and similar derivatives of the API, as well as the racemate of a single enantiomer API, are not considered final intermediates;
- be a well characterized, isolated and purified substance with its structure fully elucidated including its stereochemistry (when applicable);
- have well-defined specifications that include among others one or more specific identity tests and tests and limits for assay and specified, unspecified and total impurities;
- be incorporated as a significant structural fragment into the structure of the API.

Copies of the specifications for the materials used in the synthesis, extraction, isolation and purification steps should be provided in the PD, including starting materials, reagents, solvents, catalysts and recovered materials. Confirmation should be provided that the specifications apply to materials used at each manufacturing site. A certificate of analysis of the starting material for synthesis should be provided. A summary of the information on starting materials should be provided in the QOS-PD.

The carry-over of impurities of the starting materials for synthesis into the final API should be considered and discussed.

A letter of attestation should be provided confirming that the API and the starting materials and reagents used to manufacture the API are without risk of transmitting agents of animal spongiform encephalopathies.

When available a CEP demonstrating compliance with recommendations on transmissible spongiform encephalopathy (TSE) should be provided. A complete copy of the CEP (including any annexes) should be provided in Module 1.

Reference documents: ICH Q6A (6).

3.2.S.2.4 Controls of critical steps and intermediates (name, manufacturer)

Critical steps: Tests and acceptance criteria (with justification including experimental data) performed at critical steps identified in 3.2.S.2.2 of the manufacturing process to ensure that the process is controlled should be provided.

Intermediates: Information on the quality and control of intermediates isolated during the process should be provided.

Where the APIMF procedure is used, a cross-reference to the Restricted part of the APIMF is considered sufficient for this section of the PD, with the exception of information that is also relevant for the applicant (4).

The following requirements apply to the fourth option for submission of API information where full details are provided in the dossier.

The critical steps should be identified. These can include: steps where significant impurities are removed or introduced; steps introducing an essential molecular structural element such as a chiral centre or resulting in a major chemical transformation; steps having an impact on solid-state properties and homogeneity of the API that may be relevant for use in solid dosage forms.

Specifications for isolated intermediates should be provided and should include tests and acceptance criteria for identity, purity and assay, where applicable.

Reference documents: ICH Q6A (6).

3.2.S.2.5 Process validation and/or evaluation (name, manufacturer)

Process validation and/or evaluation studies for aseptic processing and sterilization should be included.

Where the APIMF procedure is used, a cross-reference to the Restricted part of the APIMF is considered sufficient for this section of the PD.

The following requirements apply to the fourth option for submission of API information where full details are provided in the dossier.

It is expected that the manufacturing processes for all APIs are properly controlled. If the API is prepared as sterile a complete description should be provided of the aseptic processing and/or sterilization methods. A description of the controls used to maintain the sterility of the API during storage and transportation should also be provided. Alternative processes should be justified and described (see guidance in 3.2.S.2.2 for the level of detail expected).

3.2.S.2.6 *Manufacturing process development (name, manufacturer)*

A description and discussion should be provided of the significant changes made to the manufacturing process and/or manufacturing site of the API used in producing comparative bioavailability or biowaiver, scale-up, pilot, and, if available, production scale batches.

Reference should be made to the API data provided in Section 3.2.S.4.4.

Where the APIMF procedure is used, a cross-reference to the Restricted part of the APIMF is considered sufficient for this section of the PD.

3.2.S.3 *Characterization (name, manufacturer)*

3.2.S.3.1 *Elucidation of structure and other characteristics (name, manufacturer)*

Confirmation of structure based on, e.g. synthetic route and spectral analyses should be provided. Information such as the potential for isomerism, the identification of stereochemistry, or the potential for forming polymorphs should also be included.

Elucidation of structure

The PD should include quality assurance (QA) certified copies of the spectra, peak assignments and a detailed interpretation of the data from the studies performed to elucidate and/or confirm the structure of the API. The QOS-PD should include a list of the studies performed and a conclusion from the studies (e.g. whether the results support the proposed structure).

For APIs that are not described in an officially recognized pharmacopoeia, the studies carried out to elucidate and/or confirm the chemical structure normally include elemental analysis, infrared (IR), ultraviolet (UV), nuclear magnetic resonance (NMR) and mass spectra (MS) studies. Other tests could include X-ray powder diffraction (XRPD) and differential scanning calorimetry (DSC).

For APIs that are described in an officially recognized pharmacopoeia it is generally sufficient to provide copies of the IR spectrum of the API from each

of the proposed manufacturer(s) run concomitantly with an officially recognized pharmacopoeial reference standard. See section 3.2.S.5 for details on acceptable reference standards or materials.

Isomerism/stereochemistry

When an API is chiral, it should be specified whether specific stereoisomers or a mixture of stereoisomers have been used in the comparative biostudies, and information should be given as to the stereoisomer of the API that is to be used in the FPP.

Where the potential for stereoisomerism exists, a discussion should be included of the possible isomers that can result from the manufacturing process and the steps where chirality was introduced. The identity of the isomeric composition of the API to that of the API in the comparator product should be established. Information on the physical and chemical properties of the isomeric mixture or single enantiomer should be provided, as appropriate. The API specification should include a test to ensure isomeric identity and purity.

The potential for interconversion of the isomers in the isomeric mixture, or racemization of the single enantiomer should be discussed.

When a single enantiomer of the API is claimed for non-pharmacopoeial APIs, unequivocal proof of absolute configuration of asymmetric centres should be provided, such as determined by X-ray of a single crystal.

If, based on the structure of the API, there is not a potential for stereoisomerism, it is sufficient to include a statement to this effect.

Polymorphism

Many APIs can exist in different physical forms in the solid state. Polymorphism is characterized as the ability of an API to exist as two or more crystalline phases that have different arrangements and/or conformations of the molecules in the crystal lattice. Amorphous solids consist of disordered arrangements of molecules and do not possess a distinguishable crystal lattice. Solvates are crystal forms containing either stoichiometric or nonstoichiometric amounts of a solvent. If the incorporated solvent is water the solvates are also commonly known as hydrates.

Polymorphic forms of the same chemical compound differ in internal solid-state structure and, therefore, may possess different chemical and physical properties, including packing, thermodynamic, spectroscopic, kinetic, interfacial and mechanical properties. These properties can have a direct impact on API processability, pharmaceutical product manufacturability and product quality and performance, including stability, dissolution and bioavailability. The unexpected appearance or disappearance of a polymorphic form may lead to serious pharmaceutical consequences.

Applicants to the WHO Prequalification of Medicines Programme and API manufacturers are expected to have adequate knowledge about the polymorphism of the APIs used and/or produced. Information on polymorphism can come from the scientific literature, patents, compendia or other references to determine if polymorphism is a concern, e.g. for APIs that are not *BCS highly soluble*. In the absence of published data for APIs that are not *BSC highly soluble*, polymorphic screening will be necessary to determine if the API can exist in more than one crystalline form. Polymorphic screening is generally accomplished via crystallization studies using different solvents and conditions.

A number of methods can be used to characterize the polymorphic forms of an API. Demonstration of a non-equivalent structure by single crystal X-ray diffraction is currently regarded as the definitive evidence of polymorphism. XRPD can also be used to provide unequivocal proof of polymorphism. Other methods, including microscopy, thermal analysis (e.g. DSC, thermal gravimetric analysis and hot-stage microscopy) and spectroscopy (e.g. IR, Raman, and solid-state nuclear magnetic resonance (ssNMR)) are helpful for further characterization of polymorphic forms. Where polymorphism is a concern, the applicants or manufacturers of APIs should demonstrate that a suitable method, capable of distinguishing different polymorphs, is available to them.

Decision tree 4(1) of ICH Q6A (6) can be used where screening is necessary and 4(2) can be used to investigate if different polymorphic forms have different properties that may affect performance, bioavailability and stability of the FPP and to decide whether a preferred polymorph should be monitored at release and on storage of the API. Where there is a preferred polymorph, acceptance criteria should be incorporated into the API specification to ensure polymorphic equivalence of the commercial material and that of the API batches used in the comparative bioavailability or biowaiver studies. The polymorphic characterization of the API batches used in comparative bioavailability or biowaiver studies by the above-mentioned methods should be provided. The method used to control polymorphic form should be demonstrated to be specific for the preferred form.

Polymorphism can also include solvation or hydration products (also known as pseudopolymorphs). If the API is used in a solvated form, the following information should be provided:

- specifications for the solvent-free API in 3.2.S.2.4, if that compound is a synthetic precursor;
- specifications for the solvated API including appropriate limits on the weight ratio of API to solvent (with data to support the proposed limits);
- a description of the method used to prepare the solvate in 3.2.S.2.2.

Particle size distribution

For APIs that are not *BCS highly soluble* contained in solid FPPs, or liquid FPPs containing undissolved API, the particle size distribution of the material can have an effect on the in vitro and/or in vivo behaviour of the FPP. Particle size distribution can also be important in dosage form performance (e.g. delivery of inhalation products), achieving uniformity of content in low-dose tablets (e.g. 2 mg or less), desired smoothness in ophthalmic preparations and stability of suspensions.

If particle size distribution is an important parameter (e.g. as in the above cases), results from an investigation of several batches of the API should be provided, including characterization of the batch(es) used in the comparative bioavailability or biowaiver studies. API specifications should include controls on the particle size distribution to ensure consistency with the material in the batch(es) used in the comparative bioavailability and biowaiver studies (e.g. limits for d10, d50 and d90). The criteria should be established statistically, based on the standard deviation of the test results from the previously mentioned studies. The following example is provided for illustrative purposes as possible acceptance criteria for particle size distribution limits:

- d10 not more than (NMT) 10% of total volume less than X µm;
- d50 XX µm–XXX µm;
- d90 not less than (NLT) 90% of total volume less than XXXX µm.

Other controls on particle size distribution can be considered acceptable, if scientifically justified.

Reference documents: ICH Q6A (6).

3.2.5.3.2 *Impurities (name, manufacturer)*

Information on impurities should be provided.

Details on the principles for the control of impurities (e.g. reporting, identification and qualification) are outlined in the ICH Q3A, Q3B and Q3C impurity guidelines (10–12). Additional information elaborating on some of the elements discussed in the ICH guidelines is outlined below.

Regardless of whether a pharmacopoeial standard is claimed, a discussion should be provided of the potential and actual impurities arising from the synthesis, manufacture or degradation of the API. This should cover starting materials, by-products, intermediates, chiral impurities and degradation products and should include the chemical names, structures and origins of the impurities. The discussion of pharmacopoeial APIs should not be limited to the impurities specified in the API monograph.

The tables in the QOS-PD template should be used to summarize the information on the API-related and process-related impurities. In the QOS-PD, the term “origin” refers to how and where the impurity was introduced (e.g. “Synthetic intermediate from Step 4 of the synthesis” or “Potential by-product due to rearrangement from Step 6 of the synthesis”). It should also be indicated if the impurity is a metabolite of the API.

The ICH thresholds for reporting, identification (used to set the limit for individual unknown impurities) and qualification are determined on the basis of potential exposure to the impurity, e.g. by the maximum daily dose (MDD) of the API. For APIs available in multiple dosage forms and strengths having different MDD values, it is imperative that the thresholds and corresponding controls for each of the presentations be considered to ensure that the risks posed by impurities have been addressed. This is normally achieved by using the highest potential daily MDD, rather than the maintenance dose. For parenteral products the maximum hourly dose of the API should also be included.

It is acknowledged that APIs of semi-synthetic origin do not fall within the scope of the ICH impurity guidelines. However, depending on the nature of the API and the extent of the chemical modification steps, the principles regarding the control of impurities (e.g. reporting, identification and qualification) could be extended to apply to APIs of semi-synthetic origin. As an illustrative example, an API whose precursor molecule was derived from a fermentation process or a natural product of plant or animal origin, which has subsequently undergone several chemical modification reactions, would generally fall within the scope of the ICH impurity guidelines, whereas an API whose sole chemical step was the formation of a salt from a fermentation product generally would not. It is understood that there is some latitude for these types of APIs.

Identification of impurities

It is recognized by the pharmacopoeias that APIs can be obtained from various sources and thus can contain impurities not considered during the development of the monograph. Furthermore, a change in the production or source may give rise to additional impurities that are not adequately controlled by the official compendial monograph. As a result each PD is assessed independently to consider the potential impurities that may arise from the proposed route(s) of synthesis. For these reasons the ICH limits for unspecified impurities (e.g. NMT 0.10% or 1.0 mg per day intake (whichever is lower) for APIs having an MDD \leq 2 g/day) are generally recommended, rather than the general limits for unspecified impurities that may appear in the official compendial monograph, which could potentially be higher than the applicable ICH limit.

Qualification of impurities

The ICH impurity guidelines should be consulted for options on the qualification of impurities. The limit specified for an identified impurity in an officially recognized pharmacopoeia is generally considered to be qualified. The following is an additional option for qualification of impurities in existing APIs:

The limit for an impurity present in an existing API can be accepted by comparing the results of tests for impurities found in the existing API with those observed in an innovator product using the same validated, stability-indicating analytical procedure (e.g. comparative (high-performance liquid chromatography (HPLC) studies). If samples of the innovator product are not available, the impurity profile may also be compared to a different prequalified FPP with the same route of administration and similar characteristics (e.g. tablet versus capsule). It is recommended that the studies be conducted on comparable samples (e.g. samples of a similar age) to obtain a meaningful comparison of the impurity profiles.

Levels of impurities generated from studies under accelerated or stressed storage conditions of the innovator or prequalified FPP are not considered acceptable/qualified.

A specified impurity present in the existing API is considered qualified if the amount of the impurity in the existing API reflects the levels observed in the innovator or prequalified FPP.

Basis for setting the acceptance criteria

The basis for setting the acceptance criteria for the impurities should be provided. This is established by considering the identification and qualification thresholds for API-related impurities (e.g. starting materials, by-products, intermediates, chiral impurities or degradation products) and the concentration limits for process-related impurities (e.g. residual solvents) according to the applicable ICH guidelines (e.g. Q3A (10), Q3C (12)).

The qualified level should be considered as the maximum allowable limit. However, limits which are considerably wider than the actual manufacturing process capability are generally discouraged. For this reason the acceptance criteria are also set taking into consideration the actual levels of impurities found in several batches of the API from each manufacturer, including the levels found in the batches used for the comparative bioavailability or biowaiver studies. When reporting the results of quantitative tests, the actual numerical results should be provided rather than vague statements such as “within limits” or “conforms”. In cases where a large number of batches have been tested it is acceptable to summarize the results of all the batches tested with a range of analytical results.

If there are identified impurities specified in an official compendial monograph that are not controlled by the proposed routine in-house analytical procedure, a justification for their exclusion from routine analyses should be provided (e.g. “Impurities D, E and F listed in *The International Pharmacopoeia* (Ph.Int.) monograph are not potential impurities from the proposed route of synthesis used by manufacturer X”). If acceptable justification cannot be provided it should be demonstrated that the routine in-house method is capable of separating and detecting the impurities specified in the official compendial monograph at an acceptable level (e.g. 0.10%). If such a demonstration cannot be performed, a one-time study should be conducted applying the pharmacopoeial method to several recent batches to demonstrate the absence of the impurities listed in the pharmacopoeia.

ICH class II solvent(s) used prior to the last step of the manufacturing process may be exempted from routine control in API specifications if suitable justification is provided. Submission of results demonstrating less than 10% of the ICH Q3C limit (option I) of the solvent(s) in three consecutive production-scale batches or six consecutive pilot-scale batches of the API or a suitable intermediate would be considered acceptable justification. The last step solvents used in the process should always be routinely controlled in the final API.

For guidance on acceptable residual solvent limits refer to ICH Q3C (12). The limit for residues of triethylamine (TEA) is either 320 ppm on the basis of ICH Q3C option I or 3.2 mg/day on the basis of permitted daily exposure (PDE).

The absence of known, established highly toxic impurities (genotoxic) used in the process or formed as a by-product should be discussed and suitable limits should be proposed. The limits should be justified by appropriate reference to available guidance (e.g. EMEA/CHMP/QWP/ 251344/2006 (13) or USFDA Guidance for Industry. *Genotoxic and carcinogenic impurities in drug substances and products, recommended approaches* (14)) or by providing experimental safety data or published data in peer-reviewed journals.

Residues of metal catalysts used in the manufacturing process and determined to be present in batches of API are to be controlled in specifications. This requirement does not apply to metals that are deliberate components of the pharmaceutical substance (such as a counter ion of a salt) or metals that are used as a pharmaceutical excipient in the FPP (e.g. an iron oxide pigment). The guideline on the specification limits for residues of metal catalysts or metal reagents (EMEA/CHMP/SWP/4446/2000 (15)) or any equivalent approaches can be used to address this issue. The requirement normally does not apply to extraneous metal contaminants that are more appropriately addressed by GMP, good distribution practices (GDP) or any other relevant quality provision such as the heavy metal test in monographs of recognized pharmacopoeias that cover metal contamination originating from manufacturing equipment and the environment.

Reference documents: ICH Q6A, Q3A, Q3C (6, 10, 12).

3.2.5.4 Control of the API (name, manufacturer)

3.2.5.4.1 Specification (name, manufacturer)

The specification for the API should be provided.

As defined in ICH's Q6A guideline (6), a specification is:

“A list of tests, references to analytical procedures and appropriate acceptance criteria, which are numerical limits, ranges, or other criteria for the tests described. It establishes the set of criteria to which an API or FPP should conform to be considered acceptable for its intended use. ‘Conformance to specifications’ means that the API and/or FPP, when tested according to the listed analytical procedures, will meet the listed acceptance criteria. Specifications are critical quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities.”

Copies of the API specifications, dated and signed by authorized personnel (e.g. the person in charge of the quality control or quality assurance department) should be provided in the PD, including specifications from each API manufacturer as well as those of the FPP manufacturer.

The FPP manufacturer's API specification should be summarized according to the table in the QOS-PD template under the headings: tests, acceptance criteria and analytical procedures (including types, sources and versions for the methods).

- The *standard* declared by the applicant could be an officially recognized compendial standard (e.g. BP, JP, Ph.Eur., Ph.Int., USP) or an in-house (manufacturer's) standard.
- The specification reference number and version (e.g. revision number and/or date) should be provided for version control purposes.
- For the analytical procedures, the type should indicate the kind of analytical procedure used (e.g. visual, IR, UV, HPLC or laser diffraction), the source refers to the origin of the analytical procedure (e.g. BP, JP, Ph.Eur., Ph.Int., USP or in-house) and the version (e.g. code number/version/date) should be provided for version control purposes.

In cases where there is more than one API manufacturer, the FPP manufacturer's API specifications should be one single compiled set of specifications that is identical for each manufacturer. It is acceptable to lay down in the specification more than one acceptance criterion and/or analytical method

for a single parameter with the statement “for API from manufacturer A” (e.g. in the case of residual solvents).

Any non-routine testing should be clearly identified as such and justified together with the proposal on the frequency of non-routine testing.

The ICH Q6A guideline (6) outlines recommendations for a number of universal and specific *tests* and criteria for APIs.

Reference documents: ICH Q6A, Q3A, Q3C (6, 10, 12) and officially recognized pharmacopoeias.

3.2.S.4.2 *Analytical procedures (name, manufacturer)*

The analytical procedures used for testing the API should be provided.

Copies of the in-house analytical procedures used to generate testing results provided in the PD, as well as those proposed for routine testing of the API by the FPP manufacturer, should be provided. Unless modified it is not necessary to provide copies of officially recognized compendial analytical procedures.

Tables for summarizing a number of the different analytical procedures and validation information (e.g. HPLC assay/impurity methods, gas chromatography (GC) methods) can be found in the 2.3.R Regional information section of the QOS-PD (i.e. 2.3.R.2). These tables should be used to summarize the in-house analytical procedures of the FPP manufacturer for determination of the residual solvents, assay and purity of the API, in section 2.3.S.4.2 of the QOS-PD. Other methods used to generate assay and purity data in the PD can be summarized in 2.3.S.4.4 (c) or 2.3.S.7.3 (b) of the QOS-PD. Officially recognized compendial methods need not be summarized unless modifications have been made.

Although HPLC is normally considered the method of choice for determining API-related impurities, other chromatographic methods such as GC and thin-layer chromatography (TLC) can also be used if appropriately validated. For determination of related substances, reference standards should normally be available for each of the identified impurities, particularly those known to be toxic and the concentration of the impurities should be quantified against their own reference standards. Impurity standards may be obtained from pharmacopoeias (individual impurities or resolution mixtures), from commercial sources or prepared in-house. It is considered acceptable to use the API as an external standard to estimate the levels of impurities, provided the response factors of those impurities are sufficiently close to that of the API, i.e. between 80 and 120%. In cases where the response factor is outside this range it may still be acceptable to use the API, provided a correction factor is applied. Data to support calculation of the correction factor should be provided for an in-house method. Unspecified impurities may be quantified using a solution of the API as the reference standard at a concentration corresponding to the limit established for individual unspecified impurities

(e.g. 0.10%). The test for related substances in the Ph.Int. monograph for lamivudine serves as a typical example.

The system suitability tests (SSTs) represent an integral part of the method and are used to ensure the satisfactory performance of the chosen chromatographic system. As a minimum, HPLC and GC purity methods should include SSTs for resolution and repeatability. For HPLC methods to control API-related impurities, this is typically done using a solution of the API with a concentration corresponding to the limit for unspecified impurities. Resolution of the two closest eluting peaks is generally recommended. However, the choice of alternative peaks can be used if justified (e.g. choice of a toxic impurity). In accordance with the Ph.Int. section on Methods of analysis the repeatability test should include an acceptable number of replicate injections. HPLC assay methods should include SSTs for repeatability and in addition either peak asymmetry, theoretical plates or resolution. For TLC methods, the SSTs should verify the ability of the system to separate and detect the analyte(s) (e.g. by applying a spot corresponding to the API at a concentration corresponding to the limit of unspecified impurities).

Reference documents: ICH Q2 (16), *WHO Technical Report Series*, No. 943, Annex 3 (17).

3.2.S.4.3 *Validation of analytical procedures (name, manufacturer)*

Analytical validation information, including experimental data for the analytical procedures used for testing the API, should be provided.

Copies should be provided of the validation reports for the analytical procedures used to generate testing results provided in the PD, as well as those proposed for routine testing of the API by the FPP manufacturer.

Tables for summarizing a number of the different analytical procedures and the validation information (e.g. HPLC assay and impurity methods, GC methods) can be found in the 2.3.R Regional information section of the QOS-PD (i.e. 2.3.R.2). These tables should be used to summarize the validation information of the analytical procedures of the FPP manufacturer for determination of residual solvents, assay and purity of the API, in section 2.3.S.4.3 of the QOS-PD. The validation data for other methods used to generate assay and purity data in the PD can be summarized in 2.3.S.4.4 (c) or 2.3.S.7.3 (b) of the QOS-PD.

As recognized by regulatory authorities and pharmacopoeias themselves, verification of compendial methods can be necessary. The compendial methods as published are typically validated based on an API or an FPP originating from a specific manufacturer. Different sources of the same API or FPP can contain impurities and/or degradation products that were not considered during the development of the monograph. Therefore, the monograph and compendial

method should be demonstrated as suitable to control the impurity profile of the API from the intended source(s).

In general verification is not necessary for compendial API assay methods. However, specificity of a specific compendial assay method should be demonstrated if there are any potential impurities that are not specified in the compendial monograph. If an officially recognized compendial method is used to control API-related impurities that are not specified in the monograph, full validation of the method is expected with respect to those impurities.

If an officially recognized compendial standard is claimed and an in-house method is used in lieu of the compendial method (e.g. for assay or for specified impurities), equivalence of the in-house and compendial methods should be demonstrated. This could be accomplished by performing duplicate analyses of one sample by both methods and providing the results from the study. For impurity methods the sample analysed should be the API spiked with impurities at concentrations equivalent to their specification limits.

Reference documents: ICH Q2 (16).

3.2.5.4.4 *Batch analyses (name, manufacturer)*

Description of batches and results of batch analyses should be provided.

The information provided should include batch number, batch size, date and production site of relevant API batches used in comparative bioavailability or biowaiver studies, preclinical and clinical data (if relevant), stability, pilot, scale-up and, if available, production-scale batches. These data are used to establish the specifications and evaluate consistency in API quality.

Analytical results should be provided from at least two batches of at least pilot scale from each proposed manufacturing site of the API and should include the batch(es) used in the comparative bioavailability or biowaiver studies. A pilot-scale batch should be manufactured by a procedure fully representative of and simulating that to be applied to a full production-scale batch.

Copies of the certificates of analysis, both from the API manufacturer(s) and the FPP manufacturer, should be provided for the profiled batches and any company responsible for generating the test results should be identified. The FPP manufacturer's test results should be summarized in the QOS-PD.

The discussion of results should focus on observations noted for the various tests, rather than reporting comments such as "all tests meet specifications". For quantitative tests (e.g. individual and total impurity tests and assay tests), it should be ensured that actual numerical results are provided rather than vague statements such as "within limits" or "conforms".

A discussion and justification should be provided for any incomplete analyses (e.g. results not tested according to the proposed specification).

Reference documents: ICH Q6A, Q3A, Q3C (6, 10, 12).

3.2.5.4.5 *Justification of specification (name, manufacturer)*

Justification for the API specification should be provided.

A discussion should be provided on the inclusion of certain tests, evolution of tests, analytical procedures and acceptance criteria, and differences from the officially recognized compendial standard(s). If the officially recognized compendial methods have been modified or replaced a discussion of the modifications or replacement method(s) should be included.

The justification for certain tests, analytical procedures and acceptance criteria may have been discussed in other sections of the PD (e.g. for impurities or particle size distribution) and does not need to be repeated here, although a cross-reference should be provided.

Reference documents: ICH Q6A, Q3A, Q3C (6, 10, 12), and officially recognized pharmacopoeias.

3.2.5.5 *Reference standards or materials (name, manufacturer)*

Information on the reference standards or reference materials used for testing of the API should be provided.

Information should be provided on the reference standard(s) used to generate data in the PD, as well as those to be used by the FPP manufacturer in routine API and FPP testing.

The source(s) of the reference standards or materials used in the testing of the API should be provided (e.g. those used for the identification, purity and assay tests). These could be classified as primary or secondary reference standards.

A suitable primary reference standard should be obtained from an officially recognized pharmacopoeial source (e.g. BP, JP, Ph.Eur., Ph.Int., USP) where one exists, and the lot number should be provided. Where a pharmacopoeial standard is claimed for the API and/or the FPP, the primary reference standard should be obtained from that pharmacopoeia when available. Primary reference standards from officially recognized pharmacopoeial sources do not need further structural elucidation.

Otherwise a primary standard may be a batch of the API that has been fully characterized (e.g. by IR, UV, NMR and mass spectrometry (MS) analyses). Further purification techniques may be needed to render the material acceptable for use as a chemical reference standard. The purity requirements for a chemical reference substance depend upon its intended use. A chemical reference substance proposed for an identification test does not require meticulous purification since the presence of a small percentage of impurities in the substance often has no noticeable effect on the test. On the other hand, chemical reference substances that are to be used in assays should possess a high degree of purity (such as 99.5% on the dried or water/solvent free basis). Absolute content of the primary

reference standard must be declared and should follow the scheme: 100% minus organic impurities (quantified by an assay procedure, e.g. HPLC or DSC) minus inorganic impurities minus volatile impurities by loss on drying (or water content minus residual solvents).

A secondary (or in-house) reference standard can be used by establishing it against a suitable primary reference standard, e.g. by providing legible copies of the IR of the primary and secondary reference standards run concomitantly and by providing its certificate of analysis, including assay determined against the primary reference standard. A secondary reference standard is often characterized and evaluated for its intended purpose with additional procedures other than those used in routine testing (e.g. if additional solvents are used during the additional purification process that are not used for routine purposes).

Reference standards should normally be established for specified impurities. Refer to 3.2.S.4.2 for additional guidance.

Reference documents: ICH Q6A (6), *WHO Technical Report Series*, No. 943, Annex 3 (17).

3.2.5.6 Container-closure system (name, manufacturer)

A description of the container-closure system(s) should be provided, including the identity of materials of construction of each primary packaging component, and their specifications. The specifications should include description and identification (and critical dimensions with drawings, where appropriate). Non-compendial methods (with validation) should be included, where appropriate.

For non-functional secondary packaging components (e.g. those that do not provide additional protection), only a brief description should be provided. For functional secondary packaging components, additional information should be provided.

The suitability should be discussed with respect to, for example, choice of materials, protection from moisture and light, compatibility of the materials of construction with the API, including sorption to container and leaching, and/or safety of materials of construction.

The WHO *Guidelines on packaging for pharmaceutical products* (18) and the officially recognized pharmacopoeias should be consulted for recommendations on the packaging information for APIs.

Primary packaging components are those that are in direct contact with the API or FPP. The specifications for the primary packaging components should be provided and should include a specific test for identification (e.g. IR).

Copies of the labels applied on the secondary packaging of the API should be provided and should include the conditions of storage. In addition, the name and address of the manufacturer of the API should be stated on the

container, regardless of whether relabelling is conducted at any stage during the API distribution process.

3.2.S.7 Stability (name, manufacturer)

3.2.S.7.1 Stability summary and conclusions (name, manufacturer)

The types of studies conducted, protocols used, and the results of the studies should be summarized. The summary should include results, for example, from forced degradation studies and stress conditions, as well as conclusions with respect to storage conditions and retest date or shelf-life, as appropriate.

The WHO guidelines *Stability testing of active pharmaceutical ingredients and finished pharmaceutical products* (19) should be consulted for recommendations on the core stability data package required for the prequalification of APIs and FPPs.

As outlined in the WHO stability guidelines, the purpose of stability testing is to: “provide evidence of how the quality of an API or FPP varies with time under the influence of a variety of environmental factors such as temperature, humidity and light.”

The tables in the QOS-PD template should be used to summarize the results from the stability studies and related information (e.g. conditions, testing parameters, conclusions and commitments).

Stress testing

As outlined in the ICH Q1A guidance document (20), stress testing of the API can help identify the likely degradation products which, in turn, can help to establish the degradation pathways and the intrinsic stability of the molecule and validate the stability-indicating power of the analytical procedures used. The nature of the stress testing will depend on the individual API and the type of FPP involved.

Stress testing may be carried out on a single batch of the API. For examples of typical stress conditions refer to section 2.1.2 of *WHO Technical Report Series*, No. 953, Annex 2 (19), as well as, “A typical set of studies of the degradation paths of an active pharmaceutical ingredient”, in: *WHO Technical Report Series*, No. 929, Annex 5, Table A1 (21).

The objective of stress testing is not to completely degrade the API but to cause degradation to occur to a small extent, typically 10–30% loss of API by assay when compared with non-degraded API. This target is chosen so that some degradation occurs, but not enough to generate secondary products. For this reason the conditions and duration may need to be varied when the API is especially susceptible to a particular stress factor. In the total absence of degradation products after 10 days the API is considered stable under the particular stress condition.

The tables in the QOS-PD template should be used to summarize the results of the stress testing and should include the treatment conditions (e.g. temperatures, relative humidities, concentrations of solutions and durations) and the observations for the various test parameters (e.g. assay, degradation products). The discussion of results should highlight whether mass balance was observed.

Photostability testing should be an integral part of stress testing. The standard conditions are described in ICH Q1B (22). If “protect from light” is stated in one of the officially recognized pharmacopoeias for the API, it is sufficient to state “protect from light” on labelling, in lieu of photostability studies when the container-closure system is shown to be light protective.

When available it is acceptable to provide the relevant data published in the scientific literature (including, but not limited to, WHO Public Assessment Reports (WHOPARs), European Public Assessment Reports (EPARs)) to support the identified degradation products and pathways.

Accelerated and long-term testing

Available information on the stability of the API under accelerated and long-term storage conditions should be provided, including information in the public domain or obtained from scientific literature. The source of the information should be identified.

The required long-term storage conditions for APIs in the WHO Prequalification of Medicines Programme are either $30\text{ }^{\circ}\text{C} \pm 2\text{ }^{\circ}\text{C}/65\% \pm 5\% \text{ RH}$ or $30\text{ }^{\circ}\text{C} \pm 2\text{ }^{\circ}\text{C}/75\% \pm 5\% \text{ RH}$. Studies covering the proposed retest period under the above-mentioned long-term storage conditions will provide better assurance of the stability of APIs at the conditions of the supply chain corresponding to the WHO and its Prequalification of Medicines Programme environments. Alternative conditions should be supported with appropriate evidence, which may include literature references or in-house studies, demonstrating that storage at $30\text{ }^{\circ}\text{C}$ is inappropriate for the API. For APIs intended for storage in a refrigerator and those intended for storage in a freezer, refer to the WHO stability guidelines in the *WHO Technical Report Series*, No. 953, Annex 2 (19). APIs intended for storage below $-20\text{ }^{\circ}\text{C}$ should be treated on a case-by-case basis.

To establish the retest period, data should be provided on not less than three batches of at least pilot scale. The batches should be manufactured by the same synthesis route as production batches and using a method of manufacture and a procedure that simulates the final process to be used for production batches. The stability testing programme should be summarized and the results of stability testing should be summarized in the dossier and in the tables in the QOS-PD.

The information on the stability studies should include details such as storage conditions, batch number, batch size, container-closure system and completed (and proposed) test intervals. The discussion of results should focus

on observations noted for the various tests, rather than reporting comments such as “all tests meet specifications”. Ranges of analytical results where relevant and any trends that were observed should be included. For quantitative tests (e.g. individual and total degradation product tests and assay tests), it should be ensured that actual numerical results are provided rather than vague statements such as “within limits” or “conforms”. Where methods are different from those described in S.4.2, descriptions and validation of the methodology used in stability studies should be provided.

The minimum data required at the time of submitting the dossier (in the general case) are shown in Table 1.

Table 1
Minimum data required at the time of submitting the dossier

Storage temperature (°C)	Relative humidity (%)	Minimum time period (months)
Accelerated 40 ± 2	75 ± 5	6
Intermediate ^a	— ^a	— ^a
Long-term 30 ± 2	65 ± 5 or 75 ± 5	6

^aWhere long-term conditions are 30 °C ± 2 °C/65% ± 5% RH or 30 °C ± 2 °C/75% ± 5% RH, there is no intermediate condition.

Refer to *WHO Technical Report Series*, No. 953, Annex 2 (19) for further information regarding the storage conditions, container-closure system, test specifications and testing frequency.

Proposed storage statement and retest period

A storage statement should be established for display on the label, based on the stability evaluation of the API. The WHO stability guidelines include a number of recommended storage statements that should be used when supported by the stability studies.

A retest period should be derived from the stability information and should be displayed on the container label.

After this retest period a batch of API destined for use in the manufacture of an FPP could be retested and then, if in compliance with the specification, could be used immediately (e.g. within 30 days). If retested and found compliant, the batch does not receive an additional period corresponding to the time established for the retest period. However, an API batch can be retested multiple times and a different portion of the batch used after each retest, as long as it

continues to comply with the specification. For APIs known to be labile (e.g. certain antibiotics) it is more appropriate to establish a shelf-life than a retest period (20).

Limited extrapolation of the real-time data from the long-term storage condition beyond the observed range to extend the retest period can be done at the time of assessment of the PD, if justified. Applicants should consult the ICH Q1E guideline (23) for further details on the evaluation and extrapolation of results from stability data (e.g. if significant change was not observed within 6 months at accelerated conditions and the data show little or no variability, the proposed retest period could be up to twice the period covered by the long-term data, but should not exceed the long-term data by more than 12 months).

Reference documents: ICH Q1A (20), Q1B (22), Q1D (24), Q1E (23), *WHO Technical Report Series*, No. 953, Annex 2 (19).

3.2.S.7.2 *Post-approval stability protocol and stability commitment (name, manufacturer)*

The post-approval stability protocol and stability commitment should be provided.

Primary stability study commitment

When the available long-term stability data on primary batches do not cover the proposed retest period granted at the time of assessment of the PD, a commitment should be made to continue the stability studies in order to firmly establish the retest period. A written commitment (signed and dated) to continue long-term testing over the retest period should be included in the dossier when relevant.

Commitment stability studies

The long-term stability studies for the commitment batches should be conducted through the proposed retest period on at least three production batches. Where stability data were not provided for three production batches, a written commitment (signed and dated) should be included in the dossier.

The stability protocol for the commitment batches should be provided and should include, but not be limited to, the following parameters:

- number of batch(es) and different batch sizes, if applicable;
- relevant physical, chemical, microbiological and biological test methods;
- acceptance criteria;
- reference to test methods;
- description of the container-closure system(s);

- testing frequency;
- description of the conditions of storage (standardized conditions for long-term testing as described in these guidelines and consistent with the API labelling, should be used);
- other applicable parameters specific to the API.

Ongoing stability studies

The stability of the API should be monitored according to a continuous and appropriate programme that will permit the detection of any stability issue (e.g. changes in levels of degradation products). The purpose of the ongoing stability programme is to monitor the API and to determine that the API remains stable and can be expected to remain stable within the retest period in all future batches.

At least one production batch per year of API (unless none is produced during that year) should be added to the stability monitoring programme and tested at least annually to confirm the stability. In certain situations, additional batches should be included. A written commitment (signed and dated) to ongoing stability studies should be included in the dossier.

Refer to section 2.1.11 of *WHO Technical Report Series*, No. 953, Annex 2 (19), for further information on ongoing stability studies.

Any differences between the stability protocols used for the primary batches and those proposed for the commitment batches or ongoing batches should be scientifically justified.

Reference documents: ICH Q1A (20), Q1B (22), Q1D (24), Q1E (23), *WHO Technical Report Series*, No. 953, Annex 2 (19).

3.2.5.7.3 Stability data (name, manufacturer)

Results of the stability studies (e.g. forced degradation studies and stress conditions) should be presented in an appropriate format such as tabular, graphical, or narrative. Information on the analytical procedures used to generate the data and validation of these procedures should be included.

The actual stability results used to support the proposed retest period should be included in the dossier. For quantitative tests (e.g. individual and total degradation product tests and assay tests) it should be ensured that actual numerical results are provided rather than vague statements such as “within limits” or “conforms”.

Reference documents: ICH Q1A (20), Q1B (22), Q1D (24), Q1E (23), Q2 (16) *WHO Technical Report Series*, No. 953, Annex 2 (19).

3.2.P Drug product (or finished pharmaceutical product (FPP))

3.2.P.1 Description and composition of the FPP (name, dosage form)

A description of the FPP and its composition should be provided. The information provided should include, for example:

- **Description of the dosage form**

The description of the FPP should include the physical description, available strengths, release mechanism (e.g. immediate or modified (delayed or extended)), as well as any other distinguishable characteristics, e.g.

“The proposed XYZ 50-mg tablets are available as white, oval, film-coated tablets, debossed with ‘50’ on one side and a break-line on the other side.

The proposed XYZ 100-mg tablets are available as yellow, round, film-coated tablets, debossed with ‘100’ on one side and plain on the other side.”

- **Composition, i.e. list of all components of the dosage form, and their amount on a per unit basis (including overages, if any), the function of the components, and a reference to their quality standards (e.g. compendial monographs or manufacturer’s specifications).**

The tables in the QOS-PD template should be used to summarize the composition of the FPP and express the quantity of each component on a per unit basis (e.g. mg per tablet, mg per ml, mg per vial) and a percentage basis, including a statement of the total weight or measure of the dosage unit. The individual components for mixtures prepared in-house (e.g. coatings) should be included in the tables where applicable.

All components used in the manufacturing process should be listed, including those that may not be added to every batch (e.g. acid and alkali), those that may be removed during processing (e.g. solvents) and any others (e.g. nitrogen or silicon for stoppers). If the FPP is formulated using an active moiety, then the composition for the active ingredient should be clearly indicated (e.g. “1 mg of active ingredient base = 1.075 mg active ingredient hydrochloride”). All overages should be clearly indicated (e.g. “contains 2% overage of the API to compensate for manufacturing losses”).

The components should be declared by their proper or common names, quality standards (e.g. BP, JP, Ph.Eur., Ph.Int., USP, in-house) and, if applicable, their grades (e.g. “microcrystalline cellulose NF (PH 102)”) and special technical characteristics (e.g. lyophilized, micronized, solubilized or emulsified).

The function of each component (e.g. diluent or filler, binder, disintegrant, lubricant, glidant, granulating solvent, coating agent or antimicrobial preservative) should be stated. If an excipient performs multiple functions the predominant function should be indicated.

The qualitative composition, including solvents, should be provided for all proprietary components or blends (e.g. capsule shells, colouring blends or imprinting inks). This information (excluding the solvents) is to be listed in the product information (e.g. summary of product characteristics, labelling and package leaflet).

- **Description of accompanying reconstitution diluent(s)**

For FPPs supplied with reconstitution diluent(s) that are commercially available or that have been assessed and considered acceptable in connection with another PD with the WHO Prequalification of Medicines Programme, a brief description of the reconstitution diluents(s) should be provided.

For FPPs supplied with reconstitution diluent(s) that are not commercially available or have not been assessed and considered acceptable in connection with another PD with the WHO Prequalification of Medicines Programme, information on the diluent(s) should be provided in a separate FPP portion (“3.2.P”), as appropriate.

- **Type of container and closure used for the dosage form and accompanying reconstitution diluent, if applicable**

The container-closure used for the FPP (and accompanying reconstitution diluent, if applicable) should be briefly described, with further details provided under 3.2.P.7 Container-closure system, e.g.

“The product is available in HDPE bottles with polypropylene caps (in sizes of 100s, 500s and 1000s) and in PVC/aluminium foil unit dose blisters (in packages of 100s) (cards of 5 × 2, 10 cards per package).”

Reference documents: ICH Q6A (6).

3.2.P.2 Pharmaceutical development (name, dosage form)

The Pharmaceutical development section should contain information on the development studies conducted to establish that the dosage form, the formulation, manufacturing process, container-closure system, microbiological attributes and usage instructions are appropriate for the purpose specified in the product dossier. The studies described here are distinguished from routine control tests conducted according to specifications. Additionally, this

section should identify and describe the formulation and process attributes (critical parameters) that can influence batch reproducibility, product performance and FPP quality. Supportive data and results from specific studies or published literature can be included within or attached to the Pharmaceutical development section. Additional supportive data can be referenced to the relevant nonclinical or clinical sections of the product dossier.

Pharmaceutical development information should include, at a minimum:

- the definition of the quality target product profile (QTPP) as it relates to quality, safety and efficacy, considering, for example, the route of administration, dosage form, bioavailability, strength and stability;
- identification of the potential critical quality attributes (CQAs) of the FPP so as to adequately control the product characteristics that could have an impact on quality;
- discussion of the potential CQAs of the API(s), excipients and container-closure system(s) including the selection of the type, grade and amount to deliver drug product of the desired quality;
- discussion of the selection criteria for the manufacturing process and the control strategy required to manufacture commercial lots meeting the QTPP in a consistent manner.

These features should be discussed as part of the product development using the principles of risk management over the entire life-cycle of the product (ICH Q8) (25).

For a discussion of additional pharmaceutical development issues specific to the development of FDCs reference should be made to section 6.3.2 of *WHO Technical Report Series*, No. 929, Annex 5 (21).

Reference documents: ICH Q6A (6), Q8 (25), Q9 (26), Q10 (27).

3.2.P.2.1 *Components of the FPP (name, dosage form)*

3.2.P.2.1.1 *Active pharmaceutical ingredient (name, dosage form)*

The compatibility of the API with excipients listed in 3.2.P.1 should be discussed. Additionally, key physicochemical characteristics (e.g. water content, solubility, particle size distribution, polymorphic or solid state form) of the API that can influence the performance of the FPP should be discussed. For FDCs, the compatibility of APIs with each other should be discussed.

Physicochemical characteristics of the API may influence both the manufacturing capability and the performance of the FPP.

Guidance on compatibility studies is provided in Appendix 3 of the WHO *Guidelines for registration of fixed-dose combination medicinal products* (WHO Technical Report Series, No. 929, Annex 5, 2005) (21). In addition to visual examination, chromatographic results (assay, purity) are required to demonstrate API-API and API-excipient compatibility. In general, API-excipient compatibility is not required to be established for specific excipients when evidence is provided (e.g. in the SmPC or product leaflet) that the excipients are present in the comparator product.

3.2.P.2.1.2 *Excipients (name, dosage form)*

The choice of excipients listed in 3.2.P.1, their concentration and their characteristics that can influence the FPP performance should be discussed relative to their respective functions.

When choosing excipients those with a compendial monograph are generally preferred and may be required in certain jurisdictions. Other resources are available for information on acceptable excipients and their concentrations, such as the US Food and Drug Administration (FDA) inactive ingredient guide (IIG) list (28) and the *Handbook of pharmaceutical excipients* (29). Use of excipients in concentrations outside established ranges is discouraged and generally requires justification (30). In addition, available guidelines should be referenced which discuss particular excipients to be avoided, for example azo-colourants as listed in the EMA Guideline CPMP/463/00 (31). Other guidance such as the WHO *Guidelines on development of paediatric medicines: points to consider in formulation* (32) may provide useful general guidance in this regard.

Ranges in concentrations or alternatives for excipients are normally not accepted unless supported by appropriate process validation data. Where relevant, compatibility study results (e.g. on compatibility of a primary or secondary amine API with lactose) should be included to justify the choice of excipients. Specific details should be provided where necessary (e.g. on use of potato or corn starch).

Where antioxidants are included in the formulation, the effectiveness of the proposed concentration of the antioxidant should be justified and verified by appropriate studies.

Antimicrobial preservatives are discussed in 3.2.P.2.5.

3.2.P.2.2 *Finished pharmaceutical product (name, dosage form)*

3.2.P.2.2.1 *Formulation development (name, dosage form)*

A brief summary describing the development of the FPP should be provided, taking into consideration the proposed route of administration and usage. The differences between the comparative bioavailability or biowaiver formulations and the formulation (i.e. composition) described in 3.2.P.1 should be discussed. Results from comparative in vitro studies (e.g. dissolution) or comparative in vivo studies (e.g. bioequivalence) should be discussed, when appropriate.

The WHO Prequalification of Medicines Programme defines an established multisource product as one that has been marketed by the applicant or manufacturer associated with the dossier for at least five years and for which at least 10 production batches were produced over the previous year or, if less than 10 batches were produced in the previous year, not less than 25 batches were produced in the previous three years. For products that meet the criteria of an established multisource product, all sections of P.2.2.1 of the dossier and QOS-PD should be completed with the exception of P.2.2.1 (a). In addition, a product quality review should be provided as outlined in Appendix 2.

The requirements for bioequivalence studies should be taken into consideration, for example, when formulating multiple strengths and/or when the product(s) may be eligible for a biowaiver. WHO reference documents (e.g. *WHO Technical Report Series*, No. 937, Annex 7) (33) should be consulted.

Product scoring may be recommended or required, for example, when scoring is indicated in the WHO Invitation for EOIs, or is specified for an invited FPP in the listing of recommended comparator products, or when division into fractional doses may be necessary according to approved posology.

If the proposed FPP is a functionally scored tablet a study should be undertaken to ensure the uniformity of dose in the tablet fragments. The data provided in the PD should include a description of the test method, individual values, mean and relative standard deviation (RSD) of the results. Uniformity testing (i.e. content uniformity for split portions containing less than 5 mg or less than 5% of the weight of the dosage unit portion, or mass uniformity for

other situations) should be performed on each split portion from a minimum of 10 randomly selected whole tablets. As an illustrative example, the number of units (i.e. the splits) would be 10 halves for bisected tablets (one half of each tablet is retained for the test) or 10 quarters for quadrisectioned tablets (one quarter of each tablet is retained for the test). At least one batch of each strength should be tested. Ideally the study should cover a range of the hardness values. The splitting of the tablets should be performed in a manner that would be representative of that used by the consumer (e.g. manually split by hand). The uniformity test on split portions can be demonstrated on a one-time basis and does not need to be added to the FPP specification(s). The tablet description in the FPP specification and in the product information (e.g. SmPC, labelling and package leaflet) should reflect the presence of a score.

If splitting of a tablet is intended for preparation of a paediatric dose a demonstration of content uniformity of tablet fragments may be required.

Where relevant, labelling should state that the score line is only to facilitate breaking for ease of swallowing and not to divide the tablet into equal doses.

In vitro dissolution or drug release

A discussion should be included as to how the development of the formulation relates to development of the dissolution method(s) and the generation of the dissolution profile.

The results of studies justifying the choice of in vitro dissolution or drug release conditions (e.g. apparatus, rotation speed and medium) should be provided. Data should also be submitted to demonstrate whether the method is sensitive to changes in manufacturing processes and/or changes in grades and/or amounts of critical excipients and particle size where relevant. The dissolution method should be sensitive to any changes in the product that would result in a change in one or more of the pharmacokinetic parameters. Use of a single point test or a dissolution range should be justified based on the solubility and/or biopharmaceutical classification of the API.

For slower dissolving immediate-release products (e.g. $Q = 80\%$ in 90 minutes), a second time point may be warranted (e.g. $Q = 60\%$ in 45 minutes).

Modified-release FPPs should have a meaningful *in vitro* release rate (dissolution) test that is used for routine quality control. Preferably this test should possess *in vitro*–*in vivo* correlation. Results demonstrating the effect of pH on the dissolution profile should be submitted if appropriate for the type of dosage form.

For extended-release FPPs, the testing conditions should be set to cover the entire time period of expected release (e.g. at least three test intervals chosen for a 12-hour release and additional test intervals for longer duration of release). One of the test points should be at the early stage of drug release (e.g. within the first hour) to demonstrate absence of dose dumping. At each test point, upper and lower limits should be set for individual units. Generally the acceptance range at each intermediate test point should not exceed 25% or $\pm 12.5\%$ of the targeted value. Dissolution results should be submitted for several lots, including those lots used for pharmacokinetic and bioavailability or biowaiver studies.

Recommendations for conducting and assessing comparative dissolution profiles can be found in Appendix 1.

3.2.P.2.2.2 *Overages (name, dosage form)*

Any overages in the formulation(s) described in 3.2.P.1 should be justified.

Justification of an overage to compensate for loss during manufacture should be provided, including information on the step(s) where the loss occurs, the reasons for the loss and batch analysis release data (assay results).

Overages for the sole purpose of extending the shelf-life of the FPP are generally not acceptable.

3.2.P.2.2.3 *Physicochemical and biological properties (name, dosage form)*

Parameters relevant to the performance of the FPP, such as pH, ionic strength, dissolution, redispersion, reconstitution, particle size distribution, aggregation, polymorphism, rheological properties, biological activity or potency, and/or immunological activity, should be addressed.

3.2.P.2.3 *Manufacturing process development (name, dosage form)*

The selection and optimization of the manufacturing process described in 3.2.P.3.3, in particular its critical aspects, should be explained. Where relevant, the method of sterilization should be explained and justified.

Where relevant, justification for the selection of aseptic processing or other sterilization methods over terminal sterilization should be provided.

Differences between the manufacturing process(es) used to produce comparative bioavailability or biowaiver batches and the process described in 3.2.P.3.3 that can influence the performance of the product should be discussed.

For products that meet the criteria of an established multisource product, in order to fulfil the requirements of section P.2.3, section P.2.3 (b) of the dossier and QOS-PD should be completed and a product quality review should be submitted as outlined in Appendix 2. The guidance that follows applies to all other products for which section P.2.3 should be completed in its entirety.

The rationale for choosing the particular pharmaceutical product (e.g. dosage form, delivery system) should be provided. The scientific rationale for the choice of the manufacturing, filling and packaging processes that can influence FPP quality and performance should be explained (e.g. wet granulation using high shear granulator). API stress study results may be included in the rationale. Any developmental work undertaken to protect the FPP from deterioration should also be included (e.g. protection from light or moisture).

The scientific rationale for the selection, optimization and scale-up of the manufacturing process described in 3.2.P.3.3 should be explained, in particular the critical aspects (e.g. rate of addition of granulating fluid, massing time and granulation end-point). A discussion of the critical process parameters (CPP), controls and robustness with respect to the QTPP and CQA of the product should be included (ICH Q8 (25)).

3.2.P.2.4 *Container-closure system (name, dosage form)*

The suitability of the container-closure system (described in 3.2.P.7) used for the storage, transportation (shipping) and use of the FPP should be discussed. This discussion should consider, e.g. choice of materials, protection from moisture and light, compatibility of the materials of construction with the dosage form (including sorption to container and leaching) safety of materials of construction, and performance (such as reproducibility of the dose delivery from the device when presented as part of the FPP).

Testing requirements to verify the suitability of the container-closure system contact material(s) depend on the dosage form and route of administration. The pharmacopoeias provide standards that are required for packaging materials, including, for example, the following:

- glass containers: (34, 35);
- plastic containers: (36, 37);
- rubber/elastomeric closures (38, 39).

Table 2 outlines the general recommendations for the various dosage forms for one-time studies to establish the suitability of the container-closure system contact materials.

Table 2
One-time studies to establish the suitability of the container-closure system contact materials

	Solid oral products	Oral liquid and topical products	Sterile products (including ophthalmics)
Description of any additional treatments ^a	×	×	× (sterilization and depyrogenation of the components)
Extraction studies	–	×	×
Interaction studies (migration/sorption)	–	×	×
Moisture permeability	× (uptake)	× (usually loss)	× (usually loss)
Light transmission	× ^b	×	×

× Information should be submitted.

– Information does not need to be submitted.

^aE.g. coating of tubes, siliconization of rubber stoppers, sulfur treatment of ampoules or vials.

^bNot required if product has been shown to be photostable.

For solid oral dosage forms and solid APIs, compliance with regulations on plastic materials coming into contact with food (for example (EU) No. 10/2011 (40)) can be considered acceptable.

The suitability of the container-closure system used for the storage, transportation (shipping) and use of any intermediate or in-process products (e.g. premixes or bulk FPP) should also be discussed.

A device is required to be included with the container-closure system for administration of oral liquids or solids (e.g. solutions, emulsions, suspensions and powders or granules), whenever the package provides for multiple doses.

In accordance with the Ph.Int. general chapter *Liquid preparations for oral use*:

“Each dose from a multidose container is administered by means of a device suitable for measuring the prescribed volume. The device is usually a spoon or a cup for volumes of 5 ml or multiples thereof, or an oral syringe for other volumes or, for oral drops, a suitable dropper.”

For a device accompanying a multidose container, the results of a study should be provided demonstrating the reproducibility of the device (e.g. consistent delivery of the intended volume), generally at the lowest intended dose.

A sample of the device should be provided with Module 1.

3.2.P.2.5 *Microbiological attributes (name, dosage form)*

Where appropriate, the microbiological attributes of the dosage form should be discussed, including, for example, the rationale for not performing microbial limits testing for non-sterile products and the selection and effectiveness of preservative systems in products containing antimicrobial preservatives. For sterile products, the integrity of the container-closure system to prevent microbial contamination should be addressed.

Where an antimicrobial preservative is included in the formulation, the amount used should be justified by submission of results of studies on the product formulated with different concentrations of the preservative(s) to demonstrate the least necessary but still effective concentration. The effectiveness of the agent should be justified and verified by appropriate studies (e.g. USP or Ph.Eur. general chapters on antimicrobial preservatives) using a batch of the FPP. If the lower limit for the proposed acceptance criterion for the assay of the preservative is less than 90.0%, the effectiveness of the agent should be established with a batch of the FPP containing a concentration of the antimicrobial preservative corresponding to the lower proposed acceptance criteria.

As outlined in the WHO stability guidelines (*WHO Technical Report Series*, No. 953, Annex 2, 2009 (19)), a single primary stability batch of the FPP should be tested for effectiveness of the antimicrobial preservative (in addition to preservative content) at the proposed shelf-life for verification purposes, regardless of whether there is a difference between the release and shelf-life acceptance criteria for preservative content.

3.2.P.2.6 *Compatibility (name, dosage form)*

The compatibility of the FPP with reconstitution diluent(s) or dosage devices (e.g. precipitation of API in solution, sorption on injection vessels, stability)

should be addressed to provide appropriate and supportive information for the labelling.

Where a device is required for oral liquids or solids (e.g. solutions, emulsions, suspensions and powders or granules for such reconstitution) that are intended to be administered immediately after being added to the device, the compatibility studies mentioned in the following paragraphs are not required.

Where sterile, reconstituted products are to be further diluted, compatibility should be demonstrated with all diluents over the range of dilution proposed in the labelling. These studies should preferably be conducted on aged samples. Where the labelling does not specify the type of containers, compatibility (with respect to parameters such as appearance, pH, assay, levels of individual and total degradation products, subvisible particulate matter and extractables from the packaging components) should be demonstrated in glass, PVC and polyolefin containers. However, if one or more containers are identified in the labelling, compatibility of admixtures needs to be demonstrated only in the specified containers.

Studies should cover the duration of storage reported in the labelling (e.g. 24 hours under controlled room temperature and 72 hours under refrigeration). Where the labelling specifies coadministration with other FPPs, compatibility should be demonstrated with respect to the principal FPP as well as the coadministered FPP (i.e. in addition to other aforementioned parameters for the mixture, the assay and degradation levels of each coadministered FPP should be reported).

3.2.P3 **Manufacture (name, dosage form)**

3.2.P3.1 *Manufacturer(s) (name, dosage form)*

The name, address, and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in manufacturing and testing should be provided.

The facilities involved in the manufacturing, packaging, labelling and testing should be listed. If certain companies are responsible only for specific steps (e.g. manufacturing of an intermediate), this should be clearly indicated (*WHO good distribution practices for pharmaceutical products (41)*).

The list of manufacturers or companies should specify the actual addresses of production or manufacturing site(s) involved (including block(s) and unit(s)), rather than the administrative offices.

For a mixture of an API with an excipient, the blending of the API with the excipient is considered to be the first step in the manufacture of the final product and, therefore, the mixture does not fall under the definition of an API. The only exceptions are in the cases where the API cannot exist on its own. Similarly, for a mixture of APIs, the blending of the APIs is considered to be the first step in the

manufacture of the final product. Sites for such manufacturing steps should be listed in this section.

A valid manufacturing authorization for pharmaceutical production, as well as a marketing authorization, should be submitted to demonstrate that the product is registered or licensed in accordance with national requirements (Module 1, 1.2.2).

For each site where the major production step(s) are carried out, when applicable, attach a WHO-type certificate of GMP issued by the competent authority in terms of the WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce (Module 1, 1.2.2).

Justification for any differences to the product in the country or countries issuing the WHO-type certificate(s)

When there are differences between the product for which this application is submitted and that marketed in the country or countries which provided the WHO-type certificate(s), it is necessary to provide data to support the applicability of the certificate(s) despite the differences. Depending on the case, it may be necessary to provide validation data for example for differences in site of manufacture, specifications and formulation. Note that only minor differences are likely to be acceptable. Differences in container labelling need not normally be justified.

Regulatory situation in other countries

A listing should be provided of the countries in which this product has been granted a marketing authorization, this product has been withdrawn from the market and/or this application for marketing has been rejected, deferred or withdrawn (Module 1, 1.2.2).

Reference documents: WHO Technical Report Series, No. 961, Annex 3 (42) and No. 957, Annex 5 (41).

3.2.P3.2 *Batch formula (name, dosage form)*

A batch formula should be provided that includes a list of all components of the dosage form to be used in the manufacturing process, their amounts on a per batch basis, including overages, and a reference to their quality standards.

The tables in the QOS-PD template should be used to summarize the batch formula of the FPP for each proposed commercial batch size and to express the quantity of each component on a per batch basis, including a statement of the total weight or measure of the batch.

All components used in the manufacturing process should be included, including those that may not be added to every batch (e.g. acid and alkali), those that may be removed during processing (e.g. solvents) and any others (e.g. nitrogen or silicon for stoppers). If the FPP is formulated using an active moiety, then the composition for the active ingredient should be clearly indicated (e.g.

“1 kg of active ingredient base = 1.075 kg active ingredient hydrochloride”). All overages should be clearly indicated (e.g. “Contains 5 kg (corresponding to 2%) overage of the API to compensate for manufacturing losses”).

The components should be declared by their proper or common names, quality standards (e.g. BP, JP, Ph.Eur., Ph.Int., USP, in-house) and, if applicable, their grades (e.g. “Microcrystalline cellulose NF (PH 102)”) and special technical characteristics (e.g. lyophilized, micronized, solubilized or emulsified).

3.2.P3.3 *Description of manufacturing process and process controls (name, dosage form)*

A flow diagram should be presented giving the steps of the process and showing where materials enter the process. The critical steps and points at which process controls, intermediate tests or final product controls are conducted should be identified.

A narrative description of the manufacturing process, including packaging, that represents the sequence of steps undertaken and the scale of production should also be provided. Novel processes or technologies and packaging operations that directly affect product quality should be described with a greater level of detail. Equipment should, at least, be identified by type (e.g. tumble blender, in-line homogenizer) and working capacity, where relevant.

Steps in the process should have the appropriate process parameters identified, such as time, temperature, or pH. Associated numeric values can be presented as an expected range. Numeric ranges for critical steps should be justified in Section 3.2.P3.4. In certain cases, environmental conditions (e.g. low humidity for an effervescent product) should be stated.

The maximum holding time for bulk FPP prior to final packaging should be stated. The holding time should be supported by the submission of stability data if longer than 30 days. For an aseptically processed FPP, sterile filtration of the bulk and filling into final containers should preferably be continuous; any holding time should be justified.

Proposals for the reprocessing of materials should be justified. Any data to support this justification should be either referenced or filed in this section (3.2.P3.3).

The information above should be summarized in the QOS-PD template and should reflect the production of the proposed commercial batches. See Glossary (section 2) for definitions of pilot-scale and production-scale batches.

For the manufacture of sterile products the class (e.g. A, B or C) of the areas should be stated for each activity (e.g. compounding, filling and sealing), as well as the sterilization parameters, including for equipment, container-closure system and terminal sterilization.

Reference documents: ICH Q8 (25), Q9 (26), Q10 (27).

3.2.P3.4 *Controls of critical steps and intermediates (name, dosage form)*

Critical steps: Tests and acceptance criteria should be provided (with justification, including experimental data) performed at the critical steps identified in 3.2.P.3.3 of the manufacturing process, to ensure that the process is controlled.

Intermediates: Information on the quality and control of intermediates isolated during the process should be provided.

Examples of applicable in-process controls include:

- granulations: moisture (limits expressed as a range), blend uniformity (e.g. low-dose tablets), bulk and tapped densities and particle size distribution;
- solid oral products: average weight, weight variation, hardness, thickness, friability, and disintegration checked periodically throughout compression, weight gain during coating;
- semi-solids: viscosity, homogeneity, pH;
- transdermal dosage forms: assay of API–adhesive mixture, weight per area of coated patch without backing;
- metered dose inhalers: fill weight or volume, leak testing, valve delivery;
- dry powder inhalers: assay of API–excipient blend, moisture, weight variation of individually contained doses such as capsules or blisters;
- liquids: pH, specific gravity, clarity of solutions;
- parenterals: appearance, clarity, fill volume or weight, pH, filter integrity tests, particulate matter, leak testing of ampoules, pre-filtration and/or pre-sterilization bioburden testing.

Reference documents: ICH Q2 (16), Q6A (6), Q8 (25), Q9 (26), Q10 (27), *WHO Technical Report Series*, No. 929, Annex 5 (21).

3.2.P3.5 *Process validation and/or evaluation (name, dosage form)*

Description, documentation, and results of the validation and/or evaluation studies should be provided for critical steps or critical assays used in the manufacturing process (e.g. validation of the sterilization process or aseptic processing or filling). Viral safety evaluation should be provided in 3.2.A.2, if necessary.

For products that meet the criteria of an established multisource product, a product quality review as outlined in Appendix 2 may be submitted in lieu of the information below.

The following information should be provided for all other products:

1. a copy of the process validation protocol, specific to this FPP, described below;
2. a commitment that three consecutive, production-scale batches of this FPP will be subjected to prospective validation in accordance with the above protocol. The applicant should submit a written commitment that information from these studies will be available for verification after prequalification by the WHO inspection team;
3. if the process validation studies have already been conducted (e.g. for sterile products), a copy of the process validation report should be provided in the PD in lieu of 1. and 2. above.

One of the most practical forms of process validation, mainly for non-sterile products, is the final testing of the product to an extent greater than that required in routine quality control. It may involve extensive sampling, far beyond that called for in routine quality control and testing to normal quality control specifications and often for certain parameters only. Thus, for instance, several hundred tablets per batch may be weighed to determine unit dose uniformity. The results are then analysed statistically to verify the “normality” of the distribution and to determine the standard deviation from the average weight. Confidence limits for individual results and for batch homogeneity are also estimated. Strong assurance is provided that samples taken at random will meet regulatory requirements if the confidence limits are well within compendial specifications.

Similarly, extensive sampling and testing may be performed with regard to any quality requirements. In addition, intermediate stages may be validated in the same way, e.g. dozens of samples may be assayed individually to validate mixing or granulation stages of low-dose tablet production by using the content uniformity test. Certain product characteristics may occasionally be skip-tested. Thus, subvisual particulate matter in parenteral preparations may be determined by means of electronic devices, or tablets or capsules tested for their dissolution profile if such tests are not performed on every batch.

Where ranges of batch sizes are proposed, it should be shown that variations in batch size would not adversely alter the characteristics of the finished product. It is envisaged that those parameters listed in the following validation scheme would need to be revalidated once further scale-up is proposed after prequalification.

The process validation protocol should include, but not be limited to, the following:

- a reference to the current master production document;
- a discussion of the critical equipment;

- the process parameters that can affect the quality of the FPP (critical process parameters (CPPs)) including challenge experiments and failure mode operation;
- details of the sampling: sampling points, stages of sampling, methods of sampling and the sampling plans (including schematics of blender or storage bins for uniformity testing of the final blend);
- the testing parameters and acceptance criteria including in-process and release specifications and comparative dissolution profiles of validation batches against the batch(es) used in the bioavailability or biowaiver studies;
- the analytical procedures or a reference to appropriate section(s) of the dossier;
- the methods for recording and evaluating results;
- the proposed timeframe for completion of the protocol.

The manufacture of sterile FPPs needs to take place in a well-controlled manufacturing area (e.g. a strictly controlled environment using highly reliable procedures and with appropriate in-process controls). A detailed description of these conditions, procedures and controls should be provided, together with actual copies of the standard operating procedures for the following:

- washing, treatment, sterilization and depyrogenation of containers, closures and equipment;
- filtration of solutions;
- lyophilization process;
- leaker test of filled and sealed ampoules;
- final inspection of the product;
- sterilization cycle.

The sterilization process used to destroy or remove microorganisms is probably the single most important process in the manufacture of parenteral FPPs. The process can make use of moist heat (e.g. steam), dry heat, filtration, gaseous sterilization (e.g. ethylene oxide) or radiation. It should be noted that terminal steam sterilization, when practical, is considered to be the method of choice to ensure sterility of the final FPP. Therefore, scientific justification for selecting any other method of sterilization should be provided.

The sterilization process should be described in detail and evidence should be provided to confirm that it will produce a sterile product with a high degree of reliability and that the physical and chemical properties as well as

the safety of the FPP will not be affected. Details such as Fo range, temperature range and peak dwell time for an FPP and the container-closure system should be provided. Although standard autoclaving cycles of 121 °C for 15 minutes or more would not need a detailed rationale, such justifications should be provided for reduced temperature cycles or elevated temperature cycles with shortened exposure times. If ethylene oxide is used, studies and acceptance criteria should control the levels of residual ethylene oxide and related compounds.

Any filters used should be validated with respect to pore size, compatibility with the product, absence of extractables and lack of adsorption of the API or any of the components.

For the validation of aseptic processing of parenteral products that cannot be terminally sterilized, simulation process trials should be conducted. This involves filling containers with culture media under normal conditions, followed by incubation. Refer to current WHO GMP guidelines for details.

Reference documents: ICH Q8 (25), Q9 (26), Q10 (27), *WHO Technical Report Series*, No. 961, Annex 3 (42).

3.2.P4 Control of excipients (name, dosage form)

3.2.P4.1 Specifications (name, dosage form)

The specifications for excipients should be provided.

The specifications from the applicant or the FPP manufacturer should be provided for all excipients, including those that may not be added to every batch (e.g. acid and alkali), those that do not appear in the final FPP (e.g. solvents) and any others used in the manufacturing process (e.g. nitrogen or silicon for stoppers).

If the standard claimed for an excipient is an officially recognized compendial standard, it is sufficient to state that the excipient is tested according to the requirements of that standard, rather than reproducing the specifications found in the officially recognized compendial monograph.

If the standard claimed for an excipient is a non-compendial standard (e.g. in-house standard) or includes tests that are supplementary to those appearing in the officially recognized compendial monograph, a copy of the specification for the excipient should be provided.

For products submitted to the WHO Prequalification of Medicines Programme, only excipients with an officially recognized pharmacopoeial monograph should be used. Exceptions may be justified.

For excipients of natural origin, microbial limit testing should be included in the specifications. Skip-testing is acceptable if justified (submission of acceptable results of five production batches).

For oils of plant origin (e.g. soy bean oil or peanut oil) the absence of aflatoxins or biocides should be demonstrated.

The colours permitted for use are limited to those listed in the “Japanese pharmaceutical excipients”, the European Union (EU) “List of permitted food colours”, and the FDA “Inactive ingredient guide”. For proprietary mixtures, the supplier’s product sheet with the qualitative formulation should be submitted, in addition to the FPP manufacturer’s specifications for the product, including identification testing.

For flavours, the qualitative composition should be submitted, as well as a declaration that the excipients comply with foodstuff regulations (e.g. USA or EU regulations).

Information that is considered confidential may be submitted directly to the WHO Prequalification of Medicines Programme by the supplier who should make reference in the cover letter to the specific related product.

Other certifications of at-risk components may be required on a case-by-case basis.

If additional purification is undertaken on commercially available excipients, details of the process of purification and modified specifications should be submitted.

Reference documents: ICH Q6A (6).

3.2.P4.2 *Analytical procedures (name, dosage form)*

The analytical procedures used for testing the excipients should be provided, where appropriate.

Copies of analytical procedures from officially recognized compendial monographs do not need to be submitted.

Reference document: ICH Q2 (16).

3.2.P4.3 *Validation of analytical procedures (name, dosage form)*

Analytical validation information, including experimental data, for the analytical procedures used for testing the excipients should be provided, where appropriate.

Copies of analytical validation information are generally not submitted for the testing of excipients, with the exception of the validation of in-house methods where appropriate.

Reference document: ICH Q2 (16).

3.2.P4.4 *Justification of specifications (name, dosage form)*

Justification for the proposed excipient specifications should be provided, where appropriate.

A discussion of the tests that are supplementary to those appearing in the officially recognized compendial monograph should be provided.

3.2.P4.5 *Excipients of human or animal origin (name, dosage form)*

For excipients of human or animal origin, information should be provided regarding adventitious agents (e.g. sources, specifications, description of the testing performed, viral safety data) (details in 3.2.A.2).

The following excipients should be addressed in this section: gelatin, phosphates, stearic acid, magnesium stearate and other stearates. If the excipients are of plant origin a declaration to this effect will suffice.

For excipients of animal origin, a letter of attestation should be provided confirming that the excipients used to manufacture the FPP are without risk of transmitting agents of animal spongiform encephalopathies.

Materials of animal origin should be avoided whenever possible.

When available a CEP demonstrating TSE-compliance should be provided. A complete copy of the CEP (including any annexes) should be provided in Module 1.

Reference documents: ICH Q5A (43), Q5D (44), Q6B (45), WHO Technical Report Series, No. 908, Annex 1 (46).

3.2.P4.6 *Novel excipients (name, dosage form)*

For excipient(s) used for the first time in an FPP or by a new route of administration, full details of manufacture, characterization, and controls, with cross-references to supporting safety data (non-clinical and/or clinical) should be provided according to the API and/or FPP format (details in 3.2.A.3).

Novel excipients are not accepted in the WHO Prequalification of Medicines Programme. For the purpose of these guidelines, a novel excipient is one that has not been used (at a similar level and by the same route of administration) in a product approved by an SRA or by WHO.

3.2.P5 **Control of FPP (name, dosage form)**

3.2.P5.1 *Specification(s) (name, dosage form)*

The specification(s) for the FPP should be provided.

As defined in ICH's Q6A guideline, a specification is:

“a list of tests, references to analytical procedures and appropriate acceptance criteria, which are numerical limits, ranges, or other criteria for the tests described. It establishes the set of criteria to which an API or FPP should conform to be considered acceptable for its intended use. “Conformance to specifications” means that the API and/or FPP, when tested according to the listed analytical procedures, will meet the listed acceptance criteria. Specifications are critical quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities.”

A copy of the FPP specification(s) from the applicant (as well as the company responsible for the batch release of the FPP, if different from the applicant), dated and signed by authorized personnel (i.e. the person in charge of the quality control or quality assurance department) should be provided in the PD. Two separate sets of specifications may be set out: after packaging of the FPP (release) and at the end of the shelf-life.

The specifications should be summarized according to the tables in the QOS-PD template including the tests, acceptance criteria and analytical procedures (listing types, sources and versions for the methods).

- The standard declared by the applicant could be an officially recognized compendial standard (e.g. BP, JP, Ph.Eur., Ph.Int., USP) or an in-house (manufacturer's) standard.
- The specification reference number and version (e.g. revision number and/or date) should be provided for version control purposes.
- For the analytical procedures, the type should indicate the kind of analytical procedure used (e.g. visual, IR, UV or HPLC); the source refers to the origin of the analytical procedure (e.g. BP, JP, Ph.Eur., Ph.Int., USP, in-house) and the version (e.g. code number/version/date) should be provided for version control purposes.

ICH's Q6A guideline outlines recommendations for a number of *universal* and *specific tests* and criteria for FPPs. Specifications should include, at a minimum, tests for appearance, identification, assay, purity, performance tests (e.g. dissolution), physical tests (e.g. loss on drying, hardness, friability and particle size), uniformity of dosage units, and, as applicable, identification and assay of antimicrobial or chemical preservatives (e.g. antioxidants) and microbial limit tests.

The following information provides guidance on specific tests that are not addressed by ICH's Q6A guideline:

- fixed-dose combination FPPs (FDC-FPPs):
 - analytical methods that can distinguish each API in the presence of the other API(s) should be developed and validated,
 - acceptance criteria for degradation products should be established with reference to the API they are derived from. If an impurity results from a chemical reaction between two or more APIs, its acceptance limits should in general be calculated with reference to the worst case (the API with the smaller area under the curve). Alternatively the content of such impurities could be calculated in relation to their reference standards,

- a test and limit for content uniformity is required for each API present in the FPP at less than 5 mg or less than 5% of the weight of the dosage unit,
 - for the API(s) present at ≥ 5 mg and $\geq 5\%$ of the weight of the dosage unit, a test and limit for weight variation may be established in lieu of content uniformity testing;
- modified-release products: a meaningful API release method;
 - inhalation and nasal products: consistency of delivered dose (throughout the use of the product), particle or droplet size distribution profiles (comparable to the product used in in vivo studies where applicable) and if applicable for the dosage form, moisture content, leak rate, microbial limits, preservative assay, sterility and weight loss;
 - suppositories: uniformity of dosage units, melting point;
 - transdermal dosage forms: peel or shear force, mean weight per unit area and dissolution.

Unless there is appropriate justification, the acceptable limit for the API content of the FPP in the release specifications is $\pm 5\%$ of the label claim (i.e. 95.0–105.0%).

For products such as tablets, capsules and suppositories where a test for uniformity of single-dose preparations is required, a test and limit for content uniformity is required when the API is present in the FPP at less than 5 mg or less than 5% of the weight of the dosage unit. Otherwise, the test for mass uniformity may be applied.

Skip-testing is acceptable for parameters such as identification of colouring materials and microbial limits, when justified by the submission of acceptable supportive results for five production batches. When justification for skip-testing has been accepted the specifications should include a footnote, stating, at a minimum, the following skip-testing requirements: at least every tenth batch and at least one batch annually is tested. In addition, for stability-indicating parameters such as microbial limits, testing will be performed at release and at the end of shelf-life during stability studies.

Any differences between release and shelf-life tests and acceptance criteria should be clearly indicated and justified. Note that such differences for parameters such as dissolution are normally not accepted.

Reference documents: ICH Q3B (11), Q3C (12), Q6A (6).

3.2.P.5.2 *Analytical procedures (name, dosage form)*

The analytical procedures used for testing the FPP should be provided.

Copies of the in-house analytical procedures used during pharmaceutical development (if used to generate testing results provided in the PD) as well as those proposed for routine testing should be provided. Unless modified it is not necessary to provide copies of analytical procedures described in officially recognized compendia.

Tables for summarizing a number of the different analytical procedures and the validation information (e.g. HPLC assay and impurity methods) can be found in the 2.3.R Regional information section of the QOS-PD (i.e. 2.3.R.2). These tables should be used to summarize the analytical procedures used for determination of the assay, related substances and dissolution of the FPP.

Refer to section 3.2.S.4.2 of these guidelines for additional guidance on analytical procedures.

Reference document: ICH Q2 (16).

3.2.P.5.3 *Validation of analytical procedures (name, dosage form)*

Analytical validation information, including experimental data, for the analytical procedures used for testing the FPP, should be provided.

Copies of the validation reports for the in-house analytical procedures used during pharmaceutical development (if used to support testing results provided in the PD) as well as those proposed for routine testing should be provided.

Tables for summarizing a number of the different analytical procedures and validation information (e.g. HPLC assay and impurity methods, and GC methods) can be found in the 2.3.R Regional information section of the QOS-PD (i.e. 2.3.R.2). These tables should be used to summarize the validation information of the analytical procedures used for determination of the assay, related substances and dissolution of the FPP.

As recognized by regulatory authorities and pharmacopoeias themselves, verification of compendial methods can be necessary. The compendial methods as published are typically validated based on an API or an FPP originating from a specific manufacturer. The same API or FPP obtained from different sources can contain impurities and/or degradation products or excipients that were not considered during the development of the monograph. Therefore, the monograph and compendial method(s) should be demonstrated suitable for the control of the proposed FPP.

For officially recognized compendial FPP assay methods, verification should include a demonstration of specificity, accuracy and repeatability (method precision). If an officially recognized compendial method is used to control related substances that are not specified in the monograph, full validation of the method is expected with respect to those related substances.

If an officially recognized compendial standard is claimed and an in-house method is used in lieu of the compendial method (e.g. for assay or for related compounds), equivalence of the in-house and compendial methods should be demonstrated. This could be accomplished by performing duplicate analyses of one sample by both methods and providing the results from the study. For methods for the determination of related compounds, the sample analysed should be the placebo spiked with related compounds at concentrations equivalent to their specification limits.

Reference document: ICH Q2 (16).

3.2.P5.4 *Batch analyses (name, dosage form)*

A description of batches and results of batch analyses should be provided.

Information on relevant FPP batches used to establish the specifications and evaluate consistency in manufacturing should be provided and should include strength and batch number, batch size, date and site of production and use (e.g. used in comparative bioavailability or biowaiver studies, preclinical and clinical studies (if relevant), stability, pilot, scale-up and, if available, production-scale batches).

Analytical results generated by the company responsible for the batch release of the FPP (generally the applicant or the FPP manufacturer, if different from the applicant) should be provided for not less than two batches of at least pilot scale, or in the case of an uncomplicated² FPP (e.g. immediate-release solid FPPs (with noted exceptions), or non-sterile solutions), at least one batch of at least pilot scale and a second batch which may be smaller (e.g. for solid oral dosage forms, 25 000 or 50 000 tablets or capsules) of each proposed strength of the FPP. These batches should be manufactured by a procedure fully representative of and simulating that to be applied to a full production-scale batch.

The results should include those of tests on the batch(es) used in the comparative bioavailability or biowaiver studies. Copies of the certificates of analysis for these batches should be provided in the PD and the company responsible for generating the testing results should be identified.

The discussion of results should focus on observations noted for the various tests, rather than reporting comments such as “all tests meet specifications”. The discussion should include ranges of analytical results, where relevant. For quantitative tests (e.g. individual and total impurity tests and assay tests), it should be ensured that actual numerical results are provided rather

² The term “complicated FPP” includes sterile products, metered dose inhaler products, dry powder inhaler products and transdermal delivery systems. Other specific products under “complicated FPP” include ritonavir/lopinavir FDC tablets and FDCs containing rifampicin or an artemisinin. As the invitations for EOI change over time, the listing of individual “complicated FPPs” is not meaningful and applicants should contact the Head of Assessments, WHO Prequalification of Medicines Programme in case of doubt.

than vague statements such as “within limits” or “conforms” (e.g. “levels of degradation product A ranged from 0.2 to 0.4%”). Dissolution results should be expressed, at a minimum, as both the average and the range of individual results. Recommendations for conducting and assessing comparative dissolution profiles can be found in Appendix 1.

A discussion and justification should be provided for any incomplete analyses (e.g. for any parameters not tested according to the proposed specification).

Reference documents: ICH Q3B (11), Q3C (12), Q6A (6).

3.2.P5.5 *Characterization of impurities (name, dosage form)*

Information on the characterization of impurities should be provided, if not previously provided in “3.2.S.3.2 Impurities”.

A discussion should be provided of all impurities that are potential degradation products (including those among the impurities identified in 3.2.S.3.2 as well as potential degradation products resulting from interaction of the API with other APIs (FDCs), excipients or the container-closure system) and FPP process-related impurities (e.g. residual solvents in the manufacturing process for the FPP).

Reference documents: ICH Q3B (11), Q3C (12), Q6A (6).

3.2.P5.6 *Justification of specification(s) (name, dosage form)*

Justification for the proposed FPP specification(s) should be provided.

A discussion should be provided on the omission or inclusion of certain tests, evolution of tests, analytical procedures and acceptance criteria, and differences from the officially recognized compendial standard(s). If the officially recognized compendial methods have been modified or replaced, a discussion should be included.

The justification for certain tests, analytical procedures and acceptance criteria (e.g. degradation products or dissolution method development) may have been discussed in other sections of the PD and would not need to be repeated here, although a cross-reference should be provided.

ICH Q6A (6) should be consulted for the development of specifications for FPPs.

3.2.P6 *Reference standards or materials (name, dosage form)*

Information on the reference standards or reference materials used for testing of the FPP should be provided, if not previously provided in “3.2.S.5 Reference standards or materials”.

See section 3.2.S.5 for information that should be provided on reference standards or materials. Information should be provided on reference materials of FPP degradation products, where not included in 3.2.S.5.

Reference documents: ICH Q6A (6), *WHO Technical Report Series*, No. 943, Annex 3 (17).

3.2.P.7 Container-closure system (name, dosage form)

A description of the container-closure systems should be provided, including the identity of materials of construction of each primary packaging component and its specification. The specifications should include description and identification (and critical dimensions, with drawings where appropriate). Non-compendial methods (with validation) should be included, where appropriate.

For non-functional secondary packaging components (e.g. those that neither provide additional protection nor serve to deliver the product), only a brief description should be provided. For functional secondary packaging components, additional information should be provided.

Suitability information should be located in 3.2.P.2.

The WHO *Guidelines on packaging for pharmaceutical products* (18) and the officially recognized pharmacopoeias should be consulted for recommendations on the packaging information for FPPs.

Descriptions, materials of construction and specifications (of the company responsible for packaging the FPP, generally the FPP manufacturer) should be provided for the packaging components that are:

- in direct contact with the dosage form (e.g. container, closure, liner, desiccant and filler);
- used for drug delivery (including the device(s) for multidose solutions, emulsions, suspensions and powders or granules for reconstitution into solution, emulsion or suspension);
- used as a protective barrier to help ensure stability or sterility;
- necessary to ensure FPP quality during storage and shipping.

Primary packaging components are those that are in direct contact with the API or FPP.

The specifications for the primary packaging components should include a specific test for identification (e.g. IR). Specifications for film and foil materials should include limits for thickness or area weight.

Information to establish the suitability (e.g. qualification) of the container-closure system should be discussed in section 3.2.P.2. Comparative studies may be warranted for certain changes in packaging components (e.g. a comparative delivery study (droplet size) for a change in manufacturer of dropper tips).

3.2.P8 **Stability (name, dosage form)**

3.2.P8.1 **Stability summary and conclusions (name, dosage form)**

The types of studies conducted, protocols used, and the results of the studies should be summarized. The summary should include, for example, conclusions with respect to storage conditions and shelf-life, and, if applicable, in-use storage conditions and shelf-life.

The WHO stability guidelines *Stability testing of active pharmaceutical ingredients and finished pharmaceutical products* (19) should be consulted for recommendations on the core stability data package required for the prequalification of APIs and FPPs.

As outlined in the WHO stability guidelines, the purpose of stability testing is to provide evidence of how the quality of an API or FPP varies with time under the influence of a variety of environmental factors such as temperature, humidity and light. The stability programme also includes the study of product-related factors that influence the quality of the API or FPP, for example, interaction of API with excipients, container-closure systems and packaging materials.

Stress testing

As outlined in the WHO stability guidelines, photostability testing should be conducted on at least one primary batch of the FPP if appropriate. If “protect from light” is stated in one of the officially recognized pharmacopoeias for the API or FPP it is sufficient to state “protect from light” on labelling, in lieu of photostability studies, when the container-closure system is shown to be light protective. Additional stress testing of specific types of dosage forms may be appropriate (e.g. cyclic studies for semi-solid products or freeze–thaw studies for liquid products).

Accelerated, intermediate (if necessary) and long-term testing

Stability data must demonstrate stability of the medicinal product throughout its intended shelf-life under the climatic conditions prevalent in the target countries. Merely applying the same requirements applicable to other markets could potentially lead to substandard products if stability studies are conducted at the storage conditions for countries in Climatic Zone I/II when the products are supplied in countries in Climatic Zones III and IV. Refer to *WHO Technical Report Series*, No. 953, Annex 2, Appendix 1 (7) for information on climatic zones. Effective as of September 2011, the required long-term storage conditions for the WHO Prequalification of Medicines Programme are $30\text{ °C} \pm 2\text{ °C}/75\% \pm 5\% \text{ RH}$, and after this date the long-term data submitted in the PD (see Table 3) should be at these conditions. The use of alternative long-term conditions will need to be justified and should be supported with appropriate evidence.

Other storage conditions are outlined in the WHO stability guidelines for FPPs packaged in impermeable and semi-permeable containers and those intended for storage in a refrigerator and in a freezer. FPPs intended for storage below $-20\text{ }^{\circ}\text{C}$ should be treated on a case-by-case basis.

Table 3
Minimum data required at the time of submitting the dossier (in the general case)

Storage temperature ($^{\circ}\text{C}$)	Relative humidity (%)	Minimum time period (months)
Accelerated 40 ± 2	75 ± 5	6
Intermediate ^a	N/A	N/A
Long-term 30 ± 2	75 ± 5	6

^aWhere long-term conditions are $30\text{ }^{\circ}\text{C} \pm 2\text{ }^{\circ}\text{C}/75\% \pm 5\% \text{RH}$, there is no intermediate condition.

Refer to *WHO Technical Report Series*, No. 953, Annex 2 (19) for further information regarding the storage conditions. Reference should also be made to the WHO Prequalification of Medicines Programme web site for any exceptions to the stated requirements.

To establish the shelf-life, data should be provided on not less than two batches of at least pilot scale, or in the case of an uncomplicated FPP (e.g. immediate-release solid FPPs (with noted exceptions) or non-sterile solutions), at least one batch of at least pilot scale and a second batch which may be smaller (e.g. for solid oral dosage forms, 25 000 or 50 000 tablets or capsules) of each proposed strength of the FPP. These batches should be manufactured by a procedure fully representative of and simulating that to be applied to a full production-scale batch.

The stability testing programme should be summarized and the results of stability testing should be reported in the dossier and summarized in the tables in the QOS-PD. Bracketing and matrixing of proportional strengths can be applied if scientifically justified.

For sterile products, sterility should be reported at the beginning and end of shelf-life. For parenteral products, subvisible particulate matter should be reported frequently, but not necessarily at every test interval. Bacterial endotoxins need only be reported at the initial test point. Weight loss from plastic containers should be reported over the shelf-life.

Any in-use period and associated storage conditions should be justified with experimental data, for example, after opening, reconstitution and/or dilution

of any sterile and/or multidose products or after first opening of FPPs packed in bulk multidose containers (e.g. bottles of 1000s). If applicable, the in-use period and storage conditions should be stated in the product information.

The information on the stability studies should include details such as

- storage conditions;
- strength;
- batch number, including the API batch number(s) and manufacturer(s);
- batch size;
- container-closure system including orientation (e.g. erect, inverted, on-side) where applicable;
- completed (and proposed) test intervals.

The discussion of results should focus on observations noted for the various tests, rather than reporting comments such as “all tests meet specifications”. The discussion should include ranges of analytical results and any trends that were observed. For quantitative tests (e.g. individual and total degradation product tests and assay tests) actual numerical results should be provided rather than vague statements such as “within limits” or “conforms”. Dissolution results should be expressed, at a minimum, as both the average and range of individual results.

Applicants should consult ICH’s Q1E guideline (23) for details on the evaluation and extrapolation of results from stability data (e.g. if significant change was not observed within 6 months at accelerated condition and the data show little or no variability, the proposed shelf-life could be up to twice the period covered by the long-term data, but should not exceed the long-term data by more than 12 months).

Proposed storage statement and shelf-life

The proposed storage statement and shelf-life (and in-use storage conditions and in-use period, if applicable) for the FPP should be provided.

The recommended labelling statements for use based on the stability studies, are provided in the WHO stability guidelines (19).

Reference documents: *WHO Technical Report Series*, No. 953, Annex 2 (19), ICH Q1A (20), Q1B (22), Q1C (47), Q1D (24), Q1E (23), Q3B (11), Q6A (6).

3.2.P8.2 *Post-approval stability protocol and stability commitment (name, dosage form)*

The post-approval stability protocol and stability commitment should be provided.

Primary stability study commitment

When the available data on long-term stability of primary batches do not cover the proposed shelf-life granted at the time of assessment of the PD, a commitment should be made to continue the stability studies in order to firmly establish the shelf-life. A written commitment (signed and dated) to continue long-term testing over the shelf-life period should be included in the dossier.

Commitment stability studies

The long-term stability studies for the commitment batches should be conducted throughout the proposed shelf-life on at least three production batches of each strength in each container-closure system. Where stability data were not provided for three production batches of each strength, a written commitment (signed and dated) should be included in the dossier.

Ongoing stability studies

As described in the WHO stability guidelines (19), an ongoing stability programme is established to monitor the product over its shelf-life and to determine that the product remains and can be expected to remain within specifications under the storage conditions on the label. Unless otherwise justified, at least one batch per year of product manufactured in every strength and every container-closure system, if relevant, should be included in the stability programme (unless none is produced during that year). Bracketing and matrixing may be applicable. A written commitment (signed and dated) to this effect should be included in the dossier.

Any differences between the stability protocols used for the primary batches and those proposed for the commitment batches or ongoing batches should be scientifically justified.

Reference document: ICH Q1A (20).

3.2.P.8.3 Stability data (name, dosage form)

Results of the stability studies should be presented in an appropriate format (e.g. tabular, graphical, narrative). Information on the analytical procedures used to generate the data and validation of these procedures should be included.

Information on characterization of impurities is located in 3.2.P.5.5.

The actual stability results and reports used to support the proposed shelf-life should be provided in the PD. For quantitative tests (e.g. individual and total degradation product tests and assay tests), actual numerical results should be provided rather than vague statements such as “within limits” or “conforms”.

Dissolution results should be expressed, at a minimum, as both the average and range of individual results.

Reference documents: ICH Q1A (20), Q1B (22), Q1C (47), Q1D (24), Q1E (23), Q2 (16).

3.2.A Appendices

3.2.A.1 Facilities and equipment

Not applicable (i.e. not a biotech product).

3.2.A.2 Adventitious agents safety evaluation

3.2.A.3 Novel excipients

Novel excipients are not accepted in the WHO Prequalification of Medicines Programme.

3.2.R Regional information

3.2.R.1 Production documentation

3.2.R.1.1 Executed production documents

A minimum of two batches of at least pilot scale, or in the case of an uncomplicated FPP (e.g. immediate-release solid FPPs (with noted exceptions) or non-sterile solutions), at least one batch of at least pilot scale (the batch used in comparative bioavailability or biowaiver studies) and a second batch which may be smaller (e.g. for solid oral dosage forms, 25 000 or 50 000 tablets or capsules), should be manufactured for each strength. These batches should be manufactured by a procedure fully representative of and simulating that to be applied to a full production-scale batch.

For solid oral dosage forms, pilot scale is generally, at a minimum, one-tenth that of full production scale or 100 000 tablets or capsules, whichever is the larger.

Copies of the executed production documents should be provided for the batches used in the comparative bioavailability or biowaiver studies. Any notations made by operators on the executed production documents should be clearly legible.

If not included in the executed batch records through sufficient in-process testing, data should be provided for the batch used in comparative bioavailability or biowaiver studies that demonstrate the uniformity of this batch. The data to establish the uniformity of the biobatch should involve testing to an extent greater than that required in routine quality control.

English translations of executed records should be provided where relevant.

3.2.R.1.2 *Master production documents*

Copies of the FPP master production documents should be provided for each proposed strength, commercial batch size and manufacturing site.

The details in the master production documents should include, but not be limited to, the following:

- master formula;
- dispensing, processing and packaging sections with relevant material and operational details;
- relevant calculations (e.g. if the amount of API is adjusted based on the assay results or on the anhydrous basis);
- identification of all equipment by, at a minimum, type and working capacity (including make, model and equipment number, where possible);
- process parameters (e.g. mixing time, mixing speed, milling screen size, processing temperature range, granulation end-point and tablet machine speed (expressed as target and range));
- list of in-process tests (e.g. appearance, pH, assay, blend uniformity, viscosity, particle size distribution, loss on drying, weight variation, hardness, disintegration time, weight gain during coating, leaker test, minimum fill, clarity and filter integrity checks) and specifications;
- sampling plan with regard to the:
 - steps at which sampling should be done (e.g. drying, lubrication and compression),
 - number of samples that should be tested (e.g. for blend uniformity testing of low-dose FPPs, blend drawn using a sampling thief from x positions in the blender),
 - frequency of testing (e.g. weight variation every x minutes during compression or capsule filling);
- precautions necessary to ensure product quality (e.g. temperature and humidity control and maximum holding times);
- for sterile products, reference to standard operating procedures (SOPs) in appropriate sections and a list of all relevant SOPs at the end of the document;
- theoretical and actual yield;
- compliance with the GMP requirements.

Reference document: WHO Technical Report Series, No. 961 (48).

3.2.R.2 Analytical procedures and validation information

The tables presented in section 2.3.R.2 in the QOS-PD template should be used to summarize the analytical procedures and validation information from sections 3.2.S.4.2, 3.2.S.4.3, 2.3.S.4.4 (c), 2.3.S.7.3 (b), 3.2.P.5.2 and 3.2.P.5.3 where relevant.

4.3 Literature references

References to the scientific literature relating to both the API and FPP should be included in this section of the PD when appropriate.

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Appendix 1

Recommendations for conducting and assessing comparative dissolution profiles

The dissolution measurements of the two FPPs (e.g. test and reference (comparator) or two different strengths) should be made under the same test conditions. A minimum of three time-points (zero excluded) should be included, the time-points for both reference (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 (60, 90, 120) minutes). 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. 1, 2, 3, 5 and 8 hours for a 12-hour release and additional test intervals for longer duration of release.

Studies should be performed in at least three media covering the physiological range, including pH 1.2 hydrochloric acid, pH 4.5 buffer and pH 6.8 buffer. *International Pharmacopoeia* buffers are recommended; 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):

$$f_2 = 50 \text{ LOG } \{ [1 + 1/n \sum_{t=1}^n (R_t - T_t)^2]^{-0.5} \times 100 \}$$

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 due to poor solubility of the API, the dissolution should be conducted until an asymptote (plateau) has been reached.

- At least 12 units should be used for 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 the first time-point should be not more than 20% and at other time-points should be not more than 10%.
- When delayed-release products (e.g. enteric coated) are being compared, the recommended conditions are acid medium (pH 1.2) for 2 hours and buffer pH 6.8 medium.
- When comparing extended-release beaded capsules, where different strengths have been achieved solely by means of adjusting the number of beads containing the API, one condition (normally the release condition) will suffice.
- Surfactants should be avoided in comparative dissolution testing. A statement that the API is not soluble in any of the media is not sufficient and profiles in the absence of surfactant should be provided. The rationale for the choice and concentration of surfactant should be provided. The concentration of the surfactant should be such that the discriminatory power of the test will not be compromised.

Appendix 2

Product quality review requirements for *established multisource products*

For an established multisource product, a product quality review may satisfy the requirements of sections 3.2.P.2.2.1 (a), 3.2.P.2.3 (a) and 3.2.P.3.5 of the PD and QOS-PD.

A product quality review should be submitted with the objective of verifying the consistency of the quality of the FPP and its manufacturing process.

Rejected batches should not be included in the analysis but must be reported separately together with the reports of failure investigations, as indicated below.

Reviews should be conducted with no fewer than 10 consecutive batches manufactured over the period of the past 12 months or, where 10 batches were not manufactured in the past 12 months, no fewer than 25 consecutive batches manufactured over the period of the past 36 months and should include at least:

- a review of starting and primary packaging materials used in the FPP, especially those from new sources;
- a tabulated review and statistical analysis of quality control and in-process control results;
- a review of all batches that failed to meet established specification(s);
- a review of all critical deviations or non-conformances and related investigations;
- a review of all changes carried out to the processes or analytical methods;
- a review of the results of the stability-monitoring programme;
- a review of all quality-related returns, complaints and recalls, including export-only medicinal products;
- a review of the adequacy of previous corrective actions;
- a list of validated analytical and manufacturing procedures and their revalidation dates.

Notes

- Reviews must include data from all batches manufactured during the review period.
- Data should be presented in tabular or graphical form, when applicable.
- The above listing of requirements is specific to the dossier assessment process requirements and does not relieve the applicant of related GMP requirements.

Annex 5

Development of paediatric medicines: points to consider in formulation

General note

The “points to consider” document should not contain detailed instructions for development but rather it should make reference to relevant literature. Some matters dealt with in the draft on development of multisource products have, therefore, been omitted in this proposal.

1. Introduction	199
2. Glossary	200
3. Paediatric dosage forms	200
3.1 Convenient, reliable administration	201
3.2 Acceptability and palatability	202
3.3 Minimum dosing frequency	203
3.4 End-user needs	203
4. Particular dosage forms to be considered	203
4.1 Flexible solid dosage forms	203
4.2 Oral medicines	204
4.3 Medicines for severe conditions	204
4.4 Rectal preparations	204
5. Formulation design	204
5.1 Quality	205
5.2 Biopharmaceutics classification system	205
5.3 Excipients	206
5.4 Colouring agents	208
5.5 Antimicrobial preservatives	208
5.6 Sweetening agents	208
5.7 Taste masking	209
5.8 Solubility enhancers	209
6. Oral administration	210
6.1 Oral liquid preparations	210
6.2 Administration through feeding tubes	212
6.3 Oral solid dosage forms	212

7. Rectal administration	217
7.1 Suppositories	217
7.2 Rectal liquids (enemas)	218
8. Parenteral administration	218
8.1 Formulation	219
8.2 Additional points to consider for parenteral preparations	219
9. Dermal and transdermal administration	220
9.1 Transdermal patches	221
10. Inhalations	221
11. Packaging and labelling	222
References	223

1. Introduction

Safe and effective pharmacotherapy for paediatric patients requires the timely development of medicines and information on their proper use appropriate to the age, physiological condition and body size of the child. Formulations developed specifically for children are often needed. The use of unlicensed and off-label medicines for treating children is widespread. Their effects on children have not been properly studied, age-appropriate formulations are generally not available, and the medicines are not licensed for use in children.

Pharmacists, parents or caregivers are often faced with the need to manipulate an adult medicine in a way that is not described in the Summary of product characteristics. This manipulation can be simple, e.g. breaking tablets that do not have a score line with a tablet splitter, or complex, e.g. using tablets as a source for an active pharmaceutical ingredient (API) to prepare a suspension. Pharmacists may also be faced with the need to compound a medicine on the basis of the API.

The manipulation process itself can increase the potential for inaccurate dosing and in general can increase the variability of the product. Such handling may be potentially hazardous for the patient as it may affect the stability, bioavailability and accuracy of dosing of a finished pharmaceutical product (FPP), in particular for controlled-release preparations. The use of such medicines may expose children to overdosing and unintended side-effects or to underdosing and a resultant reduction in efficacy. Moreover, excipients that are safe for adults may not necessarily be so for children.

In December 2007 WHO launched its initiative “Make medicines child size” in order to raise awareness of and accelerate action to meet the need for improved availability and access to child-specific medicines. The WHO Model Formulary for children, 2010, provides independent prescriber information on dosage and treatment guidance for medicines based on the WHO Model List of essential medicines for children, first developed in 2007 and reviewed and updated every two years.

Among actions to support the “Make medicines child size” initiative is the present “Points to consider” document on the formulation of paediatric medicines. The objective is to inform regulatory authorities and manufacturers on issues that require special attention in pharmaceutical formulation. Its focus is on the conditions and needs in developing countries. The guidance does not provide exhaustive information and does not exclude the possibility that other aspects may be relevant to the development of paediatric medicines.

It is not within the scope of this document to address extemporaneous preparations and compounding. A separate interim document entitled *Provision by health-care specialists of patient-specific preparations that are not available as authorized products – points to consider (1)* will deal with such preparations.

2. Glossary

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

child-resistant container

A form of packaging difficult for young children to open but not unduly difficult for adults to open properly.

flexible dosage form

A solid dosage form that can be administered to patients in more than one manner, e.g. may be dispersed or taken orally as a whole.

labelling information

Information to the user provided on the package label or in the patient information leaflet.

mini-tablet

A tablet of no more than 4 mm diameter.

off-label use

Use of a medicine outside the scope of regulatory authorization.

platform technology

Technique, including formulation and related processes, which can be used to obtain different dosage forms, different strengths and/or accommodate different APIs.

3. Paediatric dosage forms

The paediatric population is a heterogeneous group ranging from newborns to adolescents with wide physical and developmental differences regarding pharmacokinetics and pharmacodynamics. Organ maturation, metabolic capacity, skin maturation and other factors may change with age, especially in early infancy (2). The age groups identified by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) (3) have been derived mainly from physiological and pharmacokinetic differences from birth to adulthood:

- preterm newborn infants
- term newborn infants (0–27 days)

- infants and toddlers (28 days–23 months)
- children (2–11 years)
- adolescents (12 to 16–18 years (dependent on region)).

It is a challenge to find one formulation appropriate for all age groups. The aim should be to safely cover as wide an age range as possible with a single formulation. The guiding principle for selecting paediatric dosage forms should be – as for adults – the balance of risks and benefits taking into account the specific needs of this vulnerable population (4).

During the development of pharmaceutical products, the assessment of individual risks related to specific products and starting materials, and the recognition of hazards at specific stages of production or distribution, will enable further enhancement of the usual quality assurance mechanisms, such as implementation of good manufacturing practices (GMP), by increasing the effectiveness of the activities of all parties involved, within the limits of the available resources. Manufacturers who have chosen a more systematic approach to product development would follow the stages of development within the broader context of quality assurance principles, including the use of quality risk management and pharmaceutical quality systems (4, 5).

Current use of medicines for the paediatric population reflects the full range of dosage forms and routes of administration used for adult medicines. Common routes of administration in paediatric patients include oral, parenteral, dermal, pulmonary, nasal, rectal and ocular. There is, however, limited information on the acceptability of different paediatric dosage forms in relation to age and therapeutic needs and on the safety of excipients in relation to the development of the child. A European Medicines Agency (EMA) reflection paper on paediatric formulations (6) provides background information on these issues. Reviews by Ernest et al. (7) and Krause and Breitreutz (8) discuss the needs and challenges in developing paediatric medicines.

The desirable features of high-quality paediatric medicines common to all dosage forms are outlined below. Further information on specific dosage forms is given in the following sections.

3.1 **Convenient, reliable administration**

The administered dose should contain an amount of API adjusted to the age and needs of the child. The implication is that more than one dosage form of the API or more than one strength of a dosage form may be needed to cover different age groups. The intended dose volume or size should be appropriate for the target age group.

Paediatric medicines should preferably be presented as formulations that are ready to administer. The need for health professionals, parents or caregivers

to manipulate the dose prior to administration should be kept to a minimum. However, there might be situations, depending on the formulation properties and the dose range to be covered, where this cannot be avoided.

Alternatively, to enable accurate dosing, the dosage form should be designed to subdivide into smaller, uniform doses of appropriate size and, for liquid forms, the dose volume should be accurately measured.

3.2 Acceptability and palatability

Acceptability is the overall acceptance of the dosage form regardless of the mode of its administration. Acceptability of a dosage form depends on a variety of factors such as:

- suitability of the dosage form for the particular age group
- the dosing device used for a liquid medicine
- palatability of an oral medicine
- dose volume or size to be administered
- appropriateness of packaging
- clarity and accuracy of labelling information
- directions for use.

Acceptance of parents and caregivers is also a relevant issue, and the cultural setting may influence the understanding of and expectations of the therapy.

Palatability is the overall acceptance of the taste, flavour, smell, dose volume or size, and texture of a medicine to be administered by mouth or to be swallowed. Palatability can be crucial to adherence. Palatability of the API may influence the choice of dosage form and its design, which may include taste-masking ingredients. The dosage form should not, however, be made too attractive to the child (e.g. it should not be in the form of a sugar-coated tablet resembling a sweet or candy) in order to avoid increasing the risk of accidental poisoning.

It is preferable that the dosage form is palatable in itself without any need for further modification. The caregiver may, however, attempt to improve the ease of administration and acceptance of the patient by mixing the dose with food or a beverage. Such mixing should not be encouraged unless it can be done in such a small volume that ingestion of the full dose can be guaranteed and if there are no undesirable physical or chemical interactions between the food and the medicine. If mixing with food or a beverage (including breast milk) is foreseen, this eventuality should be evaluated by appropriate compatibility studies. Information should be provided in the patient information leaflet by the manufacturer, as supported by evidence-based studies.

3.3 Minimum dosing frequency

Parents and caregivers take care of the administration of medication to young children, whereas schoolchildren and adolescents can often manage their medication themselves. In both cases minimal dosing frequency should be aspired to. Instructions on the dosing frequency are based on the pharmacokinetic and pharmacodynamic properties of the API, but may be influenced by the design of the dosage form.

Frequent dosing, i.e. more than twice daily, may have a negative impact on adherence to the dosing scheme both by caregivers and by older children, in particular when medicines are taken in settings where a trained caregiver is not available, e.g. at school. Moreover, frequent dosing may conflict with the lifestyle of older children.

3.4 End-user needs

In addition to maximizing the acceptability and palatability of paediatric medicines it is important that they are convenient to produce and affordable. It is also important to bear in mind supply-chain considerations, such as ease of transportation and storage requirements. It is not always possible for the user to store medicines in a refrigerator.

Depending on the age and clinical condition of the child, there are restrictions to the applicable dose volume or size. Generally, when developing the product, minimum dose volume and size should be the goal.

Lack of access to clean water is an important issue to take into consideration in the development of medicines that need to be dissolved, diluted or dispersed prior to administration, as it may compromise the quality of an FPP. It may be necessary to educate patients on how to obtain water of suitable quality, e.g. by supplying instructions on boiling or filtering. Provision of the liquid vehicle as a part of the package may be an option, or the dose may be dispersed or dissolved in a suitable food or beverage prior to administration. Some instructions on such use should be included on the label or package insert. Regional and cultural differences with regard to preferred tastes may need to be considered.

4. Particular dosage forms to be considered

4.1 Flexible solid dosage forms

Dosage forms that, in general, are likely to prove most suitable for global use, including for developing countries, and which should be prioritized, are flexible solid dosage forms such as tablets that are orodispersible and/or can be used for preparation of oral liquids suitable also for the younger age groups, e.g. dispersible and soluble tablets. The flexible dosage form design may be used for various APIs but may not be suitable for medicines requiring a precise dose titration.

Provided that the medicine can be dispersed in breast milk from the mother, it could potentially be used in very young children (< 6 months). When recommending mixing medicines with breast milk, the effect on the taste should be taken into account, as unpleasant tasting medicine may cause aversion in breastfed children. In addition, the compatibility of the API with breast milk will need to be considered. The same considerations apply whenever medicines are mixed with other food.

It is necessary to identify appropriate product strengths and ratios of active ingredients for each medicine as well as to ensure that package sizes will allow optimal use under public health programmatic conditions.

4.2 Oral medicines

For oral medicines that require precise dose measurement or titration, suitable dosage forms could be based on a platform technology to produce multiparticulate solids, e.g. mini-tablets or spherical granules (pellets), that allow production of dosage forms of varying strength as well as different dosage forms like tablets and capsules, and dosage forms to be dispersed to form a liquid dose or to be sprinkled onto food. Platform technology has potential flexibility for manufacturing appropriate fixed-dose combination products (FDCs). Breakable solid dosage forms specially designed to provide the appropriate dose may also serve the same purpose (1, 9).

4.3 Medicines for severe conditions

For severe disease conditions, e.g. neonatal sepsis, the use of alternative dosage forms should be carefully considered. Some alternatives may be easier for untrained caregivers to administer, e.g. a rectal preparation or a spray under the tongue. For some conditions, parenteral formulations may be the best existing option; however, their use requires a trained caregiver.

4.4 Rectal preparations

As an alternative to parenteral preparations for severely ill children or children who are unable to swallow, the use of rectal preparations for indications of severe malaria, pain, infection and also nausea and vomiting may be appropriate. There may, however, be cultural barriers to the use of rectal preparations.

5. Formulation design

When designing paediatric medicines, the route of administration, dosage form and dose of the API are decided on the basis of the disease state, API properties such as taste, aqueous solubility, pharmacokinetic and pharmacodynamic properties

and stability during manufacture, storage and use of the chosen dosage form (10). The age, size and condition of the child (e.g. critical illness, concomitant medication, or inability to swallow a dose), and the expected duration of the therapy must be taken into account. Selection of the most appropriate dosage form is, therefore, based on case-by-case considerations.

Most medicines are formulated as single compounds. FDCs are chosen only when the combination has a proven advantage over single compounds administered separately, for example, to achieve compliance in multidrug regimens for treating human immunodeficiency virus (HIV) and/or tuberculosis (TB). The development of FDCs may be more complex than for single compounds; guidance is provided in WHO guidelines (11).

5.1 Quality

In the pharmaceutical development of paediatric medicines attention should be paid to current quality guidelines, especially those provided by WHO (1).

The acceptable level of impurities in APIs and degradation products in finished dosage forms should be qualified and controlled according to regulatory guidelines, e.g. ICH guidelines (12–14). Safety margins established during toxicological studies on an API and finished dosage form usually apply to a worst-case level in adults. Such limits typically apply to both adults and children; although a child would receive a smaller dose, the exposure per kilogram is likely to be similar. Term and preterm neonates have to be considered specifically, and establishment of safety limits may require safety studies in juvenile animals. Additional guidance may be found on the EMA web site (15–17).

The final product should comply with the requirements in relevant pharmacopoeial monographs, preferably those in *The International Pharmacopoeia*.¹ With regard to dissolution testing, dissolution media should be carefully reconsidered in view of the different gastric pH of children from that of adults. Testing at other pHs should be considered in relevant cases. For dissolution testing of special dosage forms, such as chewable tablets, suspensions and patches, see the International Pharmaceutical Federation/American Association of Pharmaceutical Scientists (FIP/AAPS) guidelines for dissolution testing of special dosage forms (18).

5.2 Biopharmaceutics classification system

The biopharmaceutics classification system (BCS) is a scientific framework for classification of APIs for oral administration. The BCS is based upon aqueous

¹ *The International Pharmacopoeia*, 4th ed. First and Second Supplements (available online and on CD-ROM). Geneva, World Health Organization, 2011 (<http://www.who.int/medicines/publications/pharmacopoeia/overview/en/index.html>).

solubility and intestinal permeability. An API is considered highly soluble when the highest dose is soluble in 250 ml or less of aqueous media at 37 °C over the pH range 1.2–6.8. The volume estimate of 250 ml is derived from typical bioequivalence study protocols that prescribe administration of a medicine together with a glass of water to fasting human volunteers. A highly permeable API is absorbed orally to an extent of 85% or more of the administered dose based on a mass-balance determination or in comparison to an intravenous dose (19).

Hence an API can be classified as belonging to 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).

Classification of APIs included in the WHO Model List of essential medicines is provided in the WHO Technical Report Series (20).

The BCS may be particularly helpful to assess the importance of aqueous solubility since it relates the solubility of the API to the unit dose. Aqueous solubility should not be a concern in the formulation of immediate-release dosage forms containing class 1 and 3 substances.

For class 2 substances, the effect of particle size, polymorphic form, and solubility enhancers, among others, should be considered, as the absorption of these substances may be limited by dissolution rate. The same applies to class 4 substances, although factors other than dissolution may also govern the oral absorption. However, overall the BCS classification can be used as a basis when estimating the likelihood of different absorption of paediatric medicines when the dosage form and/or excipients used in adult medicines differ from those used for paediatric medicines.

In addition, for BCS class 3 and 4 substances, where the absorption process and/or intestinal first pass also restrict bioavailability, the possibility of excipients affecting transit time (efflux), transporter function and metabolic enzymes (typically CYP3A4) should be taken into consideration.

5.3 Excipients

The use of excipients in paediatric medicines is driven by functional requirements and should be justified through a risk-based assessment, taking into account factors such as the paediatric age group, frequency of dosing and duration of treatment.

The added challenge for paediatric medicines compared to adult medicines is that excipients may lead to adverse reactions in children that are

not experienced by adults or are not seen to the same extent. Reviews of the literature on adverse reactions attributed to excipients show that the available data on excipient safety are limited in quantity and variable in quality.

Major problems with excipients in paediatric medicines, especially when used to treat infants and neonates, have been reported (21), e.g. medicines with benzyl alcohol, azo-dyes, propylene glycol, ethanol and propyl paraben. A study on the exposure to benzyl alcohol and propylene glycol of neonates receiving parenteral medication demonstrated a potential risk of toxic doses, especially for neonates receiving continuous infusion (22). The toxicity of excipients to newborns and infants can be explained by factors related to their physiological and metabolic development (2). Information on the safety of some excipients may be found, for example, in reviews published by the American Academy of Pediatrics (23). Alternative sources of information should also be consulted, e.g. the WHO Technical Report Series on Evaluation of certain food additives (24).

In the development of paediatric medicines, the number of excipients and their quantity in a formulation should be the minimum required to ensure an appropriate product with respect to performance, stability, palatability, microbial control, dose uniformity and other considerations necessary to support product quality. Risks for adverse reactions are mostly associated with excipients used for liquid dosage forms.

In the choice of excipients consideration should be given to:

- the safety profile of the excipient for children of the target age groups;
- the route of administration;
- the single and daily dose of the excipient;
- duration of the treatment;
- acceptability for the intended paediatric population;
- potential alternatives;
- regulatory status in the intended market.

Potential alternatives to excipients which pose a significant risk to children should always be considered. Another dosage form or even a different route of administration might be necessary to avoid significant risk. Although well-known excipients with well-defined safety profiles are preferred, new excipients cannot be excluded. Novel excipients should only be used when their safety, quality and appropriateness for use in children have been established. It may also be necessary to look at alternative excipients because of different cultural attitudes or for religious reasons, e.g. the use of gelatin may not be acceptable for all patients.

5.4 Colouring agents

The use of colouring agents in paediatric medicines is generally discouraged, in particular in medicines for infants and young children. Their use may, however, be justified in certain cases, e.g. to avoid accidental dosing errors in connection with medicines produced in several strengths. In this case, a solid dosage form of the types mentioned in section 3 may be preferred because size, shape and embossing can facilitate identification of different strengths of the preparation.

Some colouring agents used in paediatric medicines have been associated with hypersensitivity (25). The number of colouring agents that are acceptable for use in medicines is limited. Azo-dyes should be avoided in children's medicines and attention should be paid to the risk of allergic reactions associated with natural colourants (26).

5.5 Antimicrobial preservatives

FPPs may require antimicrobial preservatives to avoid microbial proliferation during storage, in particular under in-use conditions. Preservatives are needed in particular for aqueous multidose preparations and semi-solid preparations and may also be needed for other aqueous preparations. Usually solid dosage forms do not require preservatives.

Preservatives may have a potential to cause adverse reactions, in particular in infants and neonates, and should be avoided where possible. Furthermore, complex preservative systems should be avoided.

Ophthalmic preparations without preservatives are strongly recommended for use in children, especially neonates. Therefore, preparations without preservatives should be developed wherever possible in order to cater for the diversity of patients' needs. When preservatives are required, their concentration should be the minimum level consistent with satisfactory antimicrobial function in each individual preparation and a thorough justification for the choice of the preservative should be established. Ophthalmic preparations without any mercury-containing preservatives, e.g. thiomersal, should also be considered. Further details on this topic are provided in a public statement (27) published on the EMA web site.

5.6 Sweetening agents

Oral paediatric medicines often use sweetening agents to make them palatable. These may be either cariogenic or non-cariogenic sweeteners. In addition to the considerations listed in section 4.3, attention should be paid to:

- safety of the sweetening agent in relation to specific conditions of the child, e.g. diabetes, fructose intolerance, and avoiding use of aspartame in patients with phenylketonuria;

- the laxative effect of poorly absorbed or non-digestible sweeteners in high concentrations;
- the severity of the condition to be treated, i.e. are potential adverse reactions of the sweetening agent secondary to patient adherence?

5.7 Taste masking

Taste masking in medicines for oral use or for use in the mouth is often needed to improve palatability of the medicine. Children have a well-developed sensory system for detecting tastes, smells and chemical irritants. They are able to recognize sweetness and saltiness from an early stage and are also able to recognize a sweet taste in oral liquids and the degree of sweetness (28). Children seem to prefer sweeter tastes than adults do. The unpleasant taste of an API, e.g. bitterness or a metallic taste, is, therefore, often masked in an oral liquid by the use of sweetening agents and flavours. Additional use of colouring agents that match the flavour is discouraged (see section 4.4) unless this is necessary to disguise an unpleasant colour related to the API. Some successful approaches to taste masking are discussed by Ernest et al. (7).

A child's preference for particular flavours is determined by individual experiences and culture. The target for taste masking need not necessarily be good-tasting medicines; it should simply be a taste that is acceptable in as many countries as possible taking into account cultural differences.

An example of a "qualitative evaluation of the taste by a taste panel" for zinc formulations can be found in the United Nations Children's Fund (UNICEF)/WHO publication on production of zinc formulations (29, 30).

Consideration should be given to the items listed in sections 4.3 and 4.6.

Taste masking for orodispersible tablets and chewable tablets is in principle similar to taste masking for oral liquids. Non-cariogenic sweeteners and flavours are preferred.

5.8 Solubility enhancers

The aqueous solubility of the API may limit the concentration achievable in formulated solutions and, hence, the desirable dose volume. In many cases an acceptable solution requires solubility enhancing methods, e.g. use of non-ionic surfactants and of co-solvents such as glycerol, liquid macrogols and ethanol. If solubility enhancers are to be used, consideration should be given to the safety of both the agent and the formulation, for example, the risk of irritation and damage of intestinal tissues in neonates caused by hyperosmolality or other local toxicity. Risks associated with the use of solubility enhancers are higher when they are included in parenteral preparations than when used in oral preparations.

Ethanol, especially in large amounts, should not be administered to children (aged 0–17 years) through FPPs without a clear demonstration of benefit.

Although it is recognized that ethanol may not always be eliminated from FPPs, and replacements may raise other issues, the smallest possible amount should be used. When ethanol is used, adequate development data demonstrating that the lowest possible concentration of ethanol is used should be established.

Children, especially under the age of 6 years, are more vulnerable to the effects of ethanol. Adverse effects on the central nervous system are already evident at blood ethanol concentrations of 10 mg/100 ml in children. Higher peak ethanol blood concentrations are also observed in children than in adults for a similar intake. Chronic exposure to ethanol (> 1 week), even to small doses, through FPPs is, in principle, contraindicated in children aged less than 6 years and should be limited to 2 weeks in children aged over 6 years, if a positive risk–benefit balance is not demonstrated. Toxic effects on brain maturation in young children are highly probable and also supported by non-clinical data. Additionally, chronic exposure has been shown to be linked to ethanol dependence in adults and adolescents.

6. Oral administration

The oral route is the preferred and most appropriate route of administration to paediatric patients. This route is generally acceptable in all age groups if the medicine is administered in a suitable dosage form, e.g. in liquid form for children in the youngest age groups who have difficulty in swallowing solid dosage forms. Strictly speaking, the choice of dosage form for oral administration depends on the gut function and, thus, on both age and clinical condition.

Consideration should be given to the effects of increased gastric pH and intestinal mobility at birth and in early infancy (2). In addition, gastric emptying of sick newborns is most erratic and can be delayed. Further information can be found in an EMA guideline on medicines for term and preterm neonates (31).

Mixing oral dosage forms with food or a beverage is not recommended, but may be performed to enhance compliance (see section 2.2). Potential effects of foods on bioavailability should be considered. When recommending mixing medicines with food, attention should be paid to the effect on the taste, as an unpleasant taste of medicine may cause aversion in children.

6.1 Oral liquid preparations

Oral liquid preparations include aqueous solutions, suspensions, emulsions and syrups. They are most appropriate for children in the youngest age groups who are unable to swallow solid dosage forms. The advantage of oral liquid preparations is that variable dose volumes can be measured and administered. The need for stabilizing agents, e.g. antimicrobial preservatives, is a major drawback as is the potential chemical instability, which may lead to a requirement for controlled storage

conditions during distribution and use. Oral liquid preparations are less transportable than solid-dose preparations because of their relatively high bulk volume.

The dose volume is important for the acceptability of the preparation. High-dose volumes pose a risk of incomplete ingestion and, thus, underdosage. Efforts should, therefore, be made during pharmaceutical development to minimize the dose volume while recognizing the need to ensure accurate measurements of the dose over the anticipated range. Typical target dose volumes are 5 ml or less for children under 5 years and 10 ml or less for children of 5 years and older (32). There is some uncertainty about these limits because the more palatable the formulation, the higher the dose volume that will be accepted by the child. Target volumes and electrolyte contents are critical for neonates, especially in cases of immature renal function.

Oral liquid preparations may be supplied in multidose containers or single-dose containers. Usually, both forms require antimicrobial preservatives. Special attention has to be paid to the in-use stability of multidose preparations, both microbial and physicochemical.

Multidose preparations should be packaged together with an appropriate dosing device. The correct graduation of the device and the accuracy of the volumes measured must be checked by the manufacturer. Generally, oral syringes are preferable because of the flexibility in dose measurement and superior accuracy compared to other devices such as graduated pipettes or plastic spoons. The accuracy in measuring and delivering a volume of liquid is influenced by the liquid's physical characteristics, especially its viscosity.

The risks associated with incorrect dosing should be considered. If correct dosing is critical, a single-dose preparation, e.g. a pre-filled oral syringe, should be considered.

Drops

Some liquids are administered as drops in small volumes using a dropper or a graduated pipette to measure a volume to be dissolved or dispersed in water or another diluent before the dose is swallowed. The use of this dosage form should be evaluated using a risk-based approach to ensure it is suitable given the medicine's potency and side-effect profile and the potential for dosing errors. The in-use performance of the dose-measuring device is critical for this dosage form.

Oral suspensions

Formulation of an oral suspension may be dictated by the aqueous solubility of the API and the balance between the dose of API and the dose volume. In certain cases, the unpleasant taste of an API can be reduced by choosing the suspended form.

Oral suspensions must be shaken before use to ensure a homogeneous liquid when the dose volume is measured. There might in some instances be a significant risk of dosing errors due to sedimentation or caking of the suspension during storage; therefore, resuspendability should be a stability parameter. The control strategy for oral suspensions includes dissolution testing (18) unless otherwise justified.

Powders and granules for reconstitution

Solid preparations for reconstitution as solutions or suspensions should be considered, especially when the liquid preparation has a short shelf-life due to instability (chemical, physical or microbiological). Powders and granules for reconstitution are produced as single-dose sachets or multidose preparations, usually provided in containers that can hold the reconstituted multidose preparation. The liquid vehicle can be provided together with the dry preparation, especially when the product is intended for markets where access to clean water may be difficult. Alternatively, manufacturers can recommend on the product labels and summary of product characteristics (SmPCs) how to reconstitute the product, e.g. with boiled and cooled water.

To ensure their proper use, the solids must be easily wetted and dispersed or dissolved within a short time once the vehicle is added.

The major drawbacks of this type of formulation are the bulk volume of the preparation, i.e. it is less transportable, and the in-use microbial stability of multidose preparations, which may require use of antimicrobial agents. For these reasons, single-dose preparations of the flexible types mentioned in section 3.1 are preferable.

6.2 Administration through feeding tubes

For neonates and seriously ill infants, enteral administration of liquids via feeding tubes is used. Hence the preparation will not be subject to the normal effects of saliva and/or gastric juice, which may affect its bioavailability.

Dosing accuracy should be considered, taking into account the ease of transfer along the feeding tube (including viscosity, particle size and amount of suspended components), potential absorption of the API into the tube material and rinsing by flushing of the tube. The rinsing volume should be appropriate to the target age group and an acceptable fluid intake.

These considerations should be highlighted in the SmPCs.

6.3 Oral solid dosage forms

Oral solid dosage forms include a variety of final forms from powders to coated tablets intended to be swallowed directly or after application to the mouth (chewable tablets, orally dissolving tablets or orodispersible tablets). Some are

intended for swallowing after dissolution, dispersion in water or other suitable liquids. Their advantages over oral liquid preparations are improved stability, good dosage uniformity and options for different doses. The ease of administration depends on the child and the particular dosage form. These forms are convenient for packaging and ease of transport.

While powders and multiparticulate preparations mixed with food or beverages may be acceptable from the moment when the infant is able to accept solid food, i.e. about 6 months, there are uncertainties with regard to the age at which intact tablets and capsules are acceptable. It has been thought generally that even small tablets and capsules to be taken whole are not acceptable for children below the age of 6 years. However, no good scientific evidence exists to support this notion. Recent preliminary evidence indicates that mini-tablets (with a diameter of less than 4 mm) may be acceptable even by the majority of small children (2–4 years old) (33).

Powders and multiparticulate preparations

Powders and multiparticulates are provided in sachets or in hard capsules that allow the contents to be taken directly or after manipulation, e.g. following preparation of oral liquids or to be sprinkled on to food or liquids.

Multiparticulate preparations are granules, rounded granules of uniform size (often called pellets) and mini-tablets. Pellets are often prepared by extrusion/spheronization technology, which produces uniform particles within the size range 0.5–2 mm. Mini-tablets are prepared by compression into units with a diameter of not more than 4 mm. Especially when only a portion of the provided dose is administered, the particle size distribution of the API may be critical to dosing accuracy. Control of dose uniformity should be performed on a level corresponding to the dose to be taken by the target age group.

Multiparticulate preparations offer the same advantages as conventional tablets and capsules with regard to the use of excipients, opportunities for taste masking (e.g. by coating), stability and opportunities for modifying the release profile. Furthermore, they possess great flexibility. An age-related dose may be obtained by taking an appropriate number of pellets or mini-tablets. A counting device may be necessary when a large number of pellets or mini-tablets is required. In addition, pellets and mini-tablets are suited for the platform technology mentioned in section 3.2.

Immediate-release tablets

Conventional tablets are either uncoated, film-coated or sugar-coated and are intended for immediate disintegration, release and absorption when swallowed. The coating may cover an unpleasant taste and smell and will, in general, improve palatability. Film-coating is preferable because sugar-coated tablets resemble

sweets or candies and hence may be too attractive to the child. It is critical to differentiate the appearance of tablet packs from that of confectionery packs.

Break-marks intended to enable accurate subdivision of the tablet to provide doses of less than one tablet should be proven to result in parts that comply with the requirements for uniformity of mass or uniformity of content, as appropriate. The decision whether or not to provide scored tablets will depend on a risk analysis, taking into account the safety and dose of the API. A suitable test is provided in the monograph on tablets in *The International Pharmacopoeia* (34). It is preferable that the single part of the broken tablet contains the amount of API suited to the youngest intended age group. Specially designed tablets and tablet punches may be needed.

Caregivers often crush tablets to increase user-friendliness and adherence. Crushing may, however, affect the bioavailability of some medicines. The effect of crushing of tablets should be investigated by the manufacturer and this information should be provided in the patient information leaflet.

Tablets should not be crushed unless instructions allowing crushing are provided on the label by the manufacturer. Generally a multiparticulate formulation supplied in sachets, hard capsules or blister packs is preferred.

Chewable tablets

Chewable tablets are intended to be chewed and swallowed. They should possess good organoleptic properties including a good mouth feel, which is influenced by the solubility, particle size and shape of the API, and they should not leave a bitter or unpleasant aftertaste. They are usually formulated with a high content of a water-soluble sweetener, such as mannitol, which provides a sweet, cooling taste, and microcrystalline cellulose, which assists in obtaining a good mouth feel and reduces grittiness. Other sweetening agents such as sorbitol and xylitol suitable for direct compression are also used.

A potential problem with chewable tablets is that they may be swallowed by a patient before being properly chewed or without being chewed at all. It is, therefore, strongly recommended that chewable tablets are formulated so that they may be swallowed whole and, thus, labelled as “tablets that may be chewed or swallowed whole”, or “tablets that may be chewed, swallowed or crushed and mixed with food or liquid”.

It is a consequence of the above that tablets that may be chewed or swallowed whole should meet the quality requirements for conventional tablets, including dissolution testing. Where applicable, dissolution test conditions should be the same as used for conventional tablets of the same API, but because of their non-disintegrating nature it may be necessary to alter the test conditions (18).

Effervescent dosage forms

Effervescent dosage forms are tablets, granules or powders that are dissolved in water prior to administration. The use of these dosage forms usually requires a relatively large volume of water, the intake of which may be problematic for children. It is helpful when an indication of the minimum volume of water is given on the label. Furthermore, the label should give instructions that the solution is not to be drunk before effervescence has subsided, in order to minimize ingestion of hydrogen carbonate. Effervescent tablets require continuous attention to levels of moisture and humidity during manufacture, packaging and storage.

The drawbacks of effervescent dosage forms are the need for clean water for dissolution and the ingestion of potassium or sodium, which may make them unsuitable for patients with renal insufficiency.

Dispersible and soluble tablets

Dispersible and soluble tablets are intended to be used in the same way as effervescent tablets. Their advantage is that problems with hydrogen carbonate, potassium and sodium are avoided. For the convenience of users, the formulations should disintegrate or dissolve within a short time of being added to water. It is helpful when an indication of the minimum volume of water is provided on the label.

Dispersible and soluble tablets are flexible dosage forms, the formulation of which may be suited for several water-soluble APIs (see section 3.1).

Sustained-release formulations

Sustained-release formulations are designed to slow the rate of release of the API in the gastrointestinal fluids. They may be provided in a variety of formulations, e.g. as multiparticulate solids provided with a barrier coating, in sachets, hard capsules or in quickly disintegrating tablets, coated tablets and matrix tablets. Among the advantages of the sustained-release design is the reduced dosing frequency compared to conventional formulations of the same API, a feature which may improve adherence (see section 2.3). Not all APIs can be formulated as sustained-release products. This will also depend on other factors such as aqueous solubility, intestinal permeability and plasma elimination half-life, which may differ between children and adults.

In the development of sustained-release formulations for paediatric use, special attention must be given to the physiological conditions of the child to be treated and their variability, e.g. gastric pH and emptying rate and intestinal mobility.

The majority of sustained-release formulations, especially coated tablets and matrix tablets, must not be broken or chewed and some will not withstand being mixed with food or a beverage. It is, therefore vital that clear instructions on the proper use of the formulation are included on the label.

Capsules

Capsule formulations are provided either as soft capsules, usually with a liquid or semi-solid content or as hard capsules containing powder or a multiparticulate formulation.

Capsules may be taken whole. The limitations mentioned for tablets apply with regard to the ability of the child to swallow them (see introduction to section 5.3). Hard capsules may be opened and their contents taken as such or taken after mixing with food or sprinkling on to food, but this is not always appropriate.

Instructions on the proper use of a capsule formulation should be provided on the label, e.g. whether the capsule has to be taken whole or whether the capsule contents can be mixed with food to facilitate intake and improve palatability.

Orodispersible dosage forms

Orodispersible dosage forms are orodispersible tablets, oral lyophilisates and thin films, to be placed on the tongue where they disperse rapidly into small-sized particles or “melt” by dissolution in the saliva, after which the dose is swallowed.

Orodispersible tablets designed to disintegrate rapidly are prepared by compression of a formulation containing, for example, mannitol, a super-disintegrant, and a flavouring agent. The amount of API that can be incorporated depends on its physical properties. The product may be moisture-sensitive. Orodispersible tablets are flexible dosage forms (see section 3.1), particularly well-suited for highly water-soluble APIs.

Oral lyophilisates are prepared by freeze-drying of aqueous liquids into porous units shaped like tablets. Typical excipients are gelatin or alginate, which act as structure-forming agents, and mannitol, which facilitates formation of the porous structure and contributes to palatability. Instead of mannitol, sorbitol may be used as a crystallization inhibitor. The amount of water-soluble API to be incorporated is limited (35). Oral lyophilisates are sensitive to moisture and require a vapour-tight package.

Thin, flat films (wafers) to be placed in the oral cavity are prepared by casting water-soluble polymers containing the API in dissolved or dispersed form. The amount of dissolved API that can be incorporated is limited. The release profile depends on the polymer, film thickness and API solubility. The so-called flash-release wafers may have dissolution times of less than 30 seconds.

Orodispersible and orosoluble dosage forms are attractive for several reasons. They may be acceptable to the same age groups as liquid preparations, and it is possible for children who cannot swallow a whole tablet to take an orodispersible dosage form. In some situations, especially with younger children,

the orodispersible dosage form may need to be dissolved in a small volume of liquid prior to administration.

Orodispersible dosage forms are intended for systemic effect after being swallowed but absorption may also take place in the mouth and pharynx. Taste masking may be necessary using water-soluble sweeteners and flavourings.

7. Rectal administration

Rectal administration is an important route that can be used for both local (e.g. laxative and anti-inflammatory) and systemic effects (e.g. antipyretic and anticonvulsive) in all age groups. This route of administration is especially valuable when oral administration is not possible because of the condition of the child and palatability issues. In certain cases it is possible to obtain immediate systemic effect by rectal administration of solutions. There is, however, limited absorption and bioavailability for many APIs. Erratic absorption due to faecal contents in the rectum may unpredictably delay absorption.

Dosage forms for rectal administration are primarily suppositories, rectal capsules and rectal liquids (enemas). Other dosage forms are available, e.g. rectal foams provided in pressurized containers.

When suppositories and rectal capsules are administered to paediatric patients there is a risk of premature expulsion, especially when the dosage form constituents have an irritating effect. Rectal dosage forms should be used with extreme caution in premature infants, as they can tear very delicate tissues and, thus, introduce infection.

Adherence for rectal preparations may be lower than for oral dosage forms. There are barriers to rectal administration for both caregivers and patients in some regions and cultures. Generally their acceptability among children of any age is poor.

7.1 Suppositories

Suppositories for use in paediatric patients must be tailored to the age or size of the child. Cutting of suppositories into halves should be avoided unless they are designed to be cut. The majority of suppositories contain APIs as solid particles, which may be unevenly distributed in the suppository base as a result of the manufacturing technique of moulding a molten formulation. However, it is also possible to prepare suppositories which can be cut in smaller portions, ensuring delivery of an appropriate dose. Information on acceptability of cutting suppositories should be provided. When designed to be cut, information on the technique should be provided in the patient leaflet.

Two types of suppository base are available: one is insoluble in water, e.g. hard fat, which melts below body temperature. With suppository melt formulations, special consideration has to be given to storage temperature. The

other type of suppository is soluble or miscible with water, e.g. macrogols, which are dissolved in or mixed with the rectal liquid. Both types may be irritants.

7.2 Rectal liquids (enemas)

Rectal liquids are solutions, suspensions or emulsions based on water or vegetable oil. Any volume to be administered should be appropriate to the size of the child. For systemic therapy, the volume to be administered should be as small as possible to achieve accurate delivery, good absorption and to avoid irritation. Volumes of 1–5 ml may be acceptable.

The rectal tube should be of a length appropriate to the size of the child and should not cause injury. Use of pre-filled syringes equipped with a rectal tube facilitates individual dosing and may reduce the need for several strengths of the formulation.

Formulation of aqueous rectal liquids is similar to the formulation of other aqueous liquids regarding use of stabilizing agents, including surfactants and antimicrobial agents. Non-ionic surfactants are preferred because ionic surfactants are frequently irritating to the rectal mucosa. The need for stabilizing agents, in particular antimicrobial agents, may be reduced by the formulation of rectal tablets to be dispersed or dissolved in water immediately before administration.

8. Parenteral administration

Parenteral administration by the intravenous route is preferred for seriously ill children and for clinically unstable term and preterm neonates (in developed country settings). Some parenteral preparations are administered by the subcutaneous and intramuscular routes. The limited muscle mass of newborns and, in particular of preterm infants, constrains the use of intramuscular injections. Other routes of administration, e.g. intraosseous, are used in emergency cases.

Most children have a fear of injection needles. Possible alternatives, especially suited for children undergoing frequent or long-duration treatment, such as needle-free injection devices (jet injectors), that drive small droplets through the skin by high pressure, could be considered, e.g. for subcutaneous administration. However, experience of their use in paediatric populations, especially in smaller children is limited.

Repeated injections should be avoided for children unless they can be given intravenously via catheter or injection ports that can remain in place for the length of the treatment. Reducing the number of injections by formulation of sustained-release preparations requires consideration of increased blood perfusion in children, usually increasing absorption from tissue depots. The

clinical need to limit fluid uptake, especially in very young children, must also be taken into account.

Age- and weight-related preparations (injection volume and strength) are preferred in order to provide an acceptable injection volume, and to avoid dosing errors due to improper use of multidose preparations and errors in calculation of the dilution required to obtain measurable volumes. It is helpful to state on the label the size of syringe that permits accurate administration.

The size of the presentation should not allow significant overdosage if the dose or volume is miscalculated. In general the volume in the vial should be no greater than 10 times the smallest dose to be measured.

8.1 **Formulation**

Aqueous preparations (solutions or suspensions) must be adapted to the physiological conditions on the application site. The tolerances for deviations in pH and osmolality are dependent on the route of administration. In particular, subcutaneous administration is highly sensitive because dilution of the injected volume and its escape from the injection site proceed slowly. Hyperosmolar injections and injections with extreme pH may cause pain and irritate peripheral veins.

Formulations for neonatal patients are usually aqueous solutions intended for intravenous administration. Target volumes and electrolyte contents are important for all paediatric patients; however, these are critical for neonates (19).

It is crucial to consider the safety profile of each excipient and its suitability for the intended use (see section 4.3).

Attention should be paid to the potential adsorption of the API on to the surfaces of plastic containers and catheters, and to leaching of plasticizers from containers and catheters to the parenteral preparation.

Some APIs are presented as powders or lyophilisates to be reconstituted before administration. It is important that clear instructions on the reconstitution and information on storage conditions and duration appear on the label or product information.

8.2 **Additional points to consider for parenteral preparations**

- There should be a minimal need for complex calculations for prescribing, dispensing and administration (e.g. dose in micrograms/kg/hour prescribed to be converted to volume per hour administered; conversion between mmol prescribed and mg on the label; conversion between mg prescribed and percentage concentration on the label; and decimal points).
- The need for additional steps in the preparation of the product for administration should be minimized, for example, by developing ready-to-use preparations.

- Measurement of volumes smaller than 0.1 ml should not be required. Dose volumes in hundredths of a millilitre should be avoided. Tables should be included in the product information clearly stating the dose and the volume to be measured, and how this can be achieved safely and accurately.
- Miscalculation can lead to overdose and the amount of the API in the presentation should not allow administration of a critical overdose to the smallest patient for whom the presentation is intended.
- Using several vials per dose or large vials that may contain several doses should be avoided if possible.
- Other methods of preventing overdose of critical medicines can be explored and presented for consideration, e.g. tables of weight, dose (mass) and volume (ml) of preparation required.
- Safety measures and restrictions on administration via central or peripheral cannula should be provided, including advice on maximum and minimum dilutions for safe administration.
- Consideration should be given to the contribution to the child's fluid and electrolyte balance due to the medicine administration volume and/or electrolyte content.
- Compatibility with other medicines that are part of a standard care plan should be investigated.
- Information on pH of the FPP needs to be provided in the product information.

9. Dermal and transdermal administration

Preparations for dermal (or cutaneous) administration include liquid preparations (lotions and shampoos), semi-solid preparations (ointments and creams) and solid preparations (powders). They are used to obtain local effects.

Unintended systemic absorption through the dermis is a potential risk with many APIs. The stratum corneum is deficient in preterm neonates. Children have a lower volume of distribution per unit area of skin.

Depending on the dosage form, various excipients are needed. The safety profile of each must be considered (see section 4.3) including the risk of sensitization of the skin. Preparations containing ethanol should be avoided in very young children because ethanol may dehydrate the skin and cause pain.

Liquid suspensions, semi-solid preparations and patches should be subject to dissolution testing (18).

9.1 Transdermal patches

Transdermal patches are used for systemic delivery of APIs which are capable of diffusion through the stratum corneum and are therapeutically active at the low plasma concentrations that can be achieved. The manufacture of transdermal patches of the “drug-in-adhesive” type is now well developed and less problematic than the earlier “drug-in-reservoir” type; the API is dispersed in a suitable polymeric adhesive to be fixed in a thin layer on a backing and covered by a removable liner.

The size and shape of a transdermal patch should be adapted to fit the child’s body. It should stick firmly to the skin and not be too difficult to remove. Application sites which cannot easily be reached by the child should be chosen to avoid removal of the patch by the child. The risk of deliberate removal and its consequences for therapy must be considered. The increased systemic absorption through the skin, for the reasons mentioned above, may increase the systemic delivery from transdermal patches, in particular in newborns and young infants.

When designed to be cut, information on the cutting technique should be provided in the patient leaflet and facilitated by the presence of cutting lines to ensure equal division. Reservoir systems should never be cut.

Adhesives should have a low allergenic potential to avoid irritation and infection. Local tolerance and acceptability should be tested.

10. Inhalations

Pulmonary administration of medicines by inhalation has traditionally been used to obtain a local effect. This route of administration also has a potential for systemic delivery. Preparations for inhalation include liquids for nebulization, pressurized metered dose inhalers (MDIs) and dry powder inhalers (DPIs).

The implications of the physiology of children of different ages and their ability to use the devices correctly should be considered in the development of paediatric inhalations (8). Depending on their age, children may have more or less difficulty with some of the devices. Problems with the coordination of the inhalation for MDIs and the ability to inhale strongly enough for DPIs determine the effectiveness of getting the medicine into the lung.

The total lung deposition is important for the clinical efficacy of preparations for inhalation. Generally it is affected by the formulation and delivery device controlling size distribution of the aerosol and patient-related factors such as the current disease state. The diameter of the airways is smaller in children than in adults; hence deposition by impact in the upper and central airways may be significantly higher in children (36). The particle size of the aerosol produced by the delivery device needs to be explored during development.

Nebulized liquids are potentially suitable for young children who cannot use MDIs and DPIs. Their use, however, requires nebulizing devices and access to electricity.

MDIs may be suitable for children from birth when combined with a spacer. A spacer eliminates the need for coordinating the MDI actuation and the start of inhalation. For children younger than 2–3 years a facemask is also required. This can be replaced by a mouthpiece when the child is able to manage the system.

DPIs may be used for children from the age of 4–5 years, as minimum inspiratory flow is required. DPIs and MDIs are preferred for older children because of their portability and convenience.

11. Packaging and labelling

Container-closure systems for paediatric medicines are designed and constructed from materials meeting relevant regulatory requirements, and taking into account the stability of the medicine during transport, storage and use. In addition they are designed to ensure that they:

- permit accurate dosing and convenient administration;
- are robust and convenient for the supply chain, i.e. transportable;
- are tailored to the target age group;
- contribute to in-use stability;
- provide appropriate information on the use of the medicine.

In cases where the paediatric medicine is significantly different from a similar adult medicine, it would be important to have noticeably different product packaging for the two products. It is necessary that consideration be given to whether the medicine is to be packed in a child-resistant container, i.e. a packaging that is difficult for young children to open, but not unduly difficult for adults to open properly.

Self-administration of medicine by schoolchildren and adolescents is facilitated when:

- the medicine is easy to use;
- separation of the day dose pack is facilitated; this should be easily carried by the patient in his or her bag;
- clear instructions for use are contained with the medicine.

Adequate information about the medicine and how to use it is important. Information about the dosage should be clearly spelt out, e.g. as milligrams per

weight. Specific instructions about how to measure and administer a precise dose should be provided. Drawings or pictograms showing time, method and route of administration are strongly recommended.

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Web sites

WHO World Health Organization: <http://www.who.int>

ICH International Conference on Harmonisation: <http://www.ich.org>

EMA European Medicines Agency: <http://www.ema.europa.eu>

Annex 6

Recommendations for quality requirements when artemisinin is used as a starting material in the production of antimalarial active pharmaceutical ingredients

1.	Introduction	229
2.	Characterization of artemisinin	231
3.	Tests and specifications for artemisinin starting material	232
	References	235



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;
- 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. In the eventuality that artemisinin is 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.

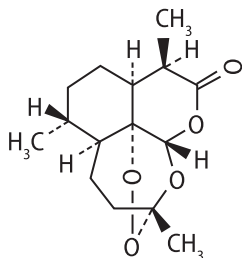
Examination of a wide variety of artemisinin samples produced in various regions indicated the consistent presence of two impurities: artemisitene and an artemisinin diastereomer with the stereochemistry inverted at C-9 (9-*epi*-artemisinin). A possible concern is that artemisinin impurities may not 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



Relative molecular mass: 282.3

Chemical name: (3*R*,5*aS*,6*R*,8*aS*,9*R*,12*S*,12*aR*)-3,6,9-trimethyloctahydro-3,12-epoxyprano[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 C₁₅H₂₂O₅ 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; $[\alpha]_{\text{D}}^{20} = 75^{\circ}$ to $+78^{\circ}$

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

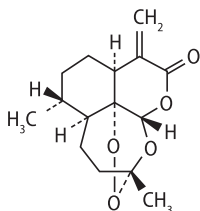
mobile phase consists of a 50:50 mixture of acetonitrile and water, pumped at a flow rate of 1.0 ml/minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 210 nm.

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.

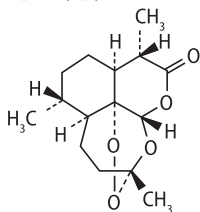
Inject separately 20 μ l of solutions (1) and (2). Record the chromatograms for about 1.5 times the retention time of artemisinin. In the chromatogram obtained with solution (2), artemisitene (impurity A) is eluted at the relative retention of 0.79 with reference to artemisinin (retention time about 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



(3*R*,5*aS*,6*R*,8*aS*,12*S*,12*aR*)-3,6-dimethyl-9-methylideneoctahydro-3,12-epoxyprano[4,3-*j*]-1,2-benzodioxepin-10(3*H*)-one (artemisitenone)



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

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