



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

WHO Technical Report Series

929

WHO EXPERT COMMITTEE ON SPECIFICATIONS FOR PHARMACEUTICAL PREPARATIONS

Thirty-ninth Report



World Health Organization

Geneva 2005

E



WHO Library Cataloguing-in-Publication Data

WHO Expert Committee on Specifications for Pharmaceutical Preparations (2004 : Geneva, Switzerland)
WHO Expert Committee on Specifications for Pharmaceutical Preparations : thirty-ninth report.

(WHO technical report series ; 929)

1.Pharmaceutical preparations — standards 2.Technology, Pharmaceutical — standards
3.Drug industry — standards 4.Quality control 5.References standards
6.Guidelines I.Title II.Series

ISBN 92 4 120929 1
ISSN 0512-3054

(LC/NLM classification: QV 771)

© World Health Organization 2005

All rights reserved. Publications of the World Health Organization can be obtained from Marketing and Dissemination, World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland (tel.: +41 22 791 2476; fax: +41 22 791 4587; email: bookorders@who.int). Requests for permission to reproduce or translate WHO publications — whether for sale or for noncommercial distribution — should be addressed to Publications, at the above address (fax: +41 22 791 4806; email: permissions@who.int).

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

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

The World Health Organization does not warrant that the information contained in this publication is complete and correct and shall not be liable for any damages incurred as a result of its use.

This publication 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.

**Typeset in Hong Kong
Printed in Singapore**

E





Contents

1.	Introduction	1
2.	General policy	2
2.1	Cross-cutting issues in the quality assurance of pharmaceuticals	2
2.2	Pharmacopoeial Discussion Group	3
2.3	International Conference on Harmonisation	3
2.4	International Conference of Drug Regulatory Authorities	3
2.5	Counterfeit drugs	4
3.	Quality control — specifications and tests	5
3.1	<i>The International Pharmacopoeia</i>	5
3.2	Pharmacopoeial monographs on antiretrovirals	6
3.3	Specifications for radiopharmaceuticals	7
3.4	Quality specifications for antituberculosis drugs	7
3.5	Revision of <i>International Pharmacopoeia</i> monograph on artemisinin derivatives	8
3.6	Screening tests for antiretroviral drugs	8
3.7	Screening tests for antituberculosis products	8
4.	Quality control — International Reference Materials	8
4.1	International Chemical Reference Substances	8
5.	Quality control — national laboratories	9
5.1	External quality assurance assessment scheme	9
6.	Quality assurance — good manufacturing practices	9
6.1	Concept of sampling starting materials	9
6.2	Heating, ventilation and air-conditioning	9
6.3	Manufacture of herbal medicines	10
6.4	Validation	10
6.5	Water for pharmaceutical use	10
7.	Quality assurance — inspection	10
7.1	Sampling of pharmaceuticals and related materials	10
7.2	Training modules for inspectors	11
8.	Quality assurance — distribution and trade-related	11
8.1	Good trade and distribution practices for pharmaceutical starting materials	11
8.2	WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce	12
8.3	WHO Scheme for the certification of pharmaceutical starting materials moving in international commerce	12
8.4	Good distribution practices for pharmaceutical products	12
9.	Quality assurance — risk analysis	13
9.1	New approach to inspections and manufacture	13



10. Quality assurance — stability	13
10.1 Stability testing conditions	13
11. Quality assurance — drug supply	13
11.1 Prequalification project managed by WHO	13
11.2 Prequalification of quality control laboratories and procurement agencies	14
11.3 Update of prequalification procedure	15
12. Regulatory guidance on interchangeability for multisource medicines	15
12.1 Main guidelines for interchangeability	15
12.2 Medicines qualifying for waiver on in vivo bioequivalence studies	16
12.3 Dissolution testing	16
12.4 List of comparator products	16
13. Fixed-dose combination products for priority communicable diseases	17
13.1 Draft guidelines for registration of fixed-dose combination products	17
14. International Nonproprietary Names	17
15. Summary and recommendations	18
15.1 New standards and guidelines adopted and recommended for use	19
15.2 Activities that should be pursued and progress reported at the next Expert Committee meeting	20
15.3 New areas of work suggested	21
Acknowledgements	21
Annex 1 International Chemical Reference Substances and International Infrared Reference Spectra	30
Annex 2 Good manufacturing practices: requirement for the sampling of starting materials (amendment)	38
Annex 3 WHO Good Manufacturing Practices: water for pharmaceutical use	40
Annex 4 WHO guidelines for sampling of pharmaceutical products and related materials	59
Annex 5 Guidelines for registration of fixed-dose combination medicinal products	94



WHO Expert Committee on Specifications for Pharmaceutical Preparations

Geneva, 25–29 October 2004

Members*

Professor I. Addae-Mensah, Professor of Chemistry, University of Ghana, Legon, Accra, Ghana

Ms K. Bremer, Director, Pharmaceutical Department, Norwegian Medicines Agency, Oslo, Norway

Dr S. Haghghi, Head, Pharmaceutical and Microbiology Department, Pasteur Institute of Iran, Tehran, Islamic Republic of Iran

Professor J. Hoogmartens, Faculty of Pharmaceutical Sciences, Laboratory for Pharmaceutical Chemistry and Drug Analysis, Leuven, Belgium (*Chairperson*)

Dr R. Jachowicz, Head, Department of Pharmaceutical Technology and Biopharmaceutics, Faculty of Pharmacy, Jagiellonian University Medical College, Medyczna, Kraków, Poland

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

Dr J.A. Molzon, Associate Director for International Programs, Center for Drug Evaluation and Research, US Food and Drug Administration, Rockville, MD, USA

Ms Metta Treebamroong, Bureau of Drug and Narcotics, Department of Medical Sciences, Ministry of Public Health, Nonthaburi, Thailand (*Co-Chairperson*)

Mr R.W. Tribe, Holder, ACT, Australia (*Rapporteur*)

Representatives of other organizations†

European Medicines Evaluation Agency (EMA)

Mr B. Cuddy, Inspections Sector, London, England

European Pharmacopoeia/European Directorate for the Quality of Medicines

Dr J.H. McB. Miller, Head of Division III (Laboratory), Council of Europe, Strasbourg, France

* Unable to attend: Professor Kim Kil-Soo, Chief, Institute of Pharmaceutical Sciences, College of Pharmacy, Ewha Woman's University, Seoul, Republic of Korea; Dr J.-L. Robert, Service du Contrôle des Médicaments, Laboratoire National de Santé, Luxembourg.

† Unable to attend: Argentinian Pharmacopoeia, Buenos Aires, Argentina; Brazilian Pharmacopoeia, Santa Maria RS, Brazil; Chinese Pharmacopoeia, Beijing, People's Republic of China; Commonwealth Pharmaceutical Association (CPA), London, England; European Chemical Industry Council (CEFIC), Brussels, Belgium; Indian Pharmacopoeia, New Delhi, India; Japanese Pharmacopoeia, Tokyo, Japan; Pharmaceutical Inspection Co-operation Scheme (PIC/S), Geneva, Switzerland; Russian Pharmacopoeia, Moscow, Russian Federation; The World Bank, Washington, DC, USA; United Nations Development Programme (UNDP), New York, NY, USA; United Nations Industrial Development Organization (UNIDO), Vienna, Austria; World Customs Organization (WCO), Brussels, Belgium; World Intellectual Property Organization (WIPO), Geneva, Switzerland; World Self-Medication Industry (WSMI), Ferney-Voltaire, France; World Trade Organization (WTO), Geneva, Switzerland.



International Pharmaceutical Federation (FIP)

Dr A.P. Sam, The Hague, The Netherlands

International Atomic Energy Agency (IAEA)

Dr K. Solanski, Division of Human Health, Department of Nuclear Sciences and Applications, Vienna, Austria

International Federation of Pharmaceutical Manufacturers Associations (IFPMA)

Mrs J. Ramsbotham, Vice President Global Quality Assurance, Solvay Pharmaceuticals, Weesp, The Netherlands

International Generic Pharmaceutical Alliance (IGPA)

Dr N. Cappuccino, Chair, Science Committee, Sandoz, Inc., Princeton, NJ, USA

International Pharmaceutical Excipients Council (IPEC)

Mr A. Bone, Chair, IPEC Europe, Basingstoke, England

Professor H. de Jong, Vice Chair, IPEC Europe, Servier, Courbevoie, France

Mr F. Milek, Chair, GDP Committee, IPEC Europe, Stuttgart, Germany

Korean Pharmacopoeia

Dr Myoengsin Choi, Department of Drug Evaluation, Korea Food and Drug Administration, Central Pharmaceutical Affairs Council, Seoul, Republic of Korea

United Nations Children's Fund (UNICEF)

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

United States Pharmacopeia

Dr T. Cecil, Rockville, MD, USA

Secretariat*

Dr R. Balocco, Quality Assurance and Safety: Medicines, Department of Medicines Policy and Standards, WHO, Geneva, Switzerland

Dr M. Couper, Quality Assurance and Safety: Medicines, Department of Medicines Policy and Standards, WHO, Geneva, Switzerland

Professor T.G. Dekker, Scientific Support, Research Institute for Industrial Pharmacy, North-West University (Potchefstroom Campus), Potchefstroom, South Africa (*Temporary Adviser*)

Professor J.B. Dressmann, Biocentre, Institute for Pharmaceutical Technology, Johann Wolfgang Goethe University, Frankfurt am Main, Germany (*Temporary Adviser*)

Mr P. Graaff, Department of HIV, AIDS Medicines Diagnostics Service, WHO, Geneva, Switzerland

Dr O. Gross, Quality Assurance and Safety: Medicines, Department of Medicines Policy and Standards, WHO, Geneva, Switzerland

* Unable to attend: Dr J.-M. Trapsida, Regional Adviser, WHO Regional Office for Africa, Brazzaville, Republic of Congo; Dr R. D'Allesio, Regional Adviser, WHO Regional Office for America, Washington, DC, USA; Dr M. Binshana, Regional Adviser, WHO Regional Office for Eastern Mediterranean, Cairo, Egypt; Dr K. de Joncheere, Regional Adviser, WHO Regional Office for Europe, Copenhagen, Denmark; Dr K. Weerasuriya, Regional Adviser, WHO Regional Office for South-East Asia, New Delhi, India; Dr B. Santoso, Regional Adviser, WHO Regional Office for the Western Pacific, Manila, Philippines.



- Mr J. Hetzke, Department of Medicines Policy and Standards, WHO, Geneva, Switzerland
- Dr H.V. Hogerzeil, Director, Department of Medicines Policy and Standards, WHO, Geneva, Switzerland
- Dr S. Kopp, Quality Assurance and Safety: Medicines, Department of Medicines Policy and Standards, WHO, Geneva, Switzerland (*Secretary*)
- Dr V.K. Lepakhin, Assistant Director-General, Health Technology and Pharmaceuticals, WHO, Geneva, Switzerland
- Dr J. Macdonald, Health Canada, Ottawa, Ontario, Canada (*Special Adviser*)
- Miss Y. Maruyama, Traditional Medicine, Department of Technical Cooperation for Essential Drugs and Traditional Medicine, WHO, Geneva, Switzerland
- Dr C. Ondari, Policy, Access and Rational Use, Department of Essential Drugs and Medicines Policy, WHO, Geneva, Switzerland
- Ms M.L. Rabouhans, Chiswick, London, England (*Temporary Adviser*)
- Dr L. Rágo, Coordinator, Quality Assurance and Safety: Medicines, Department of Medicines Policy and Standards, WHO, Geneva, Switzerland
- Dr P. Vanbel, Quality Assurance and Safety: Medicines, Department of Medicines Policy and Standards, WHO, Geneva, Switzerland
- Dr A. van Zyl, Quality Assurance and Safety: Medicines, Department of Medicines Policy and Standards, WHO, Geneva, Switzerland
- Dr D.J. Wood, Quality Assurance & Safety: Biologicals, Department of Vaccines and Biologicals, WHO, Geneva, Switzerland



1. Introduction

The WHO Expert Committee on Specifications for Pharmaceutical Preparations met in Geneva from 25 to 29 October 2004. Dr Hans V. Hogerzeil, Director ad interim, Essential Drugs and Medicines Policy (EDM), welcomed the Committee members and other participants on behalf of the Director-General, Dr LEE Jong-wook.

In his opening remarks Dr Hogerzeil emphasized the importance of the Committee's work. He indicated that a number of the Director-General's priorities and broader policy objectives were part of the Committee's mandate, including:

- “3 by 5”, whereby 3 million people with human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) will be receiving treatment by 2005;
- ready access to essential medicines for diseases such as HIV/AIDS, tuberculosis (TB) and malaria;
- development of international standards for essential medicines; and
- the agreements on trade-related aspects of intellectual property rights (TRIPS agreements) and their repercussions on access to essential medicines.

Dr Hogerzeil indicated that the successful implementation of these priorities presented new challenges for WHO. One such challenge was the development of internationally validated, publicly available specifications and international chemical reference substances for medicines still under patent in many parts of the world. Another challenge was the enhancement of the prequalification programme for medicines for HIV/AIDS, TB and malaria to include texts to provide guidance in the area of procurement, national capacity building through joint evaluation of dossiers, good manufacturing practices (GMP) inspection and implementation of WHO norms and standards. He also announced that within the context of the *Marketing newsletter*, a publication issued by the International Trade Centre/Market News Service (ITC/MNS) in collaboration with WHO/EDM/PAR (Policy, Access and Rational Use), WHO is suggesting implementation of the new mechanisms developed by this Committee, i.e. good trade and distribution practices (GTDP) and the WHO Pharmaceutical starting materials certification scheme (SMACS).

Dr Hogerzeil informed the Committee that the World Health Assembly had requested WHO to help Member States to implement and to enforce regulations, uniform standards and quality assurance programmes. He also said that WHO's involvement with the International

E



Conference on Harmonisation (ICH) at an international level had been helpful to Member States in view of the move towards regional and global harmonization of drug regulation.

2. General policy

2.1 Cross-cutting issues in the quality assurance of pharmaceuticals

Biologicals

The Committee was informed of the work undertaken in this area which included new initiatives in relation to:

- development of guidance on safety, quality, efficacy and access issues relating to transplantation, as well as the standardization of tissues and the screening and testing of donors;
- quality and safety of blood products, with a focus on the implementation of GMP for blood collection centres and provision of training of staff in this area;
- revision of the 1992 WHO GMP on biologicals adopted by both the Expert Committee on Biological Standardization and that on Specifications for Pharmaceutical Preparations;
- stability testing of vaccines;
- development of a text on establishment of secondary reference materials; and
- a proposal to seek European Union (EU) scientific opinion on biologicals intended only for markets outside the EU.

Malaria

The Committee noted the work undertaken by the Roll-Back Malaria programme, and the progress made since its implementation in 2001. The Committee was informed of work being undertaken to develop new monographs for various antimalarial medicines, including one for a fixed-dose combination product.

Traditional medicine

The Committee was informed of the work undertaken by this programme area which included:

- collaboration with the Quality Assurance & Safety of Medicines (QSM) programme towards updating the GMP for traditional herbal medicines;
- updating of quality control specifications for certain chapters of the *Quality control methods for medicinal plant materials* (WHO,



- 1998), e.g. determination of pesticide residues and microbial determination of microorganisms;
- approaches to the emergence of counterfeiting as a problem for traditional medicines; and
- the *WHO guidelines for safety monitoring of herbal medicines in pharmacovigilance systems*, available in six languages.

The Committee was informed that, according to the recent WHO global survey, 92 countries currently regulated herbal medicines. The Committee commended the joint efforts of Traditional Medicines (TRM) and QSM in this area and agreed on the need to continue these activities.

2.2 Pharmacopoeial Discussion Group

The Committee was updated on the progress of the collaboration between WHO and the Pharmacopoeial Discussion Group (PDG). This group started in 1989 and WHO was admitted as an observer in 2001. The current priority was the development of monographs for excipients. Monographs had been completed for 28 of the 50 excipients on the PDG's list.

2.3 International Conference on Harmonisation

The Committee was informed by the Secretariat of the concern within WHO that, due to new priorities and resource constraints, WHO was finding it difficult to fulfil its role as an observer at ICH meetings. However, WHO was exploring the possibility of obtaining assistance from Member States to overcome the shortage of resources and thus enable better representation at ICH meetings. The Committee encouraged the Secretariat to explore this approach to ensure WHO's continued participation and the proper representation of its Member States.

2.4 International Conference of Drug Regulatory Authorities

The Committee was informed about the eleventh International Conference of Drug Regulatory Authorities (ICDRA) meeting held in Madrid from 16–19 February 2004, and the recommendations arising from that meeting. The Committee was advised that the continues to be an important forum at which WHO and drug regulatory authorities can meet and discuss current problems and the latest developments in medicines regulation with the main objectives of improving safety, efficacy, quality of and access to medicines. The next ICDRA meeting will be held in Seoul, Republic of Korea, in 2006.

E



2.5 Counterfeit drugs

The Committee was informed of the pre-eleventh ICDRA satellite workshop held in Madrid on 13–14 February 2004 to exchange information on the growing problem of counterfeit drugs. The meeting was attended by approximately 100 participants including representatives from Interpol, World Customs Organization, Counterfeiting Intelligence Bureau, World Intellectual Property Organization, pharmaceutical regulators and industry. The participants at the workshop recommended that countries should:

- adopt the *WHO Guidelines on developing measures for combating counterfeit drugs* and make counterfeiting pharmaceuticals a criminal offence punishable with appropriate severe sanctions;
- establish effective pharmaceutical regulation, including export controls, licensing of establishments engaged in the manufacture, import, export, distribution, supply and sale of drugs, product registration, inspection and quality surveillance;
- increase local and international cooperation between drug regulatory authorities, nongovernmental organizations, law enforcement agencies and industry;
- raise public and political awareness that counterfeiting of pharmaceuticals poses a serious risk to public health;
- develop and implement best practice manuals regarding distribution and dispensing of medicines;
- publish and provide relevant information on drugs to consumers, health professionals and retailers;
- report any suspected cases of counterfeiting of drugs to the national drug regulatory authority, which should publish and disseminate the information;
- make the reporting of the discovery of counterfeit drugs obligatory;
- raise awareness of consumers and policy-makers of the link between counterfeit drugs and organized crime; and
- exchange data between drug regulatory authorities, law enforcement agencies, international organizations, industry and all stakeholders.

The Committee supported these recommendations and emphasized the urgent need for their implementation.

The participants at the workshop also discussed the possibility of establishing an international framework convention to coordinate international strategies to detect and counter counterfeiting. This proposal will be discussed further at another meeting on counterfeiting



to be held in 2005 as requested and recommended during the eleventh ICDRA meeting, and the Committee expressed interest in giving scientific input. It was recognized that it was important to address this issue at both the scientific and diplomatic levels.

3. **Quality control — specifications and tests**

3.1 ***The International Pharmacopoeia***

The Committee was informed that *The International Pharmacopoeia* was now available in CD-ROM format. The Committee was also informed of the general outline for the development of future monographs to be included in *The International Pharmacopoeia* as well as the outcome of the consultation on quality control laboratory testing of medicines for HIV/AIDS, TB and malaria held in Geneva from 28–30 June 2004. The Committee agreed that guidelines for the development of secondary reference standards should be prepared in collaboration with other interested parties. Endorsement of the development and revision of certain general chapters was also discussed.

The Committee also appreciated the clear layout of the steps to be followed in the development of monographs. These are as follows:

Step 1: Identify specific pharmaceutical products for which quality control (QC) specifications need to be developed, obtain confirmation from all WHO parties concerned (e.g. EDM, specific disease programme and prequalification project team).

Step 2: Provide contact details for manufacturers of the above products in collaboration with all parties concerned.

Step 3: Contact manufacturers to request provision of QC specifications and samples.

Step 4: Identify and contact QC laboratories to collaborate in the project (2–3 laboratories depending on how many pharmaceutical products have been identified in step 1). Contract for laboratory work.

Step 5: Prepare the contract for drafting the specifications and undertaking the necessary laboratory work.

Step 6: Search for information on QC specifications available in the public domain.

Step 7: Conduct laboratory testing, development and validation of QC specifications.

E



Step 8: Support WHO Collaborating Centre in the establishment of International Chemical Reference Substances.

Step 9: Follow the consultative process: send copies of draft specifications to Expert Panel and specialists for comments.

Step 10: Discuss comments with contract laboratories and WHO Collaborating Centres. Conduct additional laboratory testing to verify and/or validate specifications.

Step 11: Hold a consultation to discuss the comments and test results received as feedback.

Step 12: Recirculate draft monograph for comments.

Step 13: Repeat step 10.

Step 14: Present the drafts to the WHO Expert Committee on Specifications for Pharmaceutical Preparations for possible formal adoption. If not adopted, repeat steps 11–13 as often as necessary.

The Committee endorsed a proposed list of drug monographs to be developed for inclusion in *The International Pharmacopoeia*. The Committee agreed that there was no need to prioritize the drugs shown on this list as they were all equally important, but would be subject to confirmation of particular priorities from a medical viewpoint by the respective WHO departments.

The Committee welcomed the news that the third edition of *The International Pharmacopoeia* was now available on CD-ROM; this would facilitate wider use. The Committee encouraged the Secretariat to publish a fourth edition of *The International Pharmacopoeia* that includes all the volumes in a single, comprehensive publication.

3.2 Pharmacopoeial monographs on antiretrovirals

The Committee was given an overview of the status of the development of *The International Pharmacopoeia* monographs on antiretroviral drug substances and finished dosage forms. Specific monographs for antiretrovirals were discussed. The following monographs were adopted for drug substances:

- didanosine
- indinavir sulfate
- nelfinavir mesilate
- nevirapine
- ritonavir
- saquinavir
- saquinavir mesilate



The Committee recommended that the monograph on ritonavir be adopted subject to evaluation of any additional comments received during the consultation phase by an expert working group. Several draft monographs will follow the normal course of action, i.e. they will be submitted for consultation.

3.3 Specifications for radiopharmaceuticals

A representative of the International Atomic Energy Agency (IAEA) presented an update of the joint effort of WHO and IAEA on radiopharmaceuticals, as well as a draft report of the consultation on monographs and specifications for radiopharmaceuticals held in Geneva from 16–17 December 2002. The recommendations of this draft report had been endorsed by the Committee at its thirty-eighth meeting. The Committee agreed that there was a need to continue the close collaboration between IAEA and WHO to update and compile individual monographs at an international level. As radiopharmaceuticals were becoming increasingly important in the diagnosis and screening of medical conditions, the Committee emphasized the urgent need for this work to be undertaken, and recommended replacement of the texts already published in *The International Pharmacopoeia* and in the twenty-fifth report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations (WHO Technical Report Series, No. 567, 1975, Annex 2).

3.4 Quality specifications for antituberculosis drugs

The Committee received a status report on work undertaken to develop monographs on antituberculosis drugs for inclusion in *The International Pharmacopoeia*. The Committee was pleased to note that draft monographs on the following had recently been distributed for comments:

- rifampicin tablets
- rifampicin capsules
- rifampicin and isoniazid tablets
- isoniazid and ethambutol hydrochloride tablets
- rifampicin, isoniazid and pyrazinamide tablets
- rifampicin, isoniazid, pyrazinamide and ethambutol hydrochloride tablets.

The Committee reviewed the test methods developed to date and provided advice and direction to the Secretariat to facilitate the completion of this work.

E





3.5 **Revision of *International Pharmacopoeia* monograph on artemisinin derivatives**

The Committee received a status report on work being undertaken to revise *The International Pharmacopoeia* monograph on artemisinin derivatives.

The Committee emphasized the high priority of this project and recommended that this work should continue.

3.6 **Screening tests for antiretroviral drugs**

The Committee received a status report on work undertaken to develop methods for conducting basic screening tests on antiretroviral drugs.

The Committee accepted the report, but recommended that:

- there should be two thin-layer chromatography (TLC) tests, or one TLC test and one ultraviolet (UV) test available for identification; and
- identity tests should not normally be based on melting points.

3.7 **Screening tests for antituberculosis products**

The Committee received a status report on work undertaken to develop methods for conducting basic screening tests on antituberculosis products using basic chemical and TLC test methods.

As details of the test methods had only recently been distributed for comment, the Committee commended the work done so far and indicated that it would await the final draft document before commenting.

4. **Quality control — International Reference Materials**

4.1 **International Chemical Reference Substances**

The reports of the WHO Collaborating Centre for Chemical Reference Substances for 2002 and 2003 were presented to the Committee. The Committee noted that the availability of a reference standard for the series of artemisinin and its derivatives was one of the highlights of the reports and had been the subject of a WHO press release entitled *WHO releases the first ever international collection of chemical reference substances for antimalarials* (20 October, 2004).

The Committee recommended that the list of reference substances specified in the reports should be adopted (Annex 1). It also



recommended that all efforts be made to maintain this important programme.

5. **Quality control — national laboratories**

5.1 **External quality assurance assessment scheme**

The Committee was informed that 42 laboratories from the six WHO Regions participated in this scheme, which involved a comparison of five different analytical tests of medicines for HIV/AIDS, TB and malaria. This work was carried out in collaboration with the European Directorate for the Quality of Medicines (EDQM). The Committee noted that there was still an opportunity to explore the possibility of additional members participating in this scheme.

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

6.1 **Concept of sampling starting materials**

The Committee considered a proposal to amend the WHO GMP requirement for the sampling of starting materials. This currently requires that every container of a starting material be sampled for identity testing, which is not consistent with the requirement of other GMP documents such as the EU GMP Guide. The latter allows for fewer samples from starting material containers under certain conditions. The Committee recommended that in the interests of harmonization, the proposal should be adopted (Annex 2). The suggested text allows for the possibility of reduced numbers of samples being tested under defined circumstances.

6.2 **Heating, ventilation and air-conditioning**

The Committee was provided with a revised second draft of the supplementary guidelines on GMP for heating, ventilation and air-conditioning (HVAC) systems which had been distributed for comments. The need for this document arose from feedback received from GMP training workshops for GMP inspectors in different WHO Regions.

The Committee noted the second draft document and commended WHO for its work on this subject.



6.3 **Manufacture of herbal medicines¹**

The Committee was provided with a revised draft of the supplementary guidelines for the manufacture of herbal medicinal products. Comments were still being received on this draft.

The Committee noted the draft document and commended WHO for its work on this subject.

6.4 **Validation**

The Committee was provided with a revised draft of the supplementary GMP guidelines on validation. The need for this document arose from feedback received from GMP training workshops for GMP inspectors in different WHO Regions. The Committee was informed that many comments had been received on this draft document, some of which were conflicting.

The Committee noted that it would be prudent for a specially convened expert group to review the comments carefully and, in the interests of harmonization, to take note of other guideline documents on validation during this review, for example, the Pharmaceutical Inspection Co-operation Scheme (PIC/S) guidelines on validation.

6.5 **Water for pharmaceutical use**

The Committee was provided with a revised draft of the GMP guidelines for water for pharmaceutical use (WPU). The Committee reviewed the comments received and made appropriate amendments.

The Committee adopted the text as Annex 3.

7. **Quality assurance — inspection**

7.1 **Sampling of pharmaceuticals and related materials**

The Committee was provided with a revised draft of the WHO guidelines for sampling of pharmaceuticals and related materials. Many comments had been received, some expressing differing opinions on the sampling plans described in the document.

The Committee carried out a detailed review of the comments received and made appropriate amendments.

The Committee adopted the text as Annex 4.

¹ The term "herbal medicinal products" was replaced by "herbal medicines" in accordance with the terminology used in other texts published by WHO.



7.2 Training modules for inspectors

The Committee was informed that WHO had conducted several training workshops for GMP inspectors in its regions, using the CD-ROM of basic training modules on GMP issued in 2001.

Trainees had expressed strong interest in the development by WHO of supplementary training modules covering specific GMP topics such as validation, water, HVAC and quality control laboratory inspection. A CD-ROM was subsequently prepared to cover the first three topics, and this had recently been widely distributed to interested parties. The Committee noted with concern that although a CD-ROM for supplementary training on quality control laboratory inspection was in the process of being prepared, its finalization was being hampered by resource constraints.

The Committee noted that since the development of the CD-ROM of basic training modules on GMP, the WHO GMP principles for pharmaceutical products had been revised; changes would need to be made accordingly.

In view of the positive uptake of this project, the Committee recommended that appropriate resources should be made available in order to:

- revise the CD-ROM of basic training modules on GMP to reflect the content of the most recent version of the WHO GMP principles for pharmaceutical products; and
- complete the supplementary training module on quality control laboratory inspection.

8. Quality assurance — distribution and trade-related

8.1 Good trade and distribution practices for pharmaceutical starting materials

The Committee was informed that a number of incidents involving diethylene glycol had resulted in a World Health Assembly resolution (WHA52.19) which had triggered the preparation of the good trade and distribution practices (GTDP) and of the recommendations on GTDP for pharmaceutical starting materials. This guidance had been adopted during the thirty-eighth meeting of the Committee.

The Committee was informed that the International Pharmaceutical Excipients Council (IPEC) had used the WHO guidance document as the basis for developing an expanded guidance document which

E



would be launched to relevant industry sectors in 2005, backed-up by regular seminars. The Committee commended IPEC for this work. It was brought to the attention of the Committee that WHO had been invited to present this guidance at an annual meeting of the European Association of Chemical Distributors (FEEC).

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

The Committee was provided with an update on the implementation of this scheme. It was informed that the scheme was linked to harmonization and that some Member States had commented on its unreliability, particularly because some Member States were issuing certificates when they lacked legal requirements to enforce all aspects of WHO GMP, e.g. validation, and because certificates were being issued by countries that were not members of the scheme. The Committee urged WHO Member States to ensure that the scheme was properly used.

The Committee recommended that the Secretariat should prepare a proposal on a possible amendment to the scheme, including the need for national regulatory authorities to be assessed before they could join, for consideration by the Committee at its next meeting.

The Committee was informed by the European Federation of Pharmaceutical Industries and Associations (EFPIA) of the significant increase in duplication of GMP inspections by different inspectorates that was being experienced by manufacturers worldwide and of the cost burden involved. The Committee recommended that this matter should be tabled for discussion at the next meeting of ICDRA.

8.3 **WHO Scheme for the certification of pharmaceutical starting materials moving in international commerce**

Although this scheme had been adopted by the Committee at its thirty-eighth meeting, the Committee was informed that it may still be discussed by WHO's Governing Bodies. The Committee was informed that the European Agency for the Evaluation of Medicinal Products (EMA) had shown an interest in the WHO document, particularly to make use of the different certificates contained in the document for the forthcoming European system for controlling manufacturers of starting materials.

8.4 **Good distribution practices for pharmaceutical products**

The Committee was provided with a draft of the good distribution practices for pharmaceutical products which had been sent out for





comments, together with the comments received. The Committee noted the draft document and commended WHO for its work on this subject. It was agreed that a consultation was necessary to discuss the comments received.

9. Quality assurance — risk analysis

9.1 New approach to inspections and manufacture

Documents related to the use of parametric release and a risk analysis approach for the GMP inspection process, which had been developed by ICH, had been considered by the Committee at its thirty-eighth meeting. These documents were still in the process of being developed by ICH and were expected to reach stage 2 in the ICH process later in the year.

The Committee recommended that the ICH document, once available, should be circulated for feedback to Member States and examined at the next meeting of the Committee.

10. Quality assurance — stability

10.1 Stability testing conditions

The Committee was provided with a discussion paper from the Association of South-East Asian Nations regarding long-term stability testing conditions. These take account of the conditions of high humidity experienced in that region. As the approach differed from the current ICH and WHO requirements for temperature and humidity, the WHO Secretariat proposed that a meeting of interested parties be arranged in order to discuss this matter further with a view to reaching harmonization.

The Committee recommended that the Secretariat should proceed with this initiative.

11. Quality assurance — drug supply

11.1 Prequalification project managed by WHO

The Committee was provided with an update on the prequalification project. The *Procedure for assessing the acceptability, in principle, of pharmaceutical products for purchase by UN agencies* for prequalification was adopted by the Expert Committee in 2001 (WHO Technical Report Series, No. 908, Annex 8). The project

E



assists United Nations procurement agencies in providing assurance for the safety, quality and efficacy of medicines used for the treatment of HIV/AIDS, malaria and TB. To date the fifteenth edition of the list of prequalified medicines had been published; this includes 95 HIV/AIDS drugs, eight TB drugs and two malaria drugs. The Committee noted that approximately 500 product dossiers were currently being assessed. Some manufacturers had decided to withdraw their product dossiers from the assessment process for various reasons, e.g. difficulty in complying with WHO GMP requirements.

The Committee was informed that the World Health Assembly had passed a resolution to make public the results of prequalification assessments and inspections. Consequently these will be published on the WHO web site. The Committee was pleased to note that WHO would publish assessment and inspection reports in the interests of transparency and recognized this as a significant innovation. The Committee noted the additional workload required to implement this programme.

The Committee was informed that the prequalification programme had recently been expanded to include good clinical practice (GCP) inspections and that some critical noncompliances had already been identified leading to the delisting of five products. The Committee welcomed the development of additional guidance governing good practices within contract research organizations.

The Committee was informed that the prequalification programme required that requalification be undertaken at 3-yearly intervals, with the first of these to be completed before the end of 2004. Resource constraints may prevent this timetable from being followed.

The Committee recommended that sufficient resources should be made available to enable the requalification programme to be undertaken.

11.2 **Prequalification of quality control laboratories and procurement agencies**

The Committee was informed that the Interagency Pharmaceutical Coordination Group (IPC) had indicated that the prequalification of quality control laboratories should commence. However, because of resource constraints, the prequalification of quality control laboratories had been limited to those in Africa. The expression of interest for laboratories wanting to participate in this process has been posted on the World Wide Web (<http://mednet3.who.int/prequal/>).



The Committee noted that the final draft of the Model Quality Assurance System for procurement agencies was in the final stage of editing and expressed its gratitude to the International Pharmaceutical Federation (FIP) for assisting in this process.

The Committee recommended that sufficient resources be made available for this activity.

11.3 Update of prequalification procedure

The Committee was informed that the current prequalification procedure does not specify the need for conducting inspections of manufacturers of active pharmaceutical ingredients (APIs) (although some such inspections of antimalarial API manufacturers had been carried out). Furthermore the current procedure lacked provision for recovery of the costs of inspections (already done by WHO for vaccines, diagnostics and devices), inspection of contract research organizations and making assessment reports and inspection reports publicly available.

The Committee recommended that the Secretariat proceed to amend the scheme to include these additional points.

12. Regulatory guidance on interchangeability for multisource medicines

12.1 Main guidelines for interchangeability

In recognition of the need to reduce the costs of multisource (generic) product approval wherever this is scientifically and medically justifiable, and taking into account the discussion on the Biopharmaceutics Classification System (BCS) concept, WHO initiated the process of revision of its guidelines on registration requirements to establish interchangeability of multisource products about 4 years ago.

The Committee was provided with a status report on this work. The initial draft of this guideline had been prepared by Dr Rein Pähkla who had sadly passed away in September 2004. The Committee reflected in silence for 1 minute in honour of Dr Pähkla and his contributions. The Committee also acknowledged the contributions of FIP, Dr Midha, Dr Shah and all other members of the FIP/WHO BCS Task Force to this process.

The Committee endorsed the extension of the general principles currently used to allow for biowaivers (i.e. waivers on in vivo

E



bioequivalence studies). These will be taken into account when preparing the next version of the revised draft guidance text. The Committee reviewed the draft document in detail and provided advice and direction to the Secretariat to facilitate preparation by the expert working group of the next working draft.

12.2 Medicines qualifying for waiver on in vivo bioequivalence studies

The Committee was provided with a status report on the work being undertaken to prepare a proposal regarding the requirements to waive in vivo bioequivalence tests for the immediate-release, solid, oral dosage forms included in the *WHO Model list of essential medicines*. Major efforts including literature studies and laboratory testing were carried out with the aim of identifying those medicines included in the *Model list* for which a biowaiver could be considered. A proposal was being circulated for comments. This will provide a practical tool complementing the revised draft guidance on interchangeability of medicines (see 12. 1, above).

12.3 Dissolution testing

The Committee was provided with the background for the development of in vitro dissolution conditions for highly soluble and highly permeable medicines (BCS Class I drugs) and others, on the basis of the tests carried out. The Committee recommended that this document be adopted subject to the revisions discussed. The text should be included in *The International Pharmacopoeia* as a general text. In addition cross-references to this text will be made in the monographs as appropriate.

12.4 List of comparator products

The Committee was provided with an update on the guidance on products to be added to the list of international comparator products for bioequivalence assessment of interchangeable multisource (generic) products. Due to globalization, mergers and changes to the *WHO model list of essential medicines*, an update of the products listed was considered necessary.

The Committee recommended that the Secretariat should:

- review and update the list in collaboration with interested parties, such as the International Federation of Pharmaceutical Manufacturers Associations (IFPMA); and
- seek comments on the revised list.



13. **Fixed-dose combination products for priority communicable diseases**

13.1 **Guidelines for registration of fixed-dose combination products**

The development of fixed-dose combinations (FDCs) is becoming increasingly important from a public health perspective. They are being used in the treatment of a wide range of conditions and are particularly useful in the management of HIV/AIDS, malaria and TB, which are considered to be the most threatening infectious diseases in the world. Important discussions have been held in connection with the joint efforts of the Southern African Development Community (SADC), United States Health and Human Services, the Joint United Nations Programme on HIV/AIDS (UNAIDS) and WHO, which assisted in the development of this guidance text.

The Committee was provided with a revised guideline document and was informed that the comments received to date were mainly on editorial points.

The Committee recommended that the document be adopted subject to the Secretariat making the necessary amendments (Annex 5).

14. **International Nonproprietary Names**

The Committee was presented with a progress report on the work carried out since the previous meeting of the Expert Committee. The International Nonproprietary Names (INN) cumulative list was now available on CD-ROM and on a database that would facilitate searches. It was also reported that applications could now be submitted over the Internet and that computerized processes facilitated publication preparation. The link with the updated pharmacopoeial database, which is a compilation of monographs available in major pharmacopoeias, was also mentioned.

The Committee was informed of the workplan, progress and future challenges of this programme. It was also informed that priority continued to be given to upgrading the database's architecture and functionality.

The Secretariat informed the Committee that the INN procedure was being considered by the WHO Governing Bodies with a view to producing an update of the mechanisms of substitution of INNs.

E



15. Summary and recommendations

The Expert Committee made a number of recommendations in the various specific areas of work in quality assurance discussed during the meeting. Detailed recommendations can be found under the relevant section of the report. The areas covered by this Committee are extensive and range from GMP, regulatory guidance texts (e.g. regarding the interchangeability of medicines, fixed-dose combination products, stability testing), as well as the areas of counterfeit and substandard medicines. Quality control specifications and International Chemical Reference Substances are developed, focusing on essential medicines and on those medicines used in the treatment of large populations for which international quality requirements are often not publicly available.

The Expert Committee emphasized the importance of making sufficient resources available for these core normative functions of the Organization. This would enable sustainability of these functions and avoid duplication of effort worldwide. The guidelines, specifications and international nomenclature developed under the aegis of this Expert Committee serve — without always making the headlines — all Member States and regions and underpin important initiatives, including the “3 by 5” initiative launched by the Director-General, Dr LEE Jong-wook.

Making resources available for these activities is very cost-effective as national and regional drug regulatory authorities, as well as major international bodies and institutions, such as the Global Fund, and international organizations such as the United Nations Children’s Fund (UNICEF), are the direct beneficiaries. In order to respond more swiftly to the needs in this area worldwide, Expert Committee meetings should be organized more frequently (i.e. annually).

The prequalification of medicines and laboratories (and also possibly procurement agencies in the future) could not function without the set of guidelines, standards, specifications and new guidance texts adopted by this Committee after the usual, rigorous consultative process. In return the prequalification programme provides valuable feedback to the Expert Committee. As a result of using the guidelines and specifications in the field, practical suggestions for potential revision or the need for additional guidance can be transmitted directly to the Expert Committee.

Another valuable aspect of the prequalification programme is that participating members of drug regulatory authorities obtain “hands-on” experience in joint inspections and joint regulatory



assessment activities with the participation of both developed and developing countries. This practical experience is later passed on in training workshops, thus allowing even more colleagues to benefit from the programme. Manufacturers and quality control laboratories benefit from the useful advice given in the inspection reports. National authorities benefit from the availability of those inspection reports and the regulatory information with respect to each product assessed.

In conclusion, the Expert Committee oversees activities in the area of quality assurance that it considers should continue efficiently and swiftly to enable Member States, international organizations, United Nations agencies, and regional and interregional harmonization efforts to benefit therefrom. Sustainability of the activities discussed is crucial if WHO is to continue to provide the services laid down in its constitution at a sufficiently high standard.

15.1 **New standards and guidelines adopted and recommended for use**

1. List of available International Chemical Reference Substances (ICRS) (Annex 1).
2. Good manufacturing practices (GMP): requirement for the sampling of starting materials (amendment to current text, Annex 2).
3. Good manufacturing practices (GMP): water for pharmaceutical use (Annex 3).
4. Guidelines for sampling of pharmaceuticals and related materials (Annex 4).
5. Guidelines for registration of fixed-dose combination medicinal products (Annex 5).
6. Monographs on the following for inclusion in *The International Pharmacopoeia*:
 - didanosine
 - indinavir sulfate
 - nelfinavir mesilate
 - nevirapine
 - ritonavir
 - saquinavir
 - saquinavir mesilate



15.2 **Activities that should be pursued and progress reported at the next Expert Committee meeting**

The following activities should be pursued and progress should be reported at the next meeting of the Expert Committee. Development of specifications and guidelines will be carried out using the established international consultative process.

The International Pharmacopoeia

The activities related to *The International Pharmacopoeia* are as follows:

- continuation of development of specifications for medicines included in the *WHO Model List of Essential Medicines* with a focus on priority diseases;
- replacement of monographs for radiopharmaceuticals in collaboration with IAEA; and
- continuation of collaboration with TRM regarding a potential update of the general control methods for medicinal plant materials.

Regulatory guidance

The work on regulatory guidance will include:

- guidelines on registration requirements to establish interchangeability of multisource (generic) pharmaceutical products (revision, next draft in progress);
- GDP for pharmaceutical products (new, next draft in progress); and
- efforts to harmonize requirements for stability testing (in progress).

Inspection

Work on inspection will include:

- supplementary guidelines on GMP for HVAC systems (new, next draft in progress);
- supplementary guidelines on GMP for the manufacture of herbal medicines (revision, next draft in progress); and
- supplementary guidelines on GMP: validation (new, next draft in progress).

Prequalification project

The Committee strongly recommended that sufficient resources should be made available to enable the programme to continue, to support prequalification of products, quality control



laboratories, update of the procedure and requalification as necessary.

15.3 New areas of work suggested

The following new areas of work were suggested. Progress reports are requested for presentation at the next meeting of the Expert Committee.

- Consolidate *The International Pharmacopoeia* in a fourth edition both in printed and electronic forms (CD-ROM format) to facilitate its wider use.
- Revise the general chapters of *The International Pharmacopoeia*, as suggested by the group of experts and endorsed by the Expert Committee.
- Develop new guidelines for the development of secondary reference standards.
- Update the currently available GMP training modules.
- Organize a workshop to discuss the possibility of establishing an international framework convention to coordinate international strategies to detect and counter counterfeiting.
- Explore WHO's continued participation and the proper representation of its Member States at the ICH, an interregional harmonization effort in drug registration of new medicines.

Acknowledgements

Special acknowledgement was made by the Committee to Mrs W. Bonny, Mrs A.N. Lo Conte, Dr S. Kopp, Dr L. Rágo and Dr P. Vanbel, Quality Assurance and Safety: Medicines, Department of Medicines Policy and Standards, WHO, Geneva, Switzerland, who were instrumental in the preparation and proceedings of the meeting.

Technical guidance included on this report has been produced with the financial assistance of the European Community.

The Committee also acknowledged with thanks the valuable contributions made to its work by the following institutions and persons:

Bureau of Drug and Narcotics, Department of Medical Sciences, Nonthaburi, Thailand; Bureau of Food and Drugs, Department of Health, Muntinlupa City, Philippines; Caribbean Regional Drug Testing Laboratory, Kingston, Jamaica; Central Drugs Laboratory, Calcutta, India; Central Laboratory for Quality Control of Medicines of the Ministry of Health of Ukraine, Kiev, Ukraine; Central Quality Control Laboratory, Sultanate of Oman; Centre for Quality Assurance of Medicines, Potchefstroom, South Africa; Departamento de Control Nacional Unidad de control de calidad de productos farmacéuticos del mercado nacional (Control de Estantería), Santiago de Chile, Chile; Department for Quality Evaluation and





Control, National Institute of Pharmacy, Budapest, Hungary; Drug Analysis Division, National Pharmaceutical Control Bureau, Sengalor, Malaysia; Expert Analytic Laboratory, Centre of Drug and Medical Technology Expertise, Yerevan, Armenia; Food and Drug Quality Control Center, Vientiane, Lao People's Democratic Republic; Food and Drugs Board, Quality Control Laboratory, Accra, Ghana; Institute for Quality Control of Medicines, Sarajevo, Bosnia and Herzegovina; Instituto Especializado de Análisis, Universidad de Panamá, República de Panamá; Instituto Nacional de Higiene "Rafael Rangel", Caracas, Venezuela; Instituto Nacional de Medicamentos, Buenos Aires, Argentina; Laboratoire National de la Santé du Mali, Bamako, Mali; Laboratoire National de Contrôle des Médicaments, Bab Saadoun, Tunisia; Laboratoire National de Contrôle des Médicaments, Dakar Étoile, Senegal; Laboratoire National de Contrôle des Médicaments, Rabat Instituts, Rabat, Morocco; Laboratoire National de Contrôle des Produits Pharmaceutiques, Alger, Algeria; Laboratoire National de Santé Publique et d'Expertise, Niamey, Niger; Laboratorio Control de Productos MSP, Comisión Para El Control de Calidad de Medicamentos, Montevideo, Uruguay; Laboratorio de Análisis y Asesoría Farmacéutica, San Pedro de Montes de Oca, San José, Costa Rica; Laboratorio de Normas y Calidad de Medicamentos, Caja Costarricense de Seguro Social, Universidad de Costa Rica, San Jose, Costa Rica; LTD Centre for Medicine Quality Control, Tbilisi, Georgia; Medicines Control Authority, Control Laboratory of Zimbabwe, Harare, Zimbabwe; National Drug Quality Assurance Laboratory, Colombo, Sri Lanka; National Institute for the Control of Pharmaceutical and Biological Products, Beijing, People's Republic of China; National Institute of Drug Quality Control, Hanoi, Viet Nam; National Laboratory for Drug Quality Control, Phnom Penh, Cambodia; Provincial Quality Control Laboratory of Drug and Food, Yogyakarta, Indonesia; Royal Drug Research Laboratory, Department of Drug Administration, Kathmandu, Nepal; Tanzania Food and Drugs Authority, Dar-es-Salaam, United Republic of Tanzania; WHO Collaborating Centre for Chemical Reference Substances, Apoteket AB, Produktion and Laboratoriet, Centrallaboratoriet Kungens Kurva, Sweden; WHO Collaborating Centre for Drug Quality Control, Therapeutic Goods Administration Laboratories, Woden, Australian Capital Territory, Australia; WHO Collaborating Centre for Drug Quality Assurance, National Institute for the Control of Pharmaceutical and Biological Products, Temple of Heaven, Beijing, People's Republic of China; WHO Collaborating Centre for Biopharmaceutical Aspects of Drug Quality Control, Biopharmaceutical Laboratory, University of Clermont-Ferrand, Clermont-Ferrand, France; WHO Collaborating Centre for Drug Information and Quality Assurance, National Institute of Pharmacy, Budapest, Hungary; WHO Collaborating Centre for Quality Assurance of Essential Drugs, Central Drugs Laboratory, Calcutta, India; WHO Collaborating Centre for Quality Assurance of Essential Drugs, National Quality Control Laboratory of Drug and Food, Directorate General of Drug and Food Control, Ministry of Health, Jakarta, Indonesia; WHO Collaborating Centre for Regulatory Control of Pharmaceuticals, National Pharmaceutical Control Bureau, Jalan University, Ministry of Health, Petaling Jaya, Malaysia; International Pharmaceutical Federation Sections: Industrial Pharmacy, Laboratories and Medicines Control Services, Military Pharmacy and Community Pharmacy, Netherlands; WHO Collaborating Centre for Drug Quality Assurance, Pharmaceutical Laboratory, Centre for Analytical Science, Health Sciences Authority, Singapore; University for Christian Higher Education, Potchefstroom, South Africa; WHO Collaborating Centre for International Infrared Reference Spectra, Swiss Federal Institute of Technology, Zurich, Switzerland; WHO Roll Back Malaria Initiative, Geneva, Switzerland; WHO Special Programme for Research and Training in Tropical Diseases, Geneva, Switzerland; WHO Stop TB Department, Geneva, Switzerland; WHO Collaborating Centre for Quality Assurance of Essential Drugs, Department of Medical Sciences, Ministry of Public Health, Nonthaburi, Thailand.



Ms N. Abbasi and Ms Z. Abbasi, Department of Pharmaceutics, Royal Danish School of Pharmacy, Copenhagen, Denmark; Professor I. Abdoulaye, Ministère de la Santé Publique, Cotonou, Republic of Benin, Benin; Dr Z. Abeid, Pharmaceutical Department, Ministry of Health and Population, Cairo, Egypt; Dr D. Abhigantaphand, Bureau of Drug and Narcotic, Department of Medical Sciences, Nonthaburi, Thailand; Professor I. Addae-Mensah, University of Ghana, Legon, Ghana; Professor J.-M. Aiache, WHO Collaborating Centre for Biopharmaceutical Aspects of Drug Quality Control, University of Clermont-Ferrand, Clermont-Ferrand, France; Professor A. Agoumi, Medicines and Pharmacy, Ministry of Health, Rabat-Institute, Rabat, Morocco; Mrs S. Ahmed Jaffar, Directorate General of Pharmaceutical Affairs and Drugs Control, Ministry of Health, Muscat, Oman; Dr W. Akarawut, Department of Medical Science, Nonthaburi, Thailand; Professor P.I. Akubue, Department of Pharmacology and Toxicology, University of Nigeria, Nsukka, Nigeria; Mr A.H. Al-Abdullah, Ministry of Public Health, Doha, Qatar; Dr R. Alexander, Inspection Medicines and Healthcare Products, Regulatory Agency, London, England; Dr A. Al Na'amani, Supreme Board of Drugs and Medical Appliances, Ministry of Public Health, Sana'a, Yemen; Dr M.I. Al-Hail, Director, Pharmacy and Drug Control Department, Ministry of Public Health, Doha, Qatar; Dr S.L. Ali, Zentrallaboratorium Deutscher Apotheker, Eschborn, Germany; Dr R. Allman, Medicines and Medical Devices Safety Authority, Business Unit of the Ministry of Health, Auckland, New Zealand; Dr N. Anand, Lucknow, Uttar Pradesh, India; Dr O. Andriollo, Medicopharmaceutical Humanitarian Centre, Clermont-Ferrand, France; Professor M.K. Anglade, Directeur de la Pharmacie et du Médicaments, Abidjan, Côte d'Ivoire; Dr M. Argenti, National Administration of Medicaments, Food and Medical Technology, Buenos Aires, Argentina; Dr A. Artiges, European Directorate for the Quality of Medicines, Council of Europe, Strasbourg, France; Professor F. Ballereau, Centre Hospitalier Universitaire de Nantes, France; Dr D.M. Barends, Apotheker, Rijks Instituut voor Volksgezondheid Milieu RIVM, BA Bilthoven, Netherlands; Ms A.C. Baron, European Chemical Industry Council/Active Pharmaceutical Ingredients Committee, CEFIC Sector Group, Brussels, Belgium; Dr C. Barnstein, Drug Information Division, United States Pharmacopeia, Rockville, MD, USA; Dr P.M. Bazerque, Secretariat for Policies and Health Regulation, Ministry of Health, Argentina; Dr M.C. Becerril Martinez, Comisión Permanente de la Farmacopea de los Estados Unidos Mexicanos, Mexico; Dr M. Bennoson, Meopham, Kent, England; Professor Y. Bensouda, Mohammed V University, Laboratory of Galenical Pharmacy, Rabat, Morocco; Dr D. Bentley, Senior Medicines Inspector, Medicines Control Agency, York, England; Dr S.M. Binti Jaafar, Pharmaceutical Services, Ministry of Health, Bandar Seri Begawan, Brunei Darussalam; Dr C.-E. Bittes, Altana Pharma AG, Singen, Germany; Ms I. Blancho, GMP Project Department, ROQUETTE Frères, Lestrem, France; Dr Peter Bläuenstein, Paul Scherrer Institute, Villigen PSI, Switzerland; Professor H. Blume, Oberursel, Germany; Dr A. Bonneure, Specialty and Fine Chemical Programme, CEFIC European Chemical Industry Brussels, Belgium; Dr D.L. Boring, Food and Drug Administration, Rockville, MD, USA; Dr L. Borka, Oslo, Norway; Dr S. Botella, European Directorate for the Quality of Medicines, Council of Europe, Strasbourg, France; Mr B. Botwe, Food and Drugs Board, Accra, Ghana; Mr G. Bourdeau, ReMed Association, Mereville, France; Dr R. Boudet-Dalbin, Faculty of Pharmaceutical and Biological Sciences of Paris-Luxembourg, René Descartes University, Paris, France; Ms K. Bremer, Norwegian Medicines Control Agency, Oslo, Norway; Dr P.O. Bremer, Isopharma AS, Kjeller, Norway; Dr D. Calam, Wiltshire, England; Mr P. Castle, European Directorate for the Quality of Medicines, Council of Europe, Strasbourg, France; Mr G. Catto, World Federation of Proprietary Medicine Manufacturers, London, England; Dr B. Chapart, Pharma Review Manager, Global Analytical Development, Aventis Pharma, Anthony, France; Dr E. Charton, European Directorate for the Quality of Medicines, Council of Europe, Strasbourg, France; Mrs Chen Yan, Center for Certification, State Drug Administration, Beijing, People's Republic of China; Dr

E





A.M. Cheraghali, Food and Drug Department, Ministry of Health, Islamic Republic of Iran; Dr P. Christen, Analytical Pharmaceutical Chemistry Laboratory, University of Geneva, Geneva, Switzerland; Dr W.-K. Chui, Department of Pharmacy, National University of Singapore, Singapore; Dr D. Cockburn, Principal Scientific Administrator, European Medicines Agency, London, England; Miss M. Cone, PJB Publications Ltd, Richmond, England; Dr J. Cordoba, Faculty of Pharmacy, University of Costa Rica, San José, Costa Rica; Ms E.M. Cortes Montejano, Ministry of Health and Consumer Affairs, Information for Drugs, Madrid, Spain; Dr P. Cox, Consultant in Nuclear Medicine and Radiopharmacy, Bexhill on Sea, East Sussex, England; Dr P. Cranston, Australian Self Medication Industry, Sydney, NSW, Australia; Dr C.J. Dafforn, AstraZeneca Global Regulatory Affairs, Cheshire, England; Ms F. Dansereau, Health Products and Food Branch Inspectorate, National Coordination Center, Ottawa, Ontario, Canada; Mr M.N. Dauramanzi, Medicines Control Authority of Zimbabwe, Harare, Zimbabwe; Dr V.A. Dedrick, Quality and Regulatory Affairs, An International Association for Pharmaceutical and Biopharmaceutical Science and Technology, Bethesda, MD, USA; Professor H. de Jong, International Pharmaceutical Excipients Council, Courbevoie, France; Professor T. Dekker, Research Institute for Industrial Pharmacy, Potchefstroom, South Africa; Dr M. Demesmaeker, Bassins, Switzerland; Dr J. E. De Muth, Information Standards Development, United States Pharmacopeia, Rockville, MD, USA; Mrs L. Déry, International Policy Division, Bureau of Policy and Coordination, Therapeutic Products Programme, Ottawa, Canada; Mr M. Dixon, Corporate Quality Assurance, Eli Lilly and Company, Windlesham, Surrey, England; Ms L. Djukić, Institute of Pharmacy of Serbia, Authorized Institution for Medicines Testing and Control, Belgrade, Yugoslavia; Professor E. Doelker, University of Geneva, Geneva, Switzerland; Dr P. Dörr, International Affairs, Swiss Agency for Therapeutic Products, Berne, Switzerland; Professor J. Dressman, Institute for Pharmaceutical Technology, Johann Wolfgang Goethe University, Frankfurt am Main, Germany; Dr T. D. Duffy, Lowden International, North Yorkshire, England; Dr A. Dunn, Boots Healthcare International, Nottingham, England; Mr M. Dyrda, Pol-Nil Sp. z o.o., Warsaw, Poland; Dr D.I. Ellsworth, Division of Manufacturing and Product Quality, Center for Drug Evaluation and Research, Food and Drug Administration, Rockville, MD, USA; Dr E. Eppinger, Office of the Secretary, Office of Global Health Affairs, US Department of Health and Human Services, Washington, DC, USA; Dr T. Eriksen, Sudaththa Liyanaarachchi, Avissawella, Sri Lanka; Mr S. Fairchild, Brentwood, Essex, England; Dr C.J. Fallais, University of Liège and the Free University of Brussels, Brussels, Belgium; Dr A. Farina, Higher Institute of Health, Ministry of Health, Rome, Italy; Dr F.R.Y. Fazli, Ministry of Health Islamabad, Pakistan; Dr E. Fefer, International Affairs, United States Pharmacopeia, Rockville, MD, USA; Mrs S. Fuerst, The United States Adopted Names Council Program, American Medical Association, Chicago, IL, USA; Dr H. Fukuda, Society of Japanese Pharmacopoeia, Tokyo, Japan; Ms D. Gal, International Pharmaceutical Federation, The Hague, Netherlands; Mr S. Ghani, Division of Pharmaceutical Quality, Therapeutic Products Programme, Ottawa, Ontario, Canada; Ms E. Gomez Munoz, Quality Assurance, Phibro Animal Health, Fairfield, NJ, USA; Dr R. Gooch, Representative of the International Pharmaceutical Federation, Netherlands; Dr. T. Gosdschan, Intercantonal Office for the Control of Medicines, Division of Inspections, Berne, Switzerland; Dr P. Gough, Eli Lilly & Company Ltd., Hampshire, England; Dr B. Graz, Swiss Federal Office of Public Health, Berne, Switzerland; Professor A.A. Haggag, Department of Biochemistry, College of Pharmacy, University of Tanta, Tanta, Egypt; Dr S. Haghghi, Pharmaceutical and Microbiology Department, Institute Pasteur of Iran, Tehran, Islamic Republic of Iran; Ms N. Haji Naim, Pharmaceutical Services, Ministry of Health, Jalan University, Petaling Jaya, Malaysia; Dr N.G. Hartman, The Ottawa Hospital, Division of Nuclear Medicine, Ottawa, Ontario, Canada; Dr K. Hauser, International Regulatory Affairs PhRMA, NW Washington, DC, USA; Mr Y. Hayashi, Evaluation and Licensing Division, Pharmaceutical and Medical Safety Bureau,

E



Ministry of Health, Labour and Welfare, Tokyo, Japan; Dr P. Helboe, Pharmaceutical Affairs, Danish Medicines Agency, Brønshøj, Denmark; Dr E. Henriksen, Division of Manufacturing and Product Quality, Office of Compliance, US Food and Drug Administration, Rockville, MD, USA; Dr Juan Hernández, Test Site of IEA, Gamboa and Corosal Stability Program, University of Panama, Panama City, Panama; Mr H. Hofstetter, Intercantonal Office for the Control of Medicines, Berne, Switzerland; Professor J. Hoogmartens, Catholic University of Leuven, Leuven, Belgium; Dr J. Hoose, Agency for Work, Health and Social Office for Health, Health Department, Hamburg, Germany; Dr M.J. How, MJH International Ltd, Holbeton, Devon, England; Dr H. Ibrahim, DebioPharm SA, Lausanne, Switzerland; Dr J. Idänpään-Heikkilä, Council for International Organizations of Medical Sciences, World Council of Churches, Geneva, Switzerland; Dr K.E. Iddir, Direction de la Pharmacie et du Médicament, Tunis, Tunisia; Dr R. Ilyas, National Agency for Drug and Food Control, Jakarta Pusat, Indonesia; Dr E. Izeboud, Organisation des Fabricants de Produits Cellulosiques Alimen, IPEC Europe, DM Leidschendam, Netherlands; Professor R. Jachowicz, Department of Pharmaceutical Technology and Biopharmaceutics, Jagiellonian University, Kraków, Poland; Dr P. Jacquain, Inspection Generale de la Pharmacie, Service Publique Fédéral, Santé publiques, Sécurité de la Chaîne alimentaire et Environnement, Brussels, Belgium; Dr R. Jähnke, German Pharma Health Fund e.v. Oberursel, Germany; Mr M. Jahnsson, Technical Coordination Unit — Inspections, European Agency for the Evaluation of Medicinal Products, London, England; Professor Jin Shaohong, National Institute for the Control of Pharmaceutical and Biological Products, Ministry of Public Health, Beijing, People's Republic of China; Mrs G. Jiragobchaipong, Bureau of Drug and Narcotic, Department of Medical Sciences, Ministry of Public Health, Nonthaburi, Thailand; Dr K.V. Jogi, Central Drugs Testing Laboratories, ESIS Hospital, Thane, India; Dr A. Kakwemeire, National Drug Quality Control Laboratory, National Drug Authority, Kampala, Uganda; Dr K. Kawamura, Japan Parenteral Drug Association, Tokyo, Japan; Dr S. Keitel, Federal Institute for Drugs and Medical Devices, Bonn, Germany, Mr M. Keller, Intercantonal Office for the Control of Medicines, Division of Inspections, Berne, Switzerland; Dr S. Kennedy, Technical Co-ordination, Inspection Sector, European Agency for the Evaluation of Medicinal Products, London, England; Professor S. Khomvili, Hoechst Marion Roussel Industry, Thailand; Ms K. Kikule, National Drug Authority, Kampala, Uganda; Dr Kil-Soo Kim, College of Pharmacy, Ewha Woman's University, Seoul, Republic of Korea; Dr Q.L. Kintanar, Bureau of Food and Drugs, Ministry of Health, Muntinlupa, Philippines; Dr Ari Kiskonen, National Agency for Medicines, Helsinki, Finland; Dr P. Kokkinou, Pharmaceutical Services, Ministry of Health, Lefkosia, Cyprus; Mr J. Környei, Institute of Isotopes Co., Ltd, Budapest, Hungary; Dr H. Koszegi-Szalai, National Institute of Pharmacy, Budapest, Hungary; Professor M.A. Koupparis, Laboratory of Analytical Chemistry, Department of Chemistry, University of Athens, Athens, Greece; Dr D. Krause, Secretariat Research, Development & Innovation, Berlin, Germany; Dr R. Krause, International Federation of Pharmaceutical Manufacturers Associations, Geneva, Switzerland; Professor H.G. Kristensen, Royal Danish School of Pharmacy, Department of Pharmaceutics, Copenhagen, Denmark; Dr P. Kucera, Wyeth Pharmaceuticals, New York, NY, USA; Dr P.B. Kulkarni, Technical Services Division, Bhabha Atomic Research Centre, Mumbai, India; Mr A. Kumar, Drugs Controller General, Directorate General of Health and Services, Ministry of Health and Family Welfare, New Delhi, India; Dr Kunstantinah, Directorate of Inspection and Certification of Therapeutic Products, National Agency of Drug and Food Control, Jakarta, Indonesia; Dr S. Kuttatharmmakul, Quality Assurance Department, The Government Pharmaceutical Organization, Bangkok, Thailand; Mr R. Kuwana, Medicines Control Authority, Harare, Zimbabwe; Mr J. Lanet, Qualassur, Paris, France; Dr T. Lapnet Moustapha, National Drug Quality Control and Valuation Laboratory, Yaoundé, Cameroon; Mr H. Leblanc, Chairman, Active Pharmaceutical Ingredients Committee, Brussels, Belgium; Dr D. LeBlond,

E



Non-Clinical Statistics, Abbott Laboratories, IL, USA; Mr P. Lefèvre, Medicines Agency, Saint Denis, France; Ms E. Leinonen, National Agency for Medicines, Helsinki, Finland; Dr H.-H. Letzner, Letzner Pharma Wasseraufbereitung GmbH, Hückeswagen, Germany; Dr A.C. Lezama, Health Protection Groups, Ministry of Health, Bogotá, Colombia; Dr K.G. Lingner, Standard Department, International Organization for Standardization (ISO), Geneva, Switzerland; Dr J. Linn, National Pharmaceutical Administration, Ministry of Health, Merah, Singapore; Professor J. Lipták, Ministry of Health, Budapest, Hungary; Mr J. Lisman, A-CBG, The Hague, Netherlands; Dr H. Lomská, State Institute for Drug Control, Prague, Czech Republic; Ms Low Min Yong, Pharmaceutical Laboratory, Centre for Analytical Science, WHO Collaborating Centre for Drug Quality Assurance, Health Science Authority, Singapore; Dr J. Macdonald, Therapeutic Products Directorate, Health Canada, Ottawa, Ontario, Canada; Ms C. Machado, INFARMED, National Pharmacy and Medicines Institute, Lisbon, Portugal; Dr M.K. Majumdar, Damason Consultancy Services, Jadavpur, India; Dr F. Malik, National Institute of Health, Islamabad, Pakistan; Mr B. Mandal, WHO Collaborating Centre for Quality Assurance of Essential Drugs, Calcutta, India; Professor L. Martinec, State Institute for Drug Control, Bratislava, Slovak Republic; Professor A.P. Mazurek, Drug Institute, Warsaw, Poland; Dr A. Mechkovski, Moscow, Russian Federation; Dr M. Mehmandoust, French Health Products Safety Agency, Saint Denis, France; Dr S. Messner, Abbott Laboratories Corporate Regulatory and Quality Science, Illinois, USA; Ms R. Mikolajczak, Department of Chemical Analysis, Radioisotope Centre, Polatom, Otwock Swielk, Poland; Dr F. Milek, International Pharmaceutical Excipients Council Europe, Good Distribution Practice Committee, Stuttgart, Germany; Ms M. Miljkovic, Institute of Pharmacy of Serbia, Belgrade, Yugoslavia; Dr J.H. McB. Miller, European Directorate for the Quality of Medicines, Council of Europe, Strasbourg, France; Professor J. Mircheva, AESGP (Representative of WSMI), Brussels, Belgium; Dr A. Mitchell, S & D Chemicals, Harrow, England; Dr A. Mitrevej, Vice-President for Academic Affairs, Pharmaceutical Association of Thailand, Bangkok, Thailand; Mr M. Moester, Inspectorate for Health Care, Rijswijk, Netherlands; Dr G.P. Mohanta, Department of Pharmacy, Annamalai University, Tamil Nadu, India; Dr A. Mohd Moosa, Directorate General of Pharmaceutical Affairs and Drugs Control, Ministry of Health, Muscat, Oman; Professor H. Möller, Central Laboratory of German Pharmacists, Eschborn, Germany; Dr J. Molzon, Associate Director of International Programs, Center for Drug Evaluation and Research, US Food and Drug Administration, Rockville, MD, USA; Mrs A.B. Moraes da Silva, National School of Public Health (FIOCRUZ), Coordination of Technical Cooperation, Rio de Janeiro, Brazil; Dr O. Morin, Regulatory and Scientific Affairs, International Federation of Pharmaceutical Manufacturers Associations, Geneva, Switzerland; Dr G. Munro, Head of Inspection and Enforcement, Medicines Control Agency, London, England; Dr S. Myat Tun, Department of Health, Food and Drug Administration, Ministry of Health, Yangon, Myanmar; Dr Myint-Sein, Myanmar Pharmaceutical Industries, Ministry of Industry, Yangon, Myanmar; Dr D.V.S. Narasimhan, Division of Physical and Chemical Sciences, International Atomic Energy Agency, Vienna, Austria; Dr R. Nash, Mahwah, NJ, USA; Dr E. Njau, Arusha, United Republic of Tanzania; Dr K. Nodop, European Agency for the Evaluation of Medicinal Products, London, England; Dr O.P.D. Noronha, N Dutta Marg, Adheri West, Mumbai, India; Dr C. Ntege, National Drug Authority, National Drug Quality Control Laboratory, Kampala, Uganda; Professor A.A. Olaniyi, Department of Pharmaceutical Chemistry, College of Medicine, University of Ibadan, Ibadan, Nigeria; Dr C. Ondari, Department of Health Sciences, University of Nairobi, Nairobi, Kenya; Dr Kutlan Ozker, Associate Professor, Medical College of Wisconsin, Department of Radiology, Section of Nuclear Medicine, Froedtert Memorial Lutheran Hospital, Milwaukee, WI, USA; Professor T. Paál, National Institute of Pharmacy, WHO Collaborating Centre for Drug Information and Quality Assurance, Budapest, Hungary; Dr P.R. Pabrai, Sarita Vihar, New Delhi, India; Dr M.I. Pacecca, Training and Research Department, National Administration of



Medicines, Foods and Medical Technology (ANMAT), Ministry of Health, Buenos Aires, Argentina; Dr C.O. Pannenberg, Sector Leader for Health, Nutrition and Population, Africa Region, The World Bank, Washington, DC, USA; Dr K.B. Park, Radioisotope Department, Korea Atomic Energy Institute, Taejon, Republic of Korea; Dr W. Pathirana, Department of Pharmacology and Pharmacy, Faculty of Medicines, University of Colombo, Colombo, Sri Lanka; Dr I.J. Petersen, Department of Pharmaceutical Affairs, Ministry of Health and Social Security, Reykjavik, Iceland; Dr S. Phanouvong, Drug Quality, Control Global Assistance Initiatives, The United States Pharmacopeia, MD, USA; Dr L.E. Pino Arango, Ministry of Health, Bogotá, Colombia; Dr J. Pogány, Consivers Consulting and Translation Group, Budapest, Hungary; Dr W. Pohler, Pharmaceutical Sciences, Aventis Pharma, Frankfurt am Main, Germany; Miss A. Poompanich, Division of Drug Analysis, Department of Medical Sciences, Ministry of Public Health, Nonthaburi, Thailand; Dr H. Potthast, Federal Institute for Drugs and Medical Devices, Bonn, Germany; Ms M.-L. Rabouhans, Chiswick, England; Dr P. Rafidison, International Pharmaceutical Excipients Council-Europe, Good Manufacturing Practices/Good Distribution Practice Committee, Global Life Sciences, Dow Corning, Opio, France; Dr F. Rakiás, Head, Radioisotope Department, National Institute of Pharmacy, Budapest, Hungary; Dr N. Ramamoorthy, Board of Radiation and Isotope Technology, Department of Atomic Energy, Mumbai, India; Dr J. Reden, Scientific and Regulatory Affairs, European Federation of Pharmaceutical Industries and Associations, Brussels, Belgium; Dr M.M. Reidenberg, Weill Medical College of Cornell University, New York, NY, USA; Mr G. Requin, Ministry of Health and Quality of Life, Port Louis, Mauritius; Dr S. Roenninger, F. Hoffman La Roche Ltd., Basel, Switzerland; Mr P. Romagnoli, European Generic Medicines Association, Aschimfarma, Milan, Italy; Dr D. Rumel, Brazilian Health Surveillance Agency, Brasilia, Brazil; Dr B. Sabri, Health Systems and Community Development, Office of WHO Representative, Riyadh, Saudi Arabia; Dr C. Sanchez, Centre for State Control of Drug Quality, Havana, Cuba; Dr Sang Gouwei, National Institute for the Control of Pharmaceutical and Biological Products, Beijing, People's Republic of China; Dr R. Santos Ivo, INFARMED, National Pharmacy and Medicines Institute, Lisbon, Portugal; Dr J.-M. Sapin, Head, Inspection Unit, AFSSA, Lyon, France; Dr K. Satiadarma, Jl. Cipaganti 172, Bandung, Indonesia; Dr M. Schaffhauser, Intercantonal Office for the Control of Medicines, Control of Manufacture, Berne, Switzerland; Professor J. Schlebusch, Medicines Control Council, Department of Health, Pretoria, South Africa; Ms M. Schmid, Saconnex d'Arve, Switzerland; Dr C. Scholten, Coordinator, ICCTA Task Force on Pharmaceuticals and Quality Starting Materials, Germany; Dr H. Schrader, Physikalisch-Technisch Bundesanstalt, Braunschweig, Germany; Dr J. Schrank, Scientific, Technical and Regulatory Affairs, Interpharma, Basel, Switzerland; Mr G. Schwartzman, Sarasota, FL, USA; Dr V. Shah, Office of Pharmaceutical Science, Center for Drug and Evaluation Research, Food and Drug Administration, Rockville, MD, USA; Dr N. Sharif, Ministry of Health, Petaling Jaya, Sengalor, Malaysia; Dr G.V. Shashkova, Ministry of Health, Moscow, Russian Federation; Dr S. Shaw, International Pharmaceutical Federation, the Hague, Netherlands; Dr A. Sheak, Department of Drug Administration, Ministry of Health, Kathmandu, Nepal; Dr M. Sheikh, A/DHS, Syrian Arab Republic; Dr E.B. Sheinin, Information and Standards Development, United States Pharmacopeia, Rockville, MD, USA; Dr P.G. Shrotriya, M.J. Biopharm Pvt. Ltd., New Mumbai, India; Dr M. Siewert, Environmental Health and Safety, Aventis Pharma, Frankfurt am Main, Germany; Ms S. Siiskonen, International Pharmaceutical Federation, The Hague, the Netherlands; Dr G.N. Singh, Central Indian Pharmacopoeia Laboratory, Ministry of Health and Family Welfare, Ghaziabad, India; Dr S. Singh, Department of Pharmaceutical Analysis, Nagar, Punjab, India; Dr S.C. Singhai, Seapharm Forum, World Health House, New Delhi, India; Ms K. Sinivuo, National Agency for Medicines, Helsinki, Finland; Dr L.S. Slamet, Therapeutic Products, Narcotic Psychotropic and Addictive Substances, National Agency of Drug and Food

E



Control, Jakarta, Indonesia; Dr A.E. Smedstad, Norwegian Association of Proprietor Pharmacists, Oslo, Norway; Dr M. Smíd, State Institute for Drug Control, Prague, Czech Republic; Dr R.J. Smith, Therapeutic Goods Administration Laboratories, Woden, Australian Capital Territory, Australia; Ms J. Solano Galvis, Ministry of Health, Directorate-General for Public Health, Bogotá, Colombia; Dr J.-M. Spieser, European Directorate for the Quality of Medicine, Council of Europe, Strasbourg, France; Mrs L. Stefanini-Oresić, Croatian Institute for Medicine Control, Zagreb, Croatia; Dr W. Steiger, Associate Director for International Policy, Office of International Programs, US Food and Drug Administration, Rockville, MD, USA; Dr W. Stoedter, Quality and Regulatory Affairs, An International Association for Pharmaceutical and Biopharmaceutical Science and Technology, Bethesda, MD, USA; Dr A. Sulistiowati, Division of Therapeutic Products and Hazardous Substances, National Quality Control Laboratory of Drugs and Food, Jakarta, Indonesia; Dr S. Sur, State Inspection for Quality Control of Medicines, Ministry of Health of Ukraine, Kiev, Ukraine; Dr U. Suvanakoot, Pharmaceutical Technology Service Centre, Faculty of Pharmaceutical Sciences, Chulalongkorn University, Bangkok, Thailand; Mr M. Suzuki, Fuji Public Health Center, Fuji-shi, Japan; Mr P. Svarrer Jakobsen, UNICEF, Freeport, Copenhagen, Denmark; Professor M. Sznitowska, Department of Pharmaceutical Technology, Medical University of Gdańsk, Gdańsk, Poland; Dr H. Takeda, Senior Managing Director, Society of Japanese Pharmacopoeia, Tokyo, Japan; Dr S.K. Talwar, Central Indian Pharmacopoeia Laboratory, Ghaziabad, Uttar Pradesh, India; Ms Y. Tayler, The World Bank, Washington, DC, USA; Dr J. Taylor, Medicines Control Agency, London, England; Dr W. Taylor, Taylor Enterprises Inc., Libertyville, IL, USA; Dr D. Teitz, Bristol-Myers Squibb Company, NJ, USA; Dr M. ten Ham, Department of Pharmaceutical Affairs, Ministry of Public Health, Welfare and Sport, The Hague, Netherlands; Dr S. Throm, Research and Development, Association of Research Drug Manufacturers, Berlin, Germany; Dr W.D. Torres, Department of Health, Bureau of Food and Drugs, Alabang, Muntinlupa, Philippines; Professor A. Toumi, Directorate of Pharmacy and Medicines, Ministry of Public Health, Bab Saadoun, Tunisia; Ms M. Treebamroong, Quality Control Coordinator, for the Director of Bureau of Drug and Narcotic, Department of Medical Sciences, Ministry of Health, Nonthaburi, Thailand; Mr R. Tribe, Holder, ACT, Australia; Mr R.B. Trigg, British Pharmacopoeia Commission, London, England; Professor Tu Guoshi, National Institute for the Control of Pharmaceutical and Biological Products, Ministry of Public Health, Beijing, People's Republic of China; Dr J. Turner, Policy and Standards Inspection and Enforcement Division, Department of Health, Medicines Control Agency, London, England; Dr N. Turner, Glaxo Smith Kline, Ware, England; Ms E. Uramis Diaz, National Centre for Biological Products, Havana, Cuba; Mr S. Uzu, Planning Division, Pharmaceutical Affairs Bureau, Ministry of Health and Welfare, Tokyo, Japan; Dr M. Vagt, Hameln Pharmaceutical GmbH, Hameln, Germany; Dr J.G. Valentino, United States Pharmacopoeia, Rockville, MD, USA; Professor C. van Boxtel, Afd. Inwendige Geneeskunde F4, Amsterdam Zuidoost, Netherlands; Dr B. van Damme, Military and Emergency Pharmacy Section, Pharmaceutical Inspector BAF, Brussels, Belgium; Mr P. van der Hoeven, Active Pharmaceutical Ingredients Committee, European Chemical Industry Council, Brussels, Belgium; Dr J. van Oudtshoorn-Eckard, Monument Park, South Africa; Dr S. Vasanavathana, Office of Food and Drug Administration, Ministry of Public Health, Nonthaburi, Thailand; Ms M. Veek, Associate Director for Communications, US Food and Drug Administration, Rockville, MD, USA; Dr M. Venkateswarlu, Central Drugs Standard Control Organization, Mumbai, India; Dr H. Vera Ruiz, International Atomic Energy Agency, Vienna, Austria; Dr J.-Y. Videau, Humanitarian Medical and Pharmaceutical Centre, Clermont-Ferrand, France; Mr P.H. Vree, The Inspectorate of Health Care, Maasdam, Netherlands; Mr Wang Ping, Pharmacopoeia Commission of the People's Republic of China, Ministry of Health, Beijing, People's Republic of China; Dr D. Webber, World Self-Medication Industry, Centre International de Bureaux, Ferney-Voltaire, France; Dr K.



Weerasuriya, WHO South-East Asia Regional Office, World Health House, New Delhi, India; Dr T. W. Welch, Associate Director for International Policy of International Programs, US Food and Drug Administration, Rockville, MD, USA; Dr R. White, Nonprescription Drug Manufacturers Association of Canada, Ottawa, Ontario, Canada; Dr J. Whitwell, Australian Nuclear Science and Technology Organization, Menai, NSW, Australia; Dr S. Wibulpolprasert, Bureau of Health Policy and Planning, Ministry of Public Health, Nonthaburi, Thailand; Dr L. Wiebe, Dentistry-Pharmacy Building, University of Alberta, Edmonton, Alberta, Canada; Dr W. Wieniawski, Polish Pharmaceutical Society, Warsaw, Poland; Dr R.L. Williams, United States Pharmacopeia, Rockville, MD, USA; Dr Woo Soo On, Singapore; Dr S. Wyn, GAMP Forum, Llanrwst, Wales; Mr Yang Lahu, National Institute for the Control of Pharmaceutical and Biological Products, Ministry of Public Health, Beijing, People's Republic of China; Professor Yang Zhong-Yuan, Guangzhou Municipal Institute for Drug Control, Guangzhou, People's Republic of China; Dr E. Yuan, International Health Officer, Office of Global Health Affairs, Rockville, MD, USA; Dr Zhou Haijun, National Institute for the Control of Pharmaceutical and Biological Products, WHO Collaborating Centre for Drug Quality Assurance, Beijing, People's Republic of China; Mr Zhu Dan, Shen Zhen, People's Republic of China; Ms A. Zima, State Institute for Drug Control, Prague, Czech Republic; Professor I. Zolle, Ludwig Boltzmann-Institute for Nuclear Medicine, Institute for Biomedical Technology and Physics, Vienna, Austria.



Annex 1

International Chemical Reference Substances and International Infrared Reference Spectra¹

1. List of available International Chemical Reference Substances

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

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

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

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

The stability of the ICRS kept at the Collaborating Centre is monitored by regular re-examination and any material that has deteriorated is replaced by new batches when necessary. Lists giving control

¹ As updated at the thirty-ninth meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations, 25–29 October 2004.



numbers for the current batches are issued in the annual reports from the Centre and new lists may also be obtained on request.

Orders for the ICRS should be sent to:

WHO Collaborating Centre for Chemical Reference Substances
Apoteket AB
Produktion & Laboratorier
Centrallaboratoriet, ACL
Prismavägen 2
SE-141 75 Kungens Kurva
Sweden
Fax: +46 8 740 60 40
Email: who.apl@apoteket.se
Web site: <http://www.apl.apoteket.se/who>

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

Table 1

Available International Chemical Reference Substances

Catalogue number	Reference substance	Package size	Control number
9930375	<i>p</i> -acetamidobenzalazine	25 mg	290042
9930202	acetazolamide	100 mg	186128
9930204	allopurinol	100 mg	287049
9930206	amidotrizoic acid	100 mg	196205
9930191	2-amino-5-nitrothiazole	25 mg	186131
9930194	3-amino-5-pyrazole-4-carboxamide hemisulfate	100 mg	172050
9930193	3-amino-2,4,6-triiodobenzoic acid	100 mg	196206
9930208	amitriptyline hydrochloride	100 mg	181101
9930209	amodiaquine hydrochloride	200 mg	192160
9930210	amphotericin B	400 mg	191153
9930211	ampicillin (anhydrous)	200 mg	390001
9930212	ampicillin sodium	200 mg	388002
9930213	ampicillin trihydrate	200 mg	274003
9930214	anhydrotetracycline hydrochloride	25 mg	180096
9931408	artemether	100 mg	103225
9931406	artemisinin	100 mg	103222
9931407	artemotil	100 mg	103226
9931410	artenimol	100 mg	103223
9931409	artesunate	100 mg	103224
9930215	atropine sulfate	100 mg	183111
9930216	azathioprine	100 mg	172060
9930218	bacitracin zinc	200 mg	192174
9930219	beclometasone dipropionate	200 mg	192175



Table 1 (continued)

Catalogue number	Reference substance	Package size	Control number
9930225	benzylpenicillin potassium	200mg	180099
9930226	benzylpenicillin sodium	200mg	280047
9930227	bephenium hydroxynaphthoate	100mg	183112
9930228	betamethasone	100mg	183113
9930229	betamethasone sodium phosphate	100mg	196203
9930230	betamethasone valerate	100mg	190145
9930233	bupivacaine hydrochloride	100mg	289054
9930234	caffeine	100mg	181102
9930236	calcium folinate (leucovorin calcium)	100mg	194188
9930237	captopril	100mg	197214
9930238	captopril disulfide	25mg	198216
9930239	carbamazepine	100mg	189143
9930240	carbenicillin monosodium	200mg	383043
9930241	chloramphenicol	200mg	486004
9930242	chloramphenicol palmitate	1g	286072
9930243	chloramphenicol palmitate (polymorph A)	200mg	175073
9930199	5-chloro-2-methylaminobenzophenone	100mg	172061
9930245	chloroquine sulfate	200mg	195201
9930190	2-(4-chloro-3-sulfamoylbenzoyl)benzoic acid	50mg	181106
9930246	chlorphenamine hydrogen maleate	100mg	182109
9930247	chlorpromazine hydrochloride	100mg	178080
9930248	chlortalidone	100mg	183114
9930249	chlortetracycline hydrochloride	200mg	187138
9930250	cimetidine	100mg	190150
9930256	ciprofloxacin hydrochloride	400mg	197210
9930252	ciprofloxacin by-compound A	20mg	198220
9930253	ciprofloxacin desfluoro-compound	20mg	198219
9930254	ciprofloxacin ethylenediamine-compound	20mg	198218
9930255	ciprofloxacin fluoroquinolonic acid	20mg	198217
9930258	cisplatin	100mg	197207
9930259	clomifene citrate	100mg	187136
	clomifene citrate Z-isomer <i>see</i> zuclomifene		
9930261	cloxacillin sodium	200mg	274005
9930262	colecalfiferol (vitamin D ₃)	500mg	190146
9930263	cortisone acetate	100mg	167006
9930265	dapsone	100mg	183115
9930266	desoxycortone acetate	100mg	167007
9930267	dexamethasone	100mg	388008
9930268	dexamethasone acetate	100mg	288009
9930269	dexamethasone phosphoric acid	100mg	192161
9930270	dexamethasone sodium phosphate	100mg	192158
9930282	diazoxide	100mg	181103
9930283	dicloxacillin sodium	200mg	174071
9930285	dicoumarol	100mg	178077
9930287	diethylcarbamazine dihydrogen citrate	100mg	181100
9930288	digitoxin	100mg	277010
9930289	digoxin	100mg	587011



Table 1 (continued)

Catalogue number	Reference substance	Package size	Control number
9930290	dopamine hydrochloride	100mg	192159
9930292	doxorubicin hydrochloride	100mg	196202
9930294	emetine hydrochloride	100mg	187134
9930197	4-epianhydrotetracycline hydrochloride	25mg	288097
9930295	ergocalciferol (vitamin D ₂)	500mg	190147
9930296	ergometrine hydrogen maleate	50mg	277012
9930297	ergotamine tartrate	50mg	385013
9930298	erythromycin	250mg	191154
9930299	erythromycin B	150mg	194186
9930300	erythromycin C	25mg	194187
9930301	estradiol benzoate	100mg	167014
9930302	estrone	100mg	279015
9930304	ethambutol hydrochloride	100mg	179081
9930305	ethinylestradiol	100mg	301016
9930306	ethisterone	100mg	167017
9930307	ethosuximide	100mg	179088
9930309	flucloxacillin sodium	200mg	195194
9930310	flucytosine	100mg	184121
9930311	fludrocortisone acetate	200mg	195199
9930312	fluorouracil	100mg	184122
9930313	fluphenazine decanoate dihydrochloride	100mg	182107
9930314	fluphenazine enantate dihydrochloride	100mg	182108
9930315	fluphenazine hydrochloride	100mg	176076
9930316	folic acid	100mg	388019
9930195	3-formylrifamycin	200mg	202149
9930355	framycetin sulfate (neomycin B sulfate)	200mg	193178
9930318	furosemide	100mg	171044
9930322	griseofulvin	200mg	280040
9930323	haloperidol	100mg	172063
9930324	hydrochlorothiazide	100mg	179087
9930325	hydrocortisone	100mg	283020
9930326	hydrocortisone acetate	100mg	280021
9930327	hydrocortisone sodium succinate	200mg	194184
9930188	(-)-3-(4-hydroxy-3-methoxyphenyl)-2-hydrazino-2-methylalanine (3- <i>o</i> -methylcarbidopa)	25mg	193180
9930189	(-)-3-(4-hydroxy-3-methoxyphenyl)-2-methylalanine (3- <i>o</i> -methylmethylidopa)	25mg	179085
9930328	ibuprofen	100mg	183117
9930329	imipramine hydrochloride	100mg	172064
9930330	indometacin	100mg	178078
9930331	isoniazid	100mg	185124
9930332	kanamycin monosulfate	12mg	197211



Table 1 (continued)

Catalogue number	Reference substance	Package size	Control number
9930333	lanatoside C	100 mg	281022
9930334	levodopa	100 mg	295065
9930335	levonorgestrel	200 mg	194182
9930336	levothyroxine sodium	100 mg	189144
9930337	lidocaine	100 mg	181104
9930338	lidocaine hydrochloride	100 mg	181105
9930339	liothyronine sodium	50 mg	193179
9930340	loperamide hydrochloride	100 mg	194185
9930341	mebendazole	200 mg	195195
<i>Melting point reference substances</i>			
9930217	azobenzene (69 °C)	1 g	192168
9930438	vanillin (83 °C)	1 g	299169
9930222	benzil (96 °C)	4 g	294170
9930201	acetanilide (116 °C)	1 g	297171
9930380	phenacetin (136 °C)	1 g	297172
9930221	benzanilide (165 °C)	4 g	192173
9930422	sulfanilamide (166 °C)	1 g	192162
9930423	sulfapyridine (193 °C)	4 g	192163
9930286	dicyanodiamide (210 °C)	1 g	192164
9930411	saccharin (229 °C)	1 g	192165
9930235	caffeine (237 °C)	1 g	299166
9930382	phenolphthalein (263 °C)	1 g	299167
9930345	methotrexate	100 mg	194193
	3- <i>o</i> -methylcarbidopa <i>see</i> (-)-3-(4-hydroxy-3-methoxyphenyl)-2-hydrazino-2-methylalanine		
	3- <i>o</i> -methylmethylidopa <i>see</i> (-)-3-(4-hydroxy-3-methoxyphenyl)-2-methylalanine		
9930346	methylidopa	100 mg	179084
9930347	methyltestosterone	100 mg	167023
9930348	meticillin sodium	200 mg	274024
9930350	metronidazole	100 mg	183118
9930351	nafcillin sodium	200 mg	272025
9930354	neamine hydrochloride (neomycin A hydrochloride) neomycin B sulfate <i>see</i> framycetin sulfate	0.5 mg	193177
9930356	neostigmine metilsulfate	100 mg	187135
9930357	nicotinamide	100 mg	200090
9930358	nicotinic acid	100 mg	179091
9930359	nifurtimox	100 mg	194189
9930360	niridazole	200 mg	186129
9930361	niridazole-chlorethylcarboxamide	25 mg	186130
9930366	norethisterone	100 mg	186132
9930367	norethisterone acetate	100 mg	185123
9930369	nystatin	200 mg	300152



Table 1 (continued)

Catalogue number	Reference substance	Package size	Control number
9930371	ouabain	100mg	283026
9930372	oxacillin sodium	200mg	382027
9930373	oxytetracycline dihydrate	200mg	189142
9930374	oxytetracycline hydrochloride	200mg	189141
9930376	papaverine hydrochloride	100mg	185127
9930377	paracetamol	100mg	195198
9930378	paromomycin sulfate	75 mg	195197
9930383	phenoxymethylpenicillin	200mg	179082
9930384	phenoxymethylpenicillin calcium	200mg	179083
9930385	phenoxymethylpenicillin potassium	200mg	176075
9930387	phenytoin	100mg	179089
9930388	piperazine adipate	100mg	197212
9930389	piperazine citrate	100mg	197213
9930390	praziquantel	100mg	194191
9930391	prednisolone	100mg	389029
9930392	prednisolone acetate	100mg	289030
9930393	prednisolone hemisuccinate	200mg	195196
9930394	prednisolone sodium phosphate	200mg	194190
9930395	prednisone	100mg	167031
9930396	prednisone acetate	100mg	169032
9930397	probenecid	100mg	192156
9930398	procaine hydrochloride	100mg	183119
9930399	procarbazine hydrochloride	100mg	184120
9930400	progesterone	100mg	167033
9930402	propranolol hydrochloride	100mg	187139
9930403	propylthiouracil	100mg	185126
9930404	pyrantel embonate (pyrantel pamoate)	500mg	192157
9930405	pyridostigmine bromide	100mg	182110
9930406	reserpine	100mg	186133
9930408	riboflavin	250mg	382035
9930409	rifampicin	300mg	191151
9930410	rifampicin quinone	200mg	202148
9930412	sodium amidotrizoate	100mg	198221
9930413	sodium cromoglicate	100mg	188140
9930415	spectinomycin hydrochloride	200mg	193176
9930416	streptomycin sulfate	100mg	197215
9930417	sulfacetamide	100mg	196200
9930419	sulfamethoxazole	100mg	179092
9930420	sulfamethoxypyridazine	100mg	178079
9930421	sulfanilamide	100mg	179094
9930424	sulfasalazine	100mg	191155
9930425	tamoxifen citrate	100mg	196208
9930427	testosterone enantate	200mg	194192
9930428	testosterone propionate	100mg	167036
9930429	tetracycline hydrochloride	200mg	180095
9930430	thioacetazone	100mg	171046



Table 1 (continued)

Catalogue number	Reference substance	Package size	Control number
9930196	4,4'-thiodianiline thyroxine sodium <i>see</i> levothyroxine sodium	50mg	183116
9930431	tolbutamide	100mg	179086
9930432	tolnaftate	100mg	176074
9930433	toluene-2-sulfonamide	100mg	196204
9930434	trimethadione	200mg	185125
9930435	trimethoprim	100mg	179093
9930440	vincristine sulfate	9.7mg/vial	193181
9930439	warfarin	100mg	168041
9930260	zuclomifene	50mg	187137

2. List of available International Infrared Reference Spectra

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

Orders for International Infrared Reference Spectra should be sent to:

WHO Collaborating Centre for Chemical Reference Substances
Apoteket AB
Produktion & Laboratorier
Centrallaboratoriet, ACL
Prismavägen 2
SE-141 75 Kungens Kurva
Sweden
Fax: +46 8 740 60 40
Email: who.apl@apoteket.se
Web site: <http://www.apl.apoteket.se/who>

The following International Infrared Reference Spectra are currently available from the Centre:

aceclidine salicylate
acetazolamide
allopurinol
amiloride hydrochloride
amitriptyline hydrochloride
ampicillin trihydrate

beclometasone
dipropionate
benzylpenicillin potassium
biperiden
biperiden hydrochloride
bupivacaine hydrochloride



caffeine (anhydrous)	indometacin
calcium folinate	isoniazid
carbidopa	lidocaine
chlorphenamine hydrogen maleate	lidocaine hydrochloride
clofazimine	lindane
cloxacillin sodium	metronidazole
colchicine	miconazole nitrate
cytarabine	niclosamide
dexamethasone	nicotinamide
dexamethasone acetate, mono- hydrate	noscapine
dextromethorphan	oxamniquine
hydrobromide	papaverine hydrochloride
diazepam	phenobarbital
dicolinium iodide	phenoxymethylpenicillin calcium
dicoumarol	phenytoin
diethylcarbamazine dihydrogen citrate	primaquine phosphate
diphenoxylate hydrochloride	propylthiouracil
erythromycin ethylsuccinate	protionamide
erythromycin stearate	pyrimethamine
etacrynic acid	salbutamol
ethionamide	salbutamol sulfate
ethosuximide	sulfadimidine
furosemide	sulfadoxine
gallamine triethiodide	sulfamethoxazole
glibenclamide	sulfamethoxyipyridazine
haloperidol	tiabendazole
hydrochlorothiazide	trihexyphenidyl hydrochloride
ibuprofen	trimethoprim
imipramine hydrochloride	valproic acid
	verapamil hydrochloride



Annex 2

Good manufacturing practices: requirement for the sampling of starting materials (amendment)

Introduction

The WHO Expert Committee on Pharmaceutical Preparations, at its thirty-seventh meeting, adopted Good Manufacturing Practices for pharmaceutical products: main principles, which were published in its report (*I*). At its thirty-ninth meeting, the Committee considered a proposal to amend the WHO good manufacturing practices (GMP) requirement for sampling of starting materials because it is not consistent with the requirement of other GMP documents such as the European Union GMP Guide which allows reduced sampling of starting material containers under certain conditions. The Committee recommended that, in the interests of harmonization, the proposal should be adopted in amending paragraph 17.15 of the main text of the GMP.

Add to section 17.15 “An identity test should be conducted on a sample from each container of starting material (see also section 14.14)” the following:

It is permissible to sample only a proportion of the containers where a validated procedure has been established to ensure that no single container of starting material has been incorrectly labelled.

This validation should take account of at least the following aspects:

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

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



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

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

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

Reference

1. Good Manufacturing Practices for pharmaceutical products: main principles. In: *WHO Expert Committee on Pharmaceutical Preparations. Thirty-seventh report*. Geneva, World Health Organization, 2003 (WHO Technical Report Series, No. 908), Annex 4.



Annex 3

WHO Good Manufacturing Practices: water for pharmaceutical use

1. Introduction	41
1.1 Scope of the document	41
1.2 Background to water requirements and uses	41
1.3 Applicable guides	42
2. General requirements for pharmaceutical water systems	42
3. Water quality specifications	43
3.1 General	43
3.2 Drinking-water	43
3.3 Purified water	44
3.4 Highly purified water	44
3.5 Water for injections	44
3.6 Other grades of water	44
4. Application of specific waters to processes and dosage forms	45
5. Water purification methods	45
5.1 General considerations	45
5.2 Production of drinking-water	46
5.3 Production of purified water	48
5.4 Production of highly purified water	48
5.5 Production of water for injections	49
6. Water purification, storage and distribution systems	49
6.1 General	49
6.2 Materials that come into contact with systems for water for pharmaceutical use	50
6.3 System sanitization and bioburden control	51
6.4 Storage vessel requirements	51
6.5 Requirements for water distribution pipework	52
7. Operational considerations	54
7.1 Start-up and commissioning of water systems	54
7.2 Qualification	54
7.3 Continuous system monitoring	56
7.4 Maintenance of water systems	56
7.5 System reviews	56
8. Inspection of water systems	57
Bibliography	57



1. Introduction

1.1 Scope of the document

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 the good manufacturing practice (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.

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).

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.

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

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

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 drug regulatory authority.

1.2 Background to water requirements and uses

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.

E



Different grades of water quality are required depending on the route of administration of the pharmaceutical products. One source of guidance about different grades of water is the European Medicines Evaluation Agency (EMA) *Note for guidance on quality of water for pharmaceutical use* (CPMP/QWP/158/01).

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. 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 very important to minimize microbial contamination by routine sanitization and taking appropriate measures to prevent microbial proliferation.

1.3 Applicable guides

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

2. General requirements for pharmaceutical water systems

Pharmaceutical water production, storage and distribution systems should be designed, installed, commissioned, validated and maintained to ensure the reliable production of water of an appropriate quality. They should not be operated beyond their designed capacity. Water should be produced, stored and distributed in a manner that prevents unacceptable microbial, chemical or physical contamination (e.g. with dust and dirt).

The use of the systems following installation, commissioning, validation and any unplanned maintenance or modification work should be approved by the quality assurance (QA) department. If approval is obtained for planned preventive maintenance tasks, they need not be approved after implementation.



Water sources and treated water should be monitored regularly for quality and 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 and any actions taken should be maintained for an appropriate length of time.

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 agent has been effectively removed.

3. **Water quality specifications**

3.1 **General**

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

Pharmacopoeial requirements for WPU are described in national and international pharmacopoeias and limits for various contaminants are given. Companies wishing to supply multiple markets should set specifications that meet the strictest requirements from each of the relevant pharmacopoeias.

3.2 **Drinking-water**

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.

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 softening, removal of specific ions, particle reduction and antimicrobial treatment. 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 is also common for public water-supply organizations to conduct tests and guarantee that the drinking-water delivered is of potable quality.

Drinking-water quality is covered by the WHO drinking-water guidelines, standards from the International Organization for

E



Standardization (ISO) and other regional and national agencies. Drinking-water should comply with the relevant regulations laid down by the competent authority.

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 potable water.

3.3 Purified water

Purified water (PW) should be prepared from a potable water source as a minimum-quality feed-water, should meet the pharmacopoeial specifications for chemical and microbiological purity, and should be protected from recontamination and microbial proliferation.

3.4 Highly purified water

Highly purified water (HPW) should be prepared from potable water as a minimum-quality feed-water. HPW 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 methods are not considered to be as reliable as distillation. HPW may be prepared by combinations of methods such as reverse osmosis, ultrafiltration and deionization.

3.5 Water for injections

Water for injections (WFI) should be prepared from potable water as a minimum-quality feed-water. WFI is not sterile water and is not a final dosage form. It is an intermediate bulk product. WFI is the highest quality of pharmacopoeial WPU.

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

3.6 Other grades of water

When a specific process requires a special non-pharmacopoeial grade of water, this should be specified and should at least satisfy the pharmacopoeial requirements of the grade of WPU required for the type of dosage form or process step.



4. Application of specific waters to processes and dosage forms

Product licensing authorities define the requirement to use the specific grades of WPU for different dosage forms or for different stages in washing, preparation, synthesis, manufacturing or formulation.

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.

HPW 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 WFI.

WFI should be used in injectable product preparations, for dissolving or diluting substances or preparations for parenteral administration before use, and for sterile water for preparation of injections. WFI 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.

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

5. Water purification methods

5.1 General considerations

The specifications for WPU found in compendia (e.g. pharmacopoeias) are generally not prescriptive as to permissible water purification methods other than those for WFI (refer to section 3.5).

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 water quality specification;
- the yield or efficiency of the purification system;
- feed-water quality and the variation over time (seasonal changes);
- the reliability and robustness of the water-treatment equipment in operation;





- the availability of water-treatment equipment on the market;
- the ability to adequately support and maintain the water purification equipment; and
- the operation costs.

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

- 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;
- configuration to avoid proliferation of microbiological organisms;
- tolerance to cleaning and sanitizing agents (thermal and chemical);
- the system capacity and output requirements; and
- 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.

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

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

5.2 Production of drinking-water

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 potable drinking-water from a specific raw water source.

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

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



The drinking-water quality should be monitored routinely. Additional testing should be considered if there is any change in the raw-water source, treatment techniques or system configuration. If the drinking-water quality changes significantly, 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.

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 its operation should not be made until a review has been completed and the change approved by the QA department.

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, its use should ensure a turnover of the stored water sufficient to prevent stagnation.

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

Drinking-water purchased in bulk and transported to the user by tanker presents special problems and risks not associated with potable 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.

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, allow for visual inspection and for being drained and sanitized. Distribution pipework should be able to be drained, or flushed, and sanitized.

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 or thermal sanitization and frequent regeneration should be considered. Additionally, all water-treatment components should be maintained with continuous water flow to inhibit microbial growth.





5.3 Production of purified water

There are no prescribed methods for the production of PW in the pharmacopoeias. Any appropriate qualified purification technique or sequence of techniques may be used to prepare PW. Typically ion exchange, ultrafiltration and/or reverse osmosis processes are used. Distillation can also be used.

The following should be considered when configuring a water purification system:

- the feed-water quality and its variation over seasons;
- 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; and
- unit process steps should be provided with appropriate instrumentation to measure parameters such as flow, pressure, temperature, conductivity, pH and total organic carbon.

Ambient-temperature PW systems 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 following techniques should be considered:

- maintenance of flow through water-purification equipment at all times;
- control of temperature in the system by pipeline heat exchange or plant-room cooling to reduce the risk of microbial growth (guidance value $<25^{\circ}\text{C}$);
- provision of ultraviolet disinfection;
- selection of water-treatment components that can be thermally sanitized; and/or
- application of chemical sanitization (including agents such as ozone).

5.4 Production of highly purified water

There are no prescribed methods for the production of HPW in any major pharmacopoeia, including the *European Pharmacopoeia*. Any appropriate qualified purification technique or sequence of



techniques may be used to prepare HPW. Typically ion exchange, ultrafiltration and/or reverse osmosis processes are used.

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

5.5 **Production of water for injections**

The pharmacopoeias prescribe or limit the permitted final water purification stage in the production of WFI. 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.

The following should be considered when designing a water purification system:

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

6. **Water purification, storage and distribution systems**

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

6.1 **General**

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.

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.

The storage and distribution system should be configured to prevent recontamination of the water after treatment and be subjected to a

E



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**

This section applies to generation equipment for PW, HPW and WFI, and the associated storage and distribution systems.

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.* All materials used should be compatible with the temperature and chemicals used by or in the system.
- *Prevention of leaching.* All materials that come into contact with WPU should be non-leaching at the range of working temperatures.
- *Corrosion resistance.* PW, HPW and WFI 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 316L. The system should be passivated after initial installation or after 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 is employed. Smooth internal surfaces help to avoid roughness and crevices within the WPU system. Crevices are frequently sites where corrosion can commence. The internal finish should have an arithmetical average surface roughness of not greater than 0.8 micrometre arithmetical mean roughness (Ra). When stainless steel is used, mechanical and electropolishing techniques may be employed. Electropolishing improves the resistance of the stainless steel material to surface corrosion.
- *Jointing.* The selected system materials should be able to be easily jointed 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, logs of all welds and visual inspection of a defined proportions of welds.



- *Design of flanges or unions.* Where flanges or unions are used, they should be of a hygienic or sanitary design. Appropriate checks should be carried out to ensure that the correct seals are used and that they are fitted and tightened correctly.
- *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 316 L (low carbon) stainless steel, polypropylene, polyvinylidenedifluoride and perfluoroalkoxy. Other materials such as unplasticized polyvinylchloride (uPVC) may be used for treatment equipment designed for less pure water such as ion exchangers and softeners.

6.3 System sanitization and bioburden control

Water treatment equipment, storage and distribution systems used for PW, HPW and WFI should be provided with features to control the proliferation of microbiological organisms during normal use, as well as techniques for sanitizing or sterilizing the system after intervention for maintenance or modification. The techniques employed should be considered during the design of the system and their performance proven during the commissioning and qualification activities.

Systems that operate and are maintained at elevated temperatures, in the range of 70–80 °C, 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, then special precautions should be taken to prevent the ingress and proliferation of microbiological contaminants (see section 6.5.3 for guidance).

6.4 Storage vessel requirements

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

6.4.1 Capacity

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.

E





- 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 or other logical period of demand.

6.4.2 **Contamination control considerations**

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 water distribution loop should be configured to ensure that the headspace of the storage vessel is effectively wetted by a flow of water. The use of spray ball or distributor devices to wet the surfaces should be considered.
- 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 ideally be configured to allow in situ testing of integrity. Offline testing is also acceptable. The use of heated vent filters should be considered 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 over-pressurization, these devices should be of a sanitary design. Bursting discs should be provided with external rupture indicators to prevent accidental loss of system integrity.

6.5 **Requirements for water distribution pipework**

The distribution of PW, HPW and WFI should be accomplished using a continuously circulating pipework loop. Proliferation of contaminants within the storage tank and distribution loop should be controlled.



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.

6.5.1 **Temperature control and heat exchangers**

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 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.

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.

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.

6.5.2 **Circulation pumps**

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.

6.5.3 **Biocontamination control techniques**

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 maintenance of the design velocity for a specific system should be proven during the system qualification and the maintenance of satisfactory performance should be monitored. During the operation of a distribution system, short-term fluctuations in the flow velocity are unlikely to cause contamination problems provided that cessation of flow, flow reversal or pressure loss does not occur.
- The system design should ensure the shortest possible length of pipework.
- For ambient temperature systems, pipework should be isolated from adjacent hot pipes.

E





- Deadlegs in the pipework installation greater than 1.5 times the branch diameter should be avoided.
- Pressure gauges should be separated from the system by membranes.
- Hygienic pattern diaphragm valves should be used.
- Pipework should be laid to falls to allow drainage.
- The growth of microorganisms can be inhibited by:
 - ultraviolet radiation sources in pipework;
 - maintaining the system heated (guidance temperature 70–80 °C);
 - sanitizing the system periodically using hot water (guidance temperature >70 °C);
 - sterilizing or sanitizing the system periodically using superheated hot water or clean steam; and
 - 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

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

WPU, PW, HPW and WFI 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), installation qualification (IQ), operational qualification (OQ) and performance qualification (PQ).

This guidance does not define the standard requirements for the conventional validation 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.

Phase 1. A test period of 2–4 weeks should be spent monitoring the system intensively. During this period the system should operate continuously without failure or performance deviation. The following should be included in the testing approach.

- Undertake chemical and microbiological testing in accordance with a defined plan.
- Sample the incoming feed-water daily to verify its quality.
- Sample after each step in the purification process daily.
- Sample at each point of use and at other defined sample points daily.
- 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 and action levels.
- Develop and refine test-failure procedure.

Phase 2. A further test period of 2–4 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. Water can be used for manufacturing purposes during this phase. The approach should also:

- demonstrate consistent operation within established ranges; and
- 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 1 year after the satisfactory completion of phase 2. Water can be used for manufacturing purposes during this phase which has the following objectives and features.

- Demonstrate extended reliable performance.
- 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

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 online instrument monitoring 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 and specific sample points. Samples from points of use should be taken in a similar way to that adopted when the water is being used in service.

Tests should be carried out to ensure that the selected pharmacopoeia specification has been satisfied, and should include, as appropriate, determination of conductivity, pH, heavy metals, nitrates, total organic carbon, total viable count, presence of specific pathogens and endotoxins.

Monitoring data should be subject to trend analysis.

7.4 Maintenance of water systems

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 clear maintenance plan and instructions;
- review and approval of systems for use upon completion of work;
and
- record and review of problems and faults during maintenance.

7.5 System reviews

WPU (PW, HPW and WFI) systems should be reviewed at appropriate regular intervals. The review team should comprise representatives from engineering, QA, 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; and
- the status of the current SOP list.

8. Inspection of water systems

WPU (PW, HPW and WFI) 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. This GMP guidance can be used as the basis of inspection. The following list identifies items and a logical sequence for a WPU system inspection or audit:

- a sampling and monitoring plan with a drawing of all sample points;
- 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 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; and
- checking calibration and standardization of critical instruments.

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

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

- performance qualification;
- operational qualification; and
- installation qualification.

Bibliography

WHO Guidelines for drinking-water quality, 3rd edition. Geneva, World Health Organization, 2003.

Water and steam systems. International Society for Pharmaceutical Engineering, 2001. ISPE Baseline™ Pharmaceutical Engineering Guide, volume 4.

E





- American Society of Mechanical Engineers. *Bioprocessing Equipment Standard*. ASME — BPE 2000
- Biotechnology. Equipment. Guidance on testing procedures for cleanability*. British Standards Publishing Ltd. BS EN 12296.
- Harfst WH. Selecting piping materials for high-purity water systems. *Ultra Pure Water*, May/June 1994.
- Noble PT. Transport considerations for microbial control in piping. *Journal of Pharmaceutical Science and Technology*, 1994, 48:76–85.
- Baines PH. Passivation; understanding and performing procedures on austenitic stainless steel systems. *Pharmaceutical Engineering*, 1990, 10(6).
- Guide to inspections of high purity water systems*. Maryland, US Food and Drug Administration, 1993.
- Tverberg JC, Kerber SJ. Effect of nitric acid passivation on the surface composition of mechanically polished type 316 L sanitary tube. *European Journal of Parenteral Sciences* 1998, 3:117–124.
- European Pharmacopoeia*: Web site for the publishers of the *European Pharmacopoeia* and supplements; <http://www.pheur.org/>
- US Pharmacopoeia*: Published annually; see <http://www.usp.org/>
- European Medicines Evaluation Agency. *Note for guidance on the quality of water for pharmaceutical use*. London. CPMP/QWP/158-01.
- Pharmaceutical Inspection Cooperation Scheme. *PIC/S; Inspection of Utilities; P1 009-1*. Geneva, Pharmaceutical Inspection Cooperation Scheme, 2002.
- The International Pharmacopoeia*, World Health Organization, Geneva; <http://www.who.int/medicines>



Annex 4

WHO guidelines for sampling of pharmaceutical products and related materials

1. Introduction	61
1.1 General considerations	61
1.2 Glossary	61
1.3 Purpose of sampling	64
1.4 Classes and types of pharmaceutical products and related materials	65
1.5 Sampling facilities	65
1.6 Responsibilities for sampling	66
1.7 Health and safety	67
2. Sampling process	67
2.1 Preparation for sampling	67
2.2 Sampling operation and precautions	68
2.3 Storage and retention	69
3. Regulatory issues	70
3.1 Pharmaceutical inspections	71
3.2 Surveillance programmes	71
4. Sampling on receipt (for acceptance)	72
4.1 Starting materials	72
4.2 Intermediates in the manufacturing process and bulk pharmaceutical products	73
4.3 Finished products	73
4.4 Packaging materials (primary and secondary)	74
5. Sampling plans for starting materials, packaging materials and finished products	75
5.1 Starting materials	76
5.2 Packaging materials	77
5.3 Finished products	78
Bibliography	78
Appendix 1 Types of sampling tools	80
Appendix 2 Sample collection form	85
Appendix 3 Steps to be considered for inclusion in a standard operating procedure	87



Appendix 4 Examples of types of containers used to store samples of starting materials and bulk products	91
Appendix 5 Examples of use of sampling plans n , p and r	93





1. Introduction

These guidelines are primarily intended for use by governmental organizations, such as drug regulatory authorities (including inspectorates), quality control laboratories and customs and police officials, but some of the general principles may also be appropriate for application by procurement agencies, manufacturers and customers.

These guidelines should be useful when surveying the national markets for the quality of drug products in accordance with national drug quality surveillance programmes for marketed products, whether registered for sale or compounded in pharmacies.

The choice of a sampling plan should always take into consideration the specific objectives of the sampling and the risks and consequences associated with inherent decision errors. The bibliography at the end of this Annex should be consulted when justifying a sampling plan for a given purpose.

1.1 General considerations

Sampling comprises the operations designed to select a portion of a pharmaceutical product (for definition, see glossary) for a defined purpose. The sampling procedure should be appropriate to the purpose of sampling, to the type of controls intended to be applied to the samples and to the material to be sampled. The procedure should be described in writing.

All operations related to sampling should be performed with care, using proper equipment and tools. Any contamination of the sample by dust or other foreign material is liable to jeopardize the validity of the subsequent analyses.

1.2 Glossary

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

Available sample

Whatever total quantity of sample materials is available.

Batch

A quantity of any drug produced during a given cycle of manufacture. If the manufacturing process is continuous, the batch originates in a defined period of time during which the manufacturing conditions are stable and have not been modified.

E



Combined sample

Sample resulting from combining all or parts of two or more samples of the material.

Consignment

The quantity of a bulk starting material, or of a drug product, made by one manufacturer or supplied by an agent, and supplied at one time in response to a particular request or order. A consignment may comprise one or more lot-identified packages or containers and may include material belonging to more than one lot-identified batch.

Final sample

Sample ready for the application of the test procedure.

Homogeneity

A material is regarded as homogeneous when it is all of the same origin (e.g. from the same batch) and as non-homogeneous when it is of differing origins.

Original sample

Sample collected directly from the material.

Pharmaceutical product

Any material¹ or product intended for human or veterinary use presented in its finished dosage form or as a starting material for use in such a dosage form, that is subject to control by pharmaceutical legislation in the exporting state and/or the importing state.

Prequalification

The activities undertaken in defining a product or service need, seeking expressions of interest from enterprises to supply the product or service, and examining the product or service offered against the specification, and the facility where the product or service is prepared against common standards of good manufacturing practice (GMP). The examination of the product or service and of the facility where it is manufactured is performed by trained and qualified inspectors against common standards. Once the product is approved, and the facility is approved for the delivery of the specified product or service, other procurement agencies are informed of the approval. Pre-qualification is required for all pharmaceutical products regardless of

¹ "Material" is used in the document for "pharmaceutical products and related materials".



their composition and place of manufacture or registration, but the amount and type of information requested from the supplier for use in the assessment by the procurement agency may differ.

Production

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

Random sample

Sample in which the different fractions of the material have an equal probability of being represented.

Representative sample

Sample obtained according to a sampling procedure designed to ensure that the different parts of a batch or the different properties of a non-uniform material are proportionately represented.

Retention sample

Sample collected as part of the original sampling process and reserved for future testing. The size of a retention sample should be sufficient to allow for at least two confirmatory analyses. In some cases statutory regulations may require one or more retention samples, each of which should be separately identified, packaged and sealed.

Sample

A portion of a material collected according to a defined sampling procedure. The size of any sample should be sufficient to allow all anticipated test procedures to be carried out, including all repetitions and retention samples. If the quantity of material available is not sufficient for the intended analyses and for the retention samples, the inspector should record that the sampled material is the available sample (see *Sampling record*) and the evaluation of the results should take account of the limitations that arise from the insufficient sample size.

Sampler

Person responsible for performing the sampling operations.

Sampling method

That part of the sampling procedure dealing with the method prescribed for withdrawing samples.

E





Sampling plan

Description of the location, number of units and/or quantity of material that should be collected, and associated acceptance criteria.

Sampling procedure

The complete sampling operations to be performed on a defined material for a specific purpose. A detailed written description of the sampling procedure is provided in the *sampling protocol*.

Sampling record

Written record of the sampling operations carried out on a particular material for a defined purpose. The sampling record should contain the batch number, date and place of sampling, reference to the sampling protocol used, a description of the containers and of the materials sampled, notes on possible abnormalities, together with any other relevant observations, and the name and signature of the inspector.

Sampling unit

Discrete part of a consignment such as an individual package, drum or container.

Selected sample

Sample obtained according to a sampling procedure designed to select a fraction of the material that is likely to have special properties. A selected sample that is likely to contain deteriorated, contaminated, adulterated or otherwise unacceptable material is known as an *extreme sample*.

Uniformity

A starting material may be considered uniform when samples drawn from different layers do not show significant differences in the quality control tests which would result in non-conformity with specifications. The following materials may be considered uniform unless there are signs to the contrary: organic and inorganic chemicals; purified natural products; various processed natural products such as fatty oils and essential oils; and plant extracts. The assumption of uniformity is strengthened by homogeneity, i.e. when the consignment is derived from a single batch.

1.3 **Purpose of sampling**

Sampling may be required for different purposes, such as pre-qualification; acceptance of consignments; batch release testing;



in-process control; special controls; inspection for customs clearance, deterioration or adulteration; or for obtaining a retention sample.

The tests to be applied to the sample may include:

- verifying the identity;
- performing complete pharmacopoeial or analogous testing; and
- performing special or specific tests.

1.4 **Classes and types of pharmaceutical products and related materials**

The materials to be sampled may belong to the following classes:

- starting materials for use in the manufacture of finished pharmaceutical products;
- intermediates in the manufacturing process (e.g. bulk granule);
- pharmaceutical products (in-process as well as before and after packaging);
- primary and secondary packaging materials; and
- cleaning and sanitizing agents, compressed gases and other processing agents.

1.5 **Sampling facilities**

Sampling facilities should be designed to:

- prevent contamination of the opened container, the materials and the operator;
- prevent cross-contamination by other materials, products and the environment; and
- protect the individual who samples (sampler) during the sampling procedure.

Where possible, sampling should be performed in an area or booth designed for and dedicated to this purpose, although this will not be possible where samples are required to be taken from a production line (e.g. in-process control samples). The area in which the sample was taken should be recorded in the sampling record and a sequential log should be kept of all materials sampled in each area.

Sampling from large containers of starting material or bulk products can present difficulties. Whenever possible, this work should be carried out in a separate, closed cubicle within the warehouse, to reduce the risk of contamination (e.g. by dust) of either the sample or the materials remaining in the container, or of cross-contamination.

Some materials should be sampled in special or dedicated environments (e.g. when sampling articles for which contamination with dirt

E



or particles from the environment should be avoided, such as aerosol valves, hormones and penicillins).

Generally, taking the original sales pack as a sample from outlets such as pharmacies or hospitals does not present problems. However, the inspector should ensure that the quantity of sample taken is sufficient for the intended analyses and for the retention samples, and that all units sampled are derived from the same batch and preferably from the same location.

1.6 Responsibilities for sampling

Those responsible for sampling procedures include:

- *governmental organizations*, such as drug control authorities (including inspectorates); quality control laboratories; customs and police authorities responsible for the clearance of drug products held in quarantine after manufacture or importation, and for the detection of pharmaceutical products that have deteriorated or have been contaminated, adulterated or counterfeited;
- *customers* such as governmental or nongovernmental agencies involved in the acquisition of drug products; and
- *manufacturers* in the context of good manufacturing practices (GMP).

The samplers need to be adequately trained in the practical aspects of sampling, qualified to perform the sampling operation, and should have sufficient knowledge of pharmaceutical substances to allow them to execute the work effectively and safely. Given that the sampling technique itself can introduce bias, it is important that personnel carrying out the sampling should be suitably trained in the techniques and procedures used. The training should be documented in the individual's training records. Sampling records should clearly indicate the date of sampling, the sampled container and the identity of the person who sampled the batch.

A conscientious approach, with meticulous attention to detail and cleanliness, is essential. The sampler should remain alert to any signs of contamination, deterioration or tampering. Any suspicious signs should be recorded in detail in the sampling record.

If a governmental agency needs to sample a sterile or bulk pharmaceutical product at the manufacturing site, it may be best to have the manufacturer's personnel collect the sample, using their own procedures. The regulatory inspector would observe the procedure in such a way as not to increase the chance of contamination (e.g. for sterile pharmaceutical products, the inspector would observe through



a glass window outside the aseptic sampling area) and to preclude the possibility of the inspector inadvertently contaminating the remaining bulk pharmaceutical product through poor procedures, for example.

1.7 Health and safety

It is the responsibility of the sampler to read the relevant health and safety information (e.g. the safety data sheet for a pharmaceutical product and related materials) before sampling the material. The information should include necessary safety precautions and requirements for both the operator and the environment.

The sampler should wear appropriate protective clothing for the task. If specific safety precautions are required, such as the use of respiratory equipment, the sampler should be properly trained in its use.

The sampler should have safe access to and egress from the place where the sample is taken, and the places where the samples are taken for storage. The sample storage areas should have adequate light and ventilation and should be arranged to satisfy the requirements for safety as well as any special ones arising from the characteristics of the material being sampled.

Care should be taken to guard against collapse of stacked containers or solids in bulk.

2. Sampling process

2.1 Preparation for sampling

For the sampling of products, the responsible person should have at his or her disposal all the tools needed to open the containers (e.g. packages, barrels and others). Tools may include knives, pliers, saws, hammers, wrenches, implements to remove dust (preferably a vacuum cleaner), and material to reclose the packages (such as sealing tape), as well as self-adhesive labels to indicate that some of the contents have been removed from a package or container. Containers due to be sampled should be cleaned prior to sampling if necessary.

Sampling of uniform starting materials does not require complicated tools. A variety of pipettes fitted with suction bulbs, cups or beakers, dippers and funnels are needed for liquids of low viscosity. The use of glass should be avoided. A suitable inert rod can be used for highly viscous liquid, and spatulas or scoops are needed for powdered and granular solids. Sterile pharmaceutical products should be sampled under aseptic conditions, and only when deemed absolutely essential, to avoid the risk of loss of sterility.

E





The tools for sampling non-uniform materials are more complicated and more difficult to clean. For example, a sampling tube with a shutter at the lower end may be used to sample liquids in drums or other large containers and a slotted tube with a pointed end may be used to sample solids. It is important to follow the manufacturer's instructions for the use of sampling devices.

All sampling tools and implements should be made of inert materials and kept scrupulously clean. After use or before reuse, they should be thoroughly washed, rinsed with water or suitable solvent, and dried. They should be stored in clean conditions. Adequate washing facilities should be provided in, or in close proximity to, the sampling area, otherwise samplers will need to bring separate clean sets of implements for sampling each product. The cleaning procedure used for all sampling tools and implements should be documented and recorded. The adequacy of the cleaning procedure for the material from which the sampling tool is made should be demonstrated. The use of disposable sampling materials has distinct advantages.

Examples of sampling tools suitable for each type of material are given in Appendix 1.

2.2 Sampling operation and precautions

There should be a written procedure describing the sampling operation. This should include details of the health and safety aspects of sampling. It should ensure that representative samples are taken in sufficient quantity for testing in accordance with specifications. Closures and labels should preferably be such that unauthorized opening can be detected. Samples should never be returned to the bulk.

The sampling process should be appropriately supervised and documented (see Appendix 2 for an example of a sample collection form).

The sampling procedure should be such that non-uniformity of the material can be detected. During the sampling procedure, attention should be paid to any signs of nonconformity of the material.

Signs of non-uniformity include differences in shape, size or colour of particles in crystalline, granular or powdered solid substances; moist crusts on hygroscopic substances; deposits of solid pharmaceutical product in liquid or semi-liquid products; and stratification of liquid products. Such changes, some of which may be readily reversible, can occur during prolonged storage or exposure to extreme temperatures during transportation. Homogeneous portions of the material or bulk such as those mentioned above should be sampled and tested separately from the rest of the material that has a normal appearance.



Pooling of the samples from the different portions should be avoided, because this can mask contamination, low potency or other quality problems.

Labelling of samples should provide appropriate details, including the batch number and, if known, the container number from which the sample was taken, the amount taken and for what purpose. Labels should be applied at the time of sampling. The container used to store the sample should also be properly labelled with appropriate details such as sample type, name of material, identification code, batch/lot number, code, quantity, date of sampling, storage conditions, handling precautions and container number.

For finished drug products, the sampling procedure should take account of the official and non-official tests required for the individual dosage form (e.g. tablets or parenteral preparations). Non-official tests could include testing for adulteration and counterfeiting.

The sampling procedure should also take account of past experience with the pharmaceutical product or related material and with the supplier, and of the number of sampling units in the consignment.

Examples of steps for sampling are given in Appendix 3.

When a container is sampled outside the control of the consignee of the product, the following precautions should be taken. If the tamper-proof seal is broken to obtain a sample, then the consignee of the product should be informed and the container resealed with an appropriate tamper-proof seal, and the consignee of the product informed of its type and its identification. If a bag has been punctured to take a sample, then the sampling hole should be appropriately closed and identified as a sampling hole made by an authorized sampler. Sampled containers should be identified, as they may no longer contain the quantity of product stated on the label. In accordance with national legislation there may be exceptions, e.g. during ongoing investigations of cases related to counterfeit pharmaceutical products.

2.3 Storage and retention

The container used to store a sample should not interact with the sampled material nor allow contamination. It should also protect the sample from light, air and moisture, as required by the storage directions for the pharmaceutical product or related material sampled. As a general rule the container should be sealed and preferably tamper-evident.

E



Samples of loose materials, whether solid or liquid, should be placed in one or more clean containers. Liquid samples should be transported in suitable bottles closed by screw tops with inert liners that provide a good vapour-proof (moisture-proof) seal for the contents. Suitable screw-top jars in exceptional cases only should be used for solid or semi-solid pharmaceutical products. The container should be inert. Light-sensitive materials should be protected by using amber glass containers or by wrapping colourless glass containers in foil or dark-coloured paper. Headspace should be kept to a minimum to minimize any possible degradation. Any special procedures, for example, nitrogen gassing, should be discussed with the consignee of the material and carried out as appropriate.

Solid dosage forms such as tablets or granules should be protected during transit, either by totally filling the container with the product or by filling any residual space with a suitable material. All containers should be sealed and labelled, and all samples should be packaged adequately and transported in such a way as to avoid breakage and contamination during transport.

For all containers that come apart (e.g. screw-capped jars or metal tins with separate lids) precautions should be taken to avoid any mix-up when they are opened for examination, such as by labelling all parts of each container whenever possible.

If one sample is divided into several sample containers, they should be transported in a suitably sealed box, which should be labelled with the identity of the product, the consignment from which the sample was drawn, the size of the sample, the date and place of sampling, and the name of the inspector.

Security and adequate storage conditions should be ensured for the rooms in which samples are stored. Samples should be stored in accordance with the storage conditions as specified for the respective active pharmaceutical ingredient (API), excipient or drug product. Packaging materials similar to those in which the bulk is supplied should be used for long-term storage.

Examples of types of containers used to store samples of starting materials and bulk products are given in Appendix 4.

3. Regulatory issues

When sampling for regulatory purposes, additional samples for regulatory testing and verification purposes should be provided (e.g. for duplicate testing and parallel testing by different regulatory



laboratories and by the consignee of the product). The consignee of the product should be informed that samples have been taken, and should the consignee wish to conduct his/her own testing of the sample taken for regulatory purposes, regulatory authorities should provide a sample to the consignee of the goods.

Sampling of products for prequalification purposes may follow similar procedures.

3.1 **Pharmaceutical inspections**

Pharmaceutical inspectors may take samples from retail or hospital pharmacies (including samples of preparations manufactured in bulk on the premises), or from industry and wholesalers for a variety of reasons, such as:

- routine monitoring and control;
- following the suspicion or discovery of products that show signs of possible deterioration, contamination, adulteration or counterfeiting; and
- when a particular product is suspected of being either ineffective or responsible for adverse clinical reactions.

For deteriorated dosage forms, the sample should consist of one or more retail containers of the product that shows visual signs of deterioration.

When a complaint has been received about a drug product, the sample should include the original container and, if possible, one or more unopened containers containing the same product and bearing the same batch number. There should be good communication between the regulatory authority and the consignee of the goods concerning the findings and any necessary corrective action.

3.2 **Surveillance programmes**

National drug regulatory authorities are responsible for monitoring the quality of all drug products marketed in their country and as defined by legislation. The extent to which routine surveillance should be undertaken, as opposed to assessment of suspect products, will depend upon factors such as:

- the capacity of the national quality control laboratory;
- the extent to which the quality of the product has been assessed prior to registration;
- the extent to which the requirements for GMP are implemented; and
- the number of products that are imported from abroad.

E



A systematic programme of drug quality surveillance should be in place which may include sampling of marketed products, whether registered for sale or compounded in pharmacies, as deemed necessary. Each product should be assessed regularly (e.g. every 2–3 years) for inclusion in the surveillance programme, but particular attention should be accorded to products that are of prime importance to public health programmes or that are potentially dangerous, unstable or difficult to formulate properly.

The responsible laboratory should draw up the sampling programme, if necessary under the guidance of the drug regulatory authority, on a yearly or half-yearly basis. This programme should not only list the products to be sampled during a given period, but should also specify the sampling procedures and the size of the samples to be collected, taking into account the need for retention samples. The programme should state to what extent each brand of a given product will be sampled and which local authority or inspector will be responsible for each sampling operation. It should indicate to which laboratory (if more than one exists) each sample should be sent. Such a programme enables the facilities of each laboratory to be used to best advantage.

4. **Sampling on receipt (for acceptance)**

4.1 **Starting materials**

Testing of starting materials should be undertaken using samples collected in accordance with an appropriate procedure.

If the material of a consignment can be regarded as uniform, the sample can be taken from any part of the consignment. If, however, the material is not physically uniform, special sampling tools may be required to withdraw a cross-sectional portion of the material. Alternatively, where applicable, a validated procedure can be followed to restore the uniformity of the material before sampling, based on information concerning the subsequent handling and manufacturing steps. For example, a stratified liquid may be stirred or a solid deposit in a liquid may be dissolved by gentle warming and stirring. Such interventions should not be attempted without adequate knowledge of the properties of the contents and appropriate discussions with the consignee of the goods.

All partially processed natural products, both animal, herbal (dried plants and their parts) and mineral, should be treated as intrinsically non-uniform. Special procedures requiring considerable practice



are needed to prepare representative samples from such consignments, including coning and quartering and the treatment of fines. Details of appropriate procedures may be found in the relevant International Organization for Standardization (ISO) documents (see Bibliography). These procedures are not further described in these guidelines.

4.2 **Intermediates in the manufacturing process and bulk pharmaceutical products**

Pharmaceutical intermediates and products supplied in bulk may need to be examined. These include liquids and semi-solid pharmaceutical products, powdered solids or granulates transported in large containers and intended either for further processing or for direct packaging into final market containers, and unit dosage forms (tablets, capsules) supplied in bulk which are intended for repackaging into smaller containers.

There is a risk of segregation of bulk materials during transportation and this should be taken into account when drawing up the sampling plan.

Products of this kind may be assumed to be uniform where the transportation process has been validated, provided that they:

- are labelled with the name of the manufacturer and a single batch number;
- have been produced in accordance with GMP; and
- are supplied with a certificate, issued in the country of origin, according to the WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce.

In these circumstances the collection of a single sample, sufficient for the intended analyses, is adequate.

4.3 **Finished products**

The quality of finished pharmaceutical products frequently needs to be verified at the time of their importation or purchase. The necessary sampling should be performed using an appropriate method and with regard to the presumed uniformity. A single consignment of a product from a single manufacturer and labelled with a single batch number may be assumed to be uniform.

The minimum size of the samples will be determined by the requirements of the analytical procedure that will be used to test the product. Tests of unit dosage forms for uniformity of weight, volume or content can require a considerable number of units, as can tests





for sterility. Depending upon the type of material, the size of the consignment and the way in which the material is packed, a unit to be sampled may be regarded as the transport container, e.g. 20 packs shrink-wrapped or boxed together, rather than an individual container. The required number of unit dosage forms is then withdrawn from any individual container in the selected transit container.

Sampling and testing may be adjusted according to experience with the specific source (e.g. manufacturer or supplier) of the product. If the consignment consists of one very large batch, or if little experience has been obtained with the product to be sampled, it may be prudent to carry out two independent analyses. Two independent final samples should then be taken from different sampling units. Conversely, when a consignment is composed of two or three batches from the same manufacturer, a single sample taken from each batch may suffice, provided that favourable documented experience has previously been gained with the product and the manufacturer, and that there is evidence from the expiry date, or other information, that the batches were produced at approximately the same time.

Note: When sampling finished products, packaging materials may be retained for testing.

4.4 Packaging materials (primary and secondary)

There is a potential for mixing up printed packaging materials during the sampling operations and, therefore, only one material should be handled at a time. Also, samples of packaging materials should never be returned to the consignment.

Adequate protection (e.g. collapsible metal tubes) and identification should be provided for the sample to avoid mixing or damage.

Primary packaging materials should be adequately protected during the sampling operation to avoid environmental contamination. The final use of the packaging should be taken into consideration and appropriate sampling protection afforded (e.g. in the sampling of parenteral ampoules). There are several reasons why a consignment of packaging materials may not necessarily be considered homogeneous; for example:

- Materials were manufactured on different days or machines.
- Materials were manufactured on one machine, but on different stations (e.g. 16 printing dye stations or 12 moulding stations).



- Packaging was manufactured with different source materials (e.g. polyethylene from two different sources).
- A change of quality occurred during the process (e.g. container-wall thickness, colour variation, text legibility or change of printing plate).

It is, therefore, important at least to take random samples (e.g. from across the consignment), and to consider focused sampling, taking into account some of the above points.

5. Sampling plans for starting materials, packaging materials and finished products

As stated in the introduction, these guidelines are intended primarily for drug regulatory authorities and procurement agencies. The following sampling plans are, therefore, not necessarily appropriate for manufacturers, although the guiding principles may be useful. The choice of the sampling plan should always take into consideration the specific objectives of the sampling and the risks and consequences associated with inherent decision errors. It should be noted that sampling plans are not recommended for sampling of starting materials for identification tests (see *Quality assurance of pharmaceuticals. A compendium of guidelines and related materials. Volume 2, Updated edition. Good manufacturing practices and inspection.* Geneva, World Health Organization, 2004; and *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-ninth report.* Geneva, World Health Organization, 2005 (WHO Technical Report Series, No. 929, Annex 2).

Ideally each sampling unit should be examined to ensure that it is intact and also checked for possible damage to the container. The contents should be inspected for uniformity and appropriately tested for identity. Uniformity should be tested on selected layer samples at different points in the material without previous intermixing. However, in cases when this ideal procedure is not possible or justified by the purpose of sampling, a number of sampling units should be randomly selected for sampling. It is not prudent to open all containers of products, which are liable to deteriorate under the influence of moisture or oxygen when held in a transit warehouse. However, materials in damaged containers or those found to be non-uniform should either be rejected or individually sampled for a complete quality control. Unlabelled sampling units should be rejected.

E





Table 1
Values of n , p or r for the N sampling units^a

Value of n , p or r	Values of N		
	n plan	p plan	r plan
2	up to 3	up to 25	up to 2
3	4–6	26–56	3–4
4	7–13	57–100	5–7
5	14–20	101–156	8–11
6	21–30	157–225	12–16
7	31–42		17–22
8	43–56		23–28
9	57–72		29–36
10	73–90		37–44

^a An example of how these plans work is given in Appendix 5.

For random sampling, whenever possible each sampling unit should be consecutively numbered and the required number of random sampling units selected using tables of random numbers.

The number of units to be sampled depends on different assumptions and three possible plans are shown in Table 1. For more comprehensive, statistically-based sampling schemes, see Bibliography.

It is important to recognize that the “ n -plan” is not statistically based and should be used only as a guiding principle.

5.1 Starting materials

When sampling starting materials proper consideration has to be given to deciding on a sampling plan. The following are examples of sampling plans that could be used.

5.1.1 The n plan

The “ n plan” should be used with great caution and only when the material to be sampled is considered uniform and is supplied from a recognized source. Samples can be withdrawn from any part of the container (usually from the top layer). The n plan is based on the formula $n = 1 + \sqrt{N}$, where N is the number of sampling units in the consignment. The value of n is obtained by simple rounding. A minimum number of containers needs to be sampled, e.g. if N is less than or equal to 4, then every container is sampled. According to this plan, original samples are taken from n sampling units selected at random and these are subsequently placed in separate sample containers. The control laboratory inspects the appearance of the material and tests the identity of each original sample according to the



relevant specification. If the results are concordant, the original samples are combined into a final, composite sample from which an analytical sample is prepared, the remainder being kept as a retention sample.

Note: The n plan is not recommended for use by control laboratories of manufacturers who are required to analyse and release or reject each received consignment of the starting materials used to produce a drug product.

5.1.2 **The p plan**

The “ p plan” may be used when the material is uniform, is received from a recognized source and the main purpose is to test for identity. The p plan is based on the formula $p = 0.4 \sqrt{N}$, where N is the number of sampling units. The figures for p are obtained by rounding up to the next highest integer. According to this plan, samples are taken from each of the N sampling units of the consignment and placed in separate sample containers. These original samples are transferred to the control laboratory, visually inspected and tested for identity (a simplified method may be used). If the results are concordant, p final samples are formed by appropriate pooling of the original samples.

5.1.3 **The r plan**

The “ r plan” may be used when the material is suspected to be non-uniform and/or is received from a source that is not well known. The r plan may also be used for herbal medicinal products used as starting materials. This plan is based on the formula $r = 1.5\sqrt{N}$, where N is the number of sampling units. The figures for r are obtained by rounding up to the next highest integer.

Samples are taken from each of the N sampling units of the consignment and placed in separate sample containers. These original samples are transferred to the control laboratory and tested for identity. If the results are concordant, r samples are randomly selected and individually subjected to testing. If these results are concordant, the r samples are combined for the retention sample.

5.2 **Packaging materials**

Sampling plans for packaging materials should be based on defined sampling standards, for example, British Standard BS 6001-1, ISO 2859 or ANSI/ASQCZ1.4-1993.

The objective is to ensure that there is a low probability of accepting material that does not comply with the predefined acceptance level.



5.3 Finished products

As for packaging materials, sampling plans for finished products should be based on defined sampling standards such as BS 6001-1, ISO 2859 or ANSI/ASQCZ 1.4-1993.

In some cases it may be sufficient to limit examination of finished goods to visual inspection only. If physical and chemical testing is required, however, the sampling units should consist of whole packs. Individual packs should not be broken open for the purposes of sampling.

An example of the steps to be considered when sampling finished products is given in Appendix 3, based on the sampling plans given in ISO 2859-1.

Bibliography

Good practices for national pharmaceutical control laboratories. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-sixth report.* Geneva, World Health Organization, 2002 (WHO Technical Report Series, No. 902), Annex 3.

Guidelines on packaging for pharmaceutical products. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-sixth report.* Geneva, World Health Organization, 2002 (WHO Technical Report Series, No. 902), Annex 9.

Koratochvil B, Taylor JK. Sampling for chemical analysis. *Analytical Chemistry*, 1981, 53:925A.

Oakland JS. Management tools in the manufacture of chemicals: statistical quality control. *Chemistry and Industry*, 1981, 16:562–567.

Gy P. *Sampling of particulate materials — theory and practice*, 2nd edition. New York, Elsevier, 1979.

Sommer K. *Sampling of powders and bulk materials*. Heidelberg, Springer-Verlag, 1986.

Acceptance sampling plans and procedures for the inspection of bulk materials. Geneva, International Organization for Standardization, 2000. ISO 10725.

Sampling procedures for inspection by attributes. Procedures for assessment of stated quality levels. British Standard BS 6001-5:2000. Geneva, International Organization for Standardization, 1999. ISO 2859-4.

Sampling procedures for inspection by variables. Specification for single sampling plans indexed by acceptable quality level (AQL) for lot-by-lot inspection. British Standard BS 6002-1. Geneva, International Organization for Standardization, 1993. ISO 3951:1989.

Sampling procedures for inspection by attributes. Sampling schemes indexed by acceptance quality limit for lot-by-lot inspection. British Standard BS 6001-1. Geneva, International Organization for Standardization, 1999. ISO 2859-1.



American National Standards Institute/American Society for Quality. *Sampling procedures and tables for inspection by attributes*. Washington, DC, American Society for Quality, 1993. ANSI/ASQCZ1.4-1993.

Methods for sampling chemical products. Introduction and general principles. British Standard BS 5309-1. London, British Standards Publishing, 1976.

Methods for sampling chemical products. Sampling of liquids. British Standard BS 5309-3. London, British Standards Publishing, 1976.

Methods for sampling chemical products. Sampling of solids. British Standard BS 5309-4. London, British Standards Publishing, 1976.



Appendix 1

Types of sampling tools

Scoops

Small containers of solid materials may be adequately sampled using a spatula or scoop. The samples are then blended to provide a representative sample of that container. Figure 1 shows the recommended designs of scoops, which should preferably be rounded.

Figure 1
Sampling scoops for solids





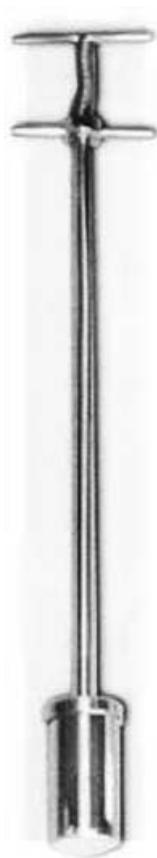
If the scoop used is too small for the sizes of particle being sampled, large particles will roll off and testing bias may be introduced. On the other hand, if the scoop is too big, an unnecessarily large sample will be obtained for a given number of increments.

A scoopful of sample should be taken in a single movement and transferred to the sample container. Avoid tapping the scoop to remove pharmaceutical product as this is likely to cause segregation of the sample.

Dip tubes

Dip tubes should be used for sampling liquid and topical products and should be made of an inert material, such as polypropylene or stainless steel. A typical dip tube is shown in Figure 2.

Figure 2
Typical dip tube





Weighted containers

For taking samples from large tanks and storage vessels, a container in a weighted carrier can be used. The container is designed such that it can be opened at the required depth. Marks on the cord used for lowering the container can be used to determine when the correct sampling depth has been reached. A typical weighted container is shown in Figure 3.

Thieves

Sample thieves should be used when taking samples from deep containers of solids. Typical thieves are shown in Figure 4.

The plug thief typically consists of a hollow tube with an inner rod that has a tip on the end to allow the thief to enter the powder bed in the closed position (see Figure 4.i). The geometry of this tip can

Figure 3
Typical weighted container

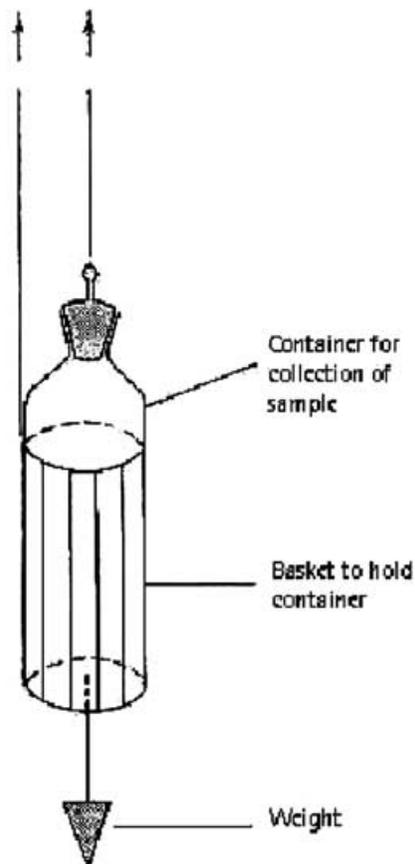
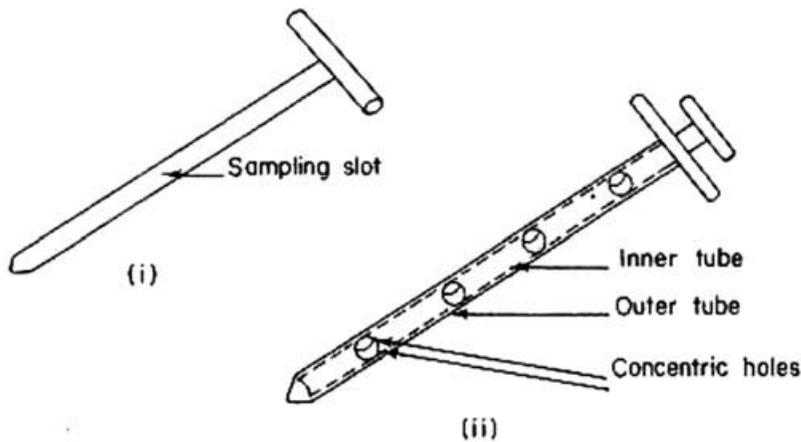




Figure 4
Typical sample thieves



influence the sample taken; pointed tips distort the powder bed less than blunt-tipped probes, thereby reducing sampling error. Some thieves have a locking device that allows the sample volume to be set to the required sample weight, thereby reducing the weight variation in the sample population.

A chamber thief generally consists of two concentric tubes (see Figure 4.ii); the inner tube is solid except for the chambers in which the sample is collected. The outer tube is hollow with openings that can be aligned with the chambers in the inner tube. A well-designed thief will have a sharp end to minimize disruption to the powder bed.

When it is inserted into a static powder blend a thief will distort the bed by carrying pharmaceutical product from the upper layers of the blend to the lower layers. The magnitude of this distortion can depend on whether the thief is inserted into the blend with a smooth, jerky or twisting action. Therefore, the correct sampling procedure should be defined and staff trained in using the appropriate technique. Thieves are also sometimes referred to as “double-tube spears”.

The angle at which the thief enters the powder bed can also influence sampling error. If a thief is inserted into the powder bed vertically, it can extract samples of different particle size from those that would be obtained using the same thief inserted at an acute angle. In addition the orientation of a chamber thief in relation to the powder bed (i.e. whether the chamber is at the top, the bottom or in the middle of the thief) may also influence the sampling error.

E





The material from which the thief is constructed, e.g. stainless steel or polypropylene, may also have an effect on sampling error due to static effects.

Sampling error can also be affected by bed depth, as the static pressure of the bulk blend forces the material into the sample chamber(s). This pressure is far greater at the bottom of a large container than it is in the middle or at the top. It is quite possible that the same thief could extract samples of different particle size from the top or bottom of a static powder blend.

Simple bag-sampling spears

Simple bag-sampling spears are the most commonly used instruments for taking samples from bags, because they are relatively cheap, simple and quick. Sampling spears generally have a maximum external diameter of about 12 mm, but can be up to 25 mm in diameter. To obtain a good cross-sectional sample, the spear should be 40–45 cm in length. The tapered type of sampling spear penetrates bags easily. Typical spears are shown in Figure 5.

Figure 5

Typical sampling spears

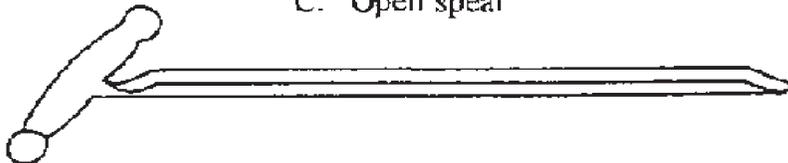
A: Closed spear for sampling large grains such as maize



B: Closed spear for sampling small grains such as wheat



C: Open spear



D: Double-tube spear





Appendix 2 Sample collection form^a

Serial number: _____

Name of location/place where sample was taken:

.....

Address (with telephone and fax number, if applicable):

.....

Date of sampling:

Names of people who took samples:

1.
2.

Product name of the sample:

Name of (active) starting material (INN, generic or scientific name)

with dosage strength:

Dosage form (tablet, capsule, etc.):

Batch/lot number:

Date of manufacture:..... Expiry date:

Registration or licence number (if applicable):

Name of the manufacturer:

Number of sample unit taken (tablet, capsule, etc.: at least 20 but not more than 30 units):

.....

^a This sample collection form should always be kept with the sample collected. Proper sampling procedures should be followed.





Brief physical/visual description of sample:

.....
.....
.....
.....
.....

Signature of person(s) taking samples

Signature of representative of the establishment where sample(s) was taken (optional)

- 1.
- 2.

.....



Appendix 3

Steps to be considered for inclusion in a standard operating procedure

The steps for inclusion in a standard operating procedure described below are derived on a purely theoretical basis and are presented for information purposes only.

Bulk liquid products

The steps to be considered when sampling bulk liquid products are as follows.

1. Read and understand the precautions to be observed for the safe handling of the material.
2. Gather together the required sampling equipment (sampling tube or weighted sampling can, sample bottles and labels) and check that all the required items are clean.
3. Locate the batch.
4. Examine the container(s) for signs of contamination of the batch. Record any faults.
5. Examine the labels for obvious differences and signs of changes including obliterations and mislabelling. Record any faults.
6. Investigate and clarify the sources of and reasons for any faults before proceeding.
7. Choose a liquid-sampling tube of size and orifice suitable for the viscosity of the liquid being sampled.
8. Sample the liquid, suspension or emulsion (well stirred, if appropriate) by slowly pushing the open sampling tube vertically downwards through the liquid so that material is collected from each layer.
9. Seal the tube, withdraw it from the bulk liquid, and allow liquid adhering to the outside of the tube to drain. Transfer all the contents of the tube to a clean, labelled sample bottle.
10. Repeat steps 8 and 9 until sufficient samples for analytical and retention purposes have been obtained.
11. Seal the sample bottle.
12. Reseal the container from which the samples were taken and label as “sampled”.
13. Clean and dry the sampling tube, observing the relevant safety precautions.
14. Sample other required containers in the same manner following steps 8–12 above.



15. Clean the sampling tube using the recommended cleaning procedure.
16. Deliver the analytical samples to the laboratory and the reserve samples to the retention sample store. Report any aspects of the sampling that should be brought to the attention of the analyst or the inspector.
17. Check supplier certificate versus the specifications, if applicable.

Powdered starting material

The steps to be considered in sampling a powdered starting material are as follows.

1. Read and understand the precautions to be observed for the safe handling of the material.
2. Gather together the required sampling equipment (sampling spear, sample bottles and labels) and check that all items are clean.
3. Locate the consignment and count the number of containers. Record this number.
4. Examine all the containers for obvious differences and signs of damage. Record any faults.
5. Examine all the labels for obvious differences and signs of changes, including obliterations and mislabelling. Record any faults.
6. Segregate any damaged containers and those with suspected spoiled contents for separate examination. These should then be *referred* or *rejected* and dealt with accordingly.
7. Segregate any containers with different batch numbers and treat these separately.
8. Number the remaining containers.
9. Choose the appropriate sampling plan (n , p or r).
10. Choose the containers to be sampled in accordance with the requirements of the chosen plan (by the use of random number tables, by drawing lots or by the use of a random number generator if applicable).
11. Open the containers one at a time and inspect the contents. Record any differences.
12. Choose a suitable, clean sampling spear and plunge this (gates closed) into the powder so that the point of the spear reaches the bottom of the container.
13. Open the gates to allow the powder to enter the spear cavities, then reclose them.
14. Withdraw the spear from the container and transfer the spear contents to a labelled sample bottle.



15. Repeat steps 12–14 until sufficient material has been collected for analytical and retention requirements.
16. Seal the sample bottle.
17. Reseal the container from which the samples were withdrawn and label as “sampled”.
18. Wipe clean the sampling spear if required, observing the safety precautions, before sampling the other chosen containers.
19. Repeat steps 12–18 for each chosen container.
20. Clean the sampling spear using the recommended cleaning procedure.
21. Deliver the analytical samples to the laboratory and the reserve samples to the retention sample store. Report any aspects of the sampling that should be brought to the attention of the analyst or inspector.
22. Check the supplier certificate versus the specifications, if applicable.

Packaging materials

The steps to be considered in sampling packaging materials are as follows.

1. Check the consignment against any associated documentation.
2. Check transit containers for the following and report any deviations as necessary:
 - 2.1 correct identification;
 - 2.2 integrity of seal, if appropriate; and
 - 2.3 absence of physical damage.
3. Obtain the required sample from the required number of containers, bearing in mind the special considerations for sampling packaging materials noted in section 4.4 of this Annex.
4. Place the sample units into identified appropriate sample containers.
5. Identify the consignment containers that have been sampled.
6. Note any special situations found during the sampling process (e.g. rogue items or component damage). Report any such observations as necessary.
7. Remove all sampled material pallets or containers from the sampling area together with all documentation.
8. Check supplier certificate against the specifications, if applicable.

Finished products

The following steps should be considered when sampling finished products.

E





1. Determine the number of pallets per batch in the consignment.
2. Work out as per ISO 2859–1 table level II, the number of pallets to be checked visually.
 - 2.1 Check condition of pallet and packaging for integrity of outer packaging material.
 - 2.2 Check outside of goods on the pallets for general cleanliness.
 - 2.3 Check that the overall labelling of the pallets matches the packing list.
 - 2.4 Count, categorize and record the number of defects.
3. Count the total number of transport packs on the number of pallets present and verify the total against the packing list.
4. From the number of pallets work out the number of transport packs to be sampled using the ISO table.
 - 4.1 Check condition of boxes for integrity of packaging material.
 - 4.2 Check for cleanliness of boxes.
 - 4.3 Check the labelling of the boxes for damage.
 - 4.4 Check the boxes for overall damage.
 - 4.5 Check the labels for spelling mistakes.
 - 4.6 Check the labels for manufacturing and expiry dates.
 - 4.7 Count, categorize and record the number of defects.
5. From the number of boxes selected work out the number of unit packs to be examined visually using the ISO table.
 - 5.1 Check condition of the containers for integrity of packaging material.
 - 5.2 Check for cleanliness of containers.
 - 5.3 Check condition of containers for shape and colour.
 - 5.4 Check the labelling of containers for damage.
 - 5.5 Check the containers for overall damage.
 - 5.6 Check the labels for spelling mistakes.
 - 5.7 Check the labels for manufacturing and expiry dates.
 - 5.8 Count, categorize and record the number of defects.
6. From the number of containers selected, determine the number of containers to be taken for physical and chemical testing and for retention.
7. Check the supplier certificate against the specifications, if applicable.



Appendix 4

Examples of types of containers used to store samples of starting materials and bulk products

Figure 1
Bag for storage of samples

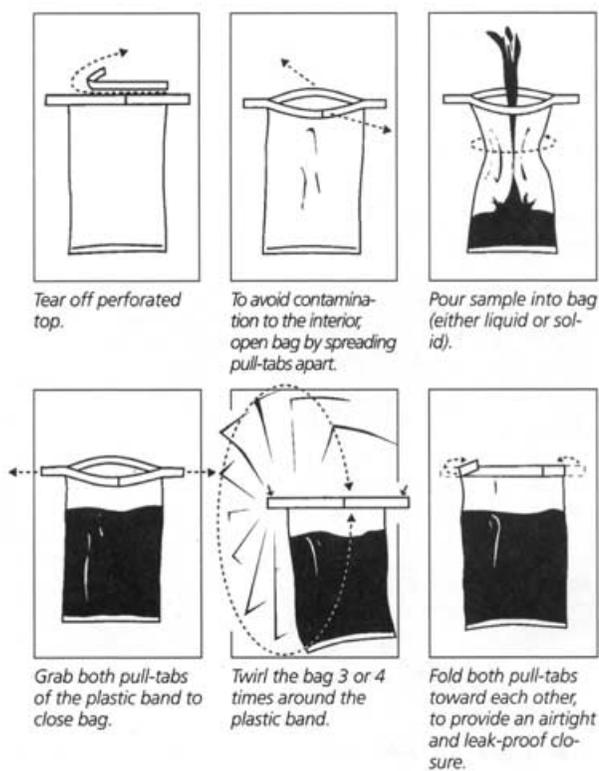
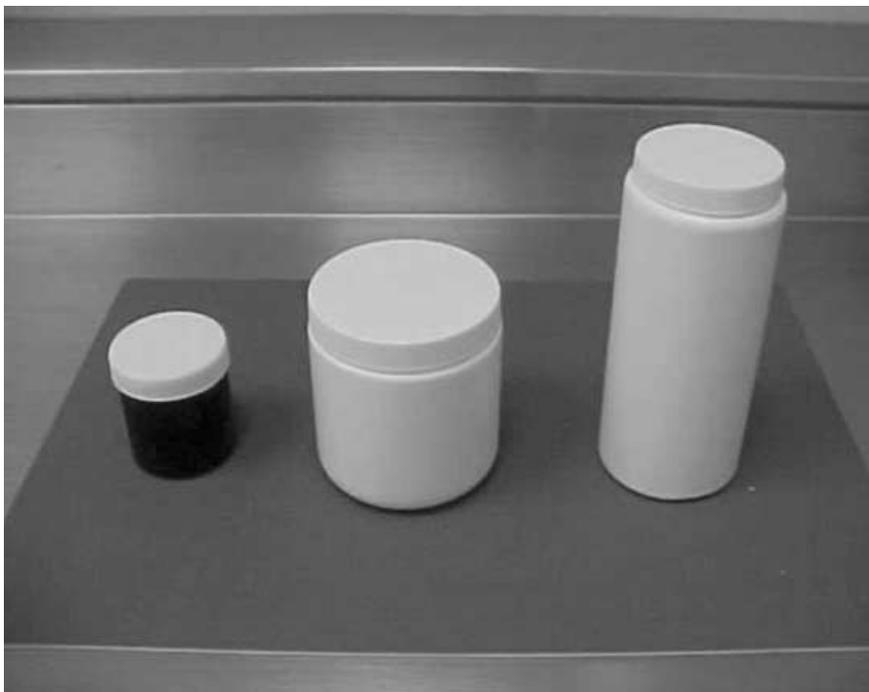




Figure 2
Screw-top containers





Appendix 5

Examples of use of sampling plans n , p and r

Consider a consignment of 40 containers of a starting material.

n Plan

Assuming a uniform material from a recognized source where there is a high degree of confidence in the source

Using the n plan, samples would be taken from seven containers selected at random. The appearance and identity of each of these seven samples is checked. If the results are concordant, the seven samples are combined to produce a single, composite sample from which an analytical sample is prepared for full testing.

p Plan

Assuming a uniform material from a recognized source with the main purpose of checking the identity

Using the p plan, samples would be taken from each container. The appearance and identity of each of these samples is checked. If the results are concordant, the samples are appropriately combined to form three final, composite samples to be used for retention (or full testing if required).

r Plan

Assuming the material is non-uniform and/or from a source that is not well-known

Using the r plan, samples would be taken from each container. The appearance and identity of each of these samples is checked. If the results are concordant, 10 samples are selected at random and individually subjected to full testing.



Annex 5

Guidelines for registration of fixed-dose combination medicinal products

Abbreviations	95
Introduction	95
1. Scope	96
2. General considerations	97
3. Definitions	106
4. Scenarios	109
5. Balancing the advantages and disadvantages of a new fixed-dose combination	110
6. Data requirements for marketing authorization of fixed-dose combination finished pharmaceutical products	113
7. Product information or summary of product characteristics for fixed-dose combination finished pharmaceutical products	131
8. Postmarketing studies and variations	132
References	133
Appendix 1 Guidelines for co-packaged fixed-dose combinations	134
Appendix 2 Principles for determining whether data from the scientific literature are acceptable	135
Appendix 3 Pharmaceutical development (or preformulation) studies	138
Appendix 4 Superiority, equivalence and non-inferiority clinical trials	141





Abbreviations

AIHW	Australian Institute of Health and Welfare
API	active pharmaceutical ingredient
BCS	Biopharmaceutics Classification Scheme
BCS #1	Biopharmaceutics class number 1 (the most favourable)
CHMP	Committee for Medicinal Products for Human Use; <i>see also</i> CPMP
CPMP	Committee for Medicinal Products for Human Use (CHMP), formerly the Committee for Proprietary Medicinal Products
CPP	certificate of pharmaceutical product
EMA	European Medicines Agency, formerly the European Medicines Evaluation Agency
EU	European Union
FDA	Food and Drug Administration of the USA
FDC	fixed-dose combination (<i>see</i> Glossary)
FDC-FPP	fixed-dose combination finished pharmaceutical product (<i>see</i> Glossary)
FPP	finished pharmaceutical product
GCP	good clinical practice
GLP	good laboratory practice
GMP	good manufacturing practice
GTDP	good trade and distribution practice
GSP	good storage practice
ICH	International Conference on Harmonisation
IUTLD	International Union of Tuberculosis and Lung Disease
MIC	minimum inhibitory concentration
PP	per-protocol (a form of clinical trial design and analysis)
SPC	summary of product characteristics (<i>see</i> Glossary)
TGA	Therapeutic Goods Administration
WHO	World Health Organization

Introduction

The development of fixed-dose combinations (FDCs) is becoming increasingly important from a public health perspective. They are being used in the treatment of a wide range of conditions and are particularly useful in the management of human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS), malaria and tuberculosis, which are considered to be the foremost infectious disease threats in the world today.

FDCs have advantages when there is an identifiable patient population for whom treatment with a particular combination of actives in a fixed ratio of doses has been shown to be safe and effective, and when

E



all of the actives contribute to the overall therapeutic effect. In addition there can be real clinical benefits in the form of increased efficacy and/or a reduced incidence of adverse effects, but such claims should be supported by evidence.

Additionally, in a situation of limited resources, the cost of an FDC finished pharmaceutical product (FDC-FPP) may be less than that of separate products given concurrently, and there are simpler logistics of distribution. Improved patient adherence and reduced development of resistance in the case of antimicrobials can be difficult to prove, but may be additional benefits.

Notwithstanding these potential benefits, FDCs must be shown to be safe and effective for the claimed indications. It should not be assumed that benefits outweigh risks. As for any new medicine, the risks and benefits should be defined and compared.

The World Health Organization has published a series of guidelines relating to marketing authorization of finished pharmaceutical products (FPPs) (see Table 1). Currently there are no specific international guidelines for FDCs. Some national authorities have developed their own guidelines, some for specific classes of medicines (see Table 2). These guidelines are intended to provide advice to those countries that do not, as yet, have guidelines for this type of product. They will also provide guidance to industry when developing new products and when considering the regulatory requirements that will need to be met.

In drafting these guidelines, existing international publications have been taken into account and in some cases text has been copied directly. The various scenarios considered below are essentially the same as those in the draft *Scientific and technical principles for fixed dose combination drug products* that followed a meeting of interested parties held in Botswana in April 2004.

1. Scope

1.1 The scope of these guidelines is restricted to medicines that in most jurisdictions would be available only on prescription.

Although similar principles would apply to the registration of non-prescription products, the risk–benefit considerations (and consequently data requirements) may be different.

1.2 The principles in these guidelines would also apply to chemical combinations and complexes that comprise more than one active.



- 1.3 Registration of co-packaged medicines is not the primary purpose of these guidelines. However, many of the same considerations apply in balancing the advantages and disadvantages of co-packaged medicines, although the quality issues are different (see Appendix 1).

2. General considerations

2.1 These are not intended to be stand-alone guidelines.

2.1.1 Many general guidelines are also applicable to FDCs. Table 1 lists some relevant WHO publications.

2.1.2 Other international guidelines that pertain to FDCs in particular are summarized in Table 2, together with brief notes as to their content. Some of these relate to particular therapeutic groups such as antihypertensives, or particular topics such as bioavailability.

2.1.3 Table 3 lists other guidelines that were consulted in preparing this text.

2.1.4 A number of International Conference on Harmonisation (ICH) guidelines are referred to in this text when, as at the date of writing, there was no applicable WHO guideline (see Tables 4 and 5).

2.1.5 When a guideline is cited in the text or tables below, the most recent edition should normally be substituted.

2.1.6 If an applicant makes reference to guidelines not cited here, this may be acceptable depending on the case in point and provided that the applicant justifies the alternative reference.

2.1.7 Appendices 2, 3 and 4 provide guidance on subjects that are not exclusive to FDCs, but are nevertheless important in this context, and for which suitable guidance is not otherwise readily available.

2.1.8 The guidelines in Tables 1–5 may not be a comprehensive list of all relevant guidelines.

2.2 It is important that access to useful, new FDCs should not be delayed by unnecessary constraints. These guidelines are not intended to define the only means of demonstrating the advantages and disadvantages of a new FDC. In some cases an alternative approach may be appropriate, for example when:

E



Table 1

WHO guidelines relevant to marketing authorization

Title	Date
<i>Marketing authorization of pharmaceutical products with special reference to multisource (generic) products: a manual for a drug regulatory authority.</i> A general text with relevant annexes (see below). Also known as “the Blue book”. ^a	1999
<i>National drug regulatory legislation: guiding principles for small drug regulatory authorities.</i> Blue book, Annex 1.	1999
<i>WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-fourth report</i> (WHO Technical Report Series, No. 863), Annex 10: Guidelines for Implementation of the WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce and Guidelines for implementation of the WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce. Blue book, Annex 2.	1996 1999
<i>WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-fourth report</i> (WHO Technical Report Series, No. 863), Annex 9: Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability and Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. Blue book, Annex 3. ^a	1996 1999
<i>Model guidelines on conflict of interest and model proforma for a signed statement on conflict of interest.</i> Blue book, Annex 4.	1999
<i>Model contract between a regulatory authority and an external evaluator of chemistry, pharmaceutical and bioavailability data.</i> Blue book, Annex 5.	1999
<i>Model application form for new marketing authorizations, periodic reviews and variations, with notes to the applicant.</i> Blue book, Annex 6.	1999
<i>Detailed advice on evaluation of data by the drug regulatory authority.</i> Blue book, Annex 7.	1999
<i>Ethical criteria for medicinal drug promotion.</i> Blue book, Annex 8.	1999
<i>Model marketing authorization letter.</i> Blue Book, Annex 9.	1999
<i>Model list of variations (changes) to pharmaceutical aspects of registered products which may be made without prior approval.</i> Blue book, Annex 10.	1999
<i>WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-fourth report.</i> (WHO Technical Report Series, No. 863), Annex 5: Guidelines for stability testing of pharmaceutical products containing well established drug substances in conventional dosage forms and	1996



Table 1 (continued)

Title	Date
<i>WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-seventh report</i> (WHO Technical Report Series, No. 908) and Guidelines for stability testing of pharmaceutical products containing well established drug substances in conventional dosage forms. Blue book, Annex 11. ^a	2003 1999 (and 2001 rev)
<i>WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-seventh report</i> (WHO Technical Report Series, No. 908), Annex 4: Good manufacturing practices for pharmaceutical products and inspection: main principles and <i>WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-ninth report</i> (WHO Technical Report Series, No. 929, Annex 2) and Quality assurance of pharmaceuticals. A compendium of guidelines and related materials, Volume 2, updated edition.	2003 2005 2004
<i>WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-eighth report</i> (WHO Technical Report Series, No. 917), Annex 2: Good trade and distribution practices for pharmaceutical starting materials.	2004
<i>WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-eighth report</i> (WHO Technical Report Series, No. 917), Annex 3: WHO pharmaceutical starting materials certification scheme (SMACS): Guidelines on implementation.	2004
<i>WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-seventh report</i> (WHO Technical Report Series, No. 908), Annex 9: Guide to good storage practices for pharmaceuticals	2003
<i>The importance of pharmacovigilance: safety monitoring of medicinal products^a</i>	2002
<i>WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-sixth report</i> (WHO Technical Report Series, No. 902), Annex 11: Guidance on the selection of comparator pharmaceutical products for equivalence assessment of interchangeable multisource (generic) products (under revision).	2002
<i>WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-sixth report</i> (WHO Technical Report Series, No. 902), Annex 3: Good practices for national pharmaceutical control laboratories.	2002
<i>Handbook: good laboratory practice: quality practices for regulated non-clinical research and development</i> (WHO document TDR/PRD/GLP/01.2,WHO-TDR) in collaboration with the United Nations and World Bank.	2001
<i>Establishing the bioequivalence of rifampicin in fixed-dose formulations containing isoniazid with or without pyrazinamide and/or ethambutol compared to the single drug reference preparations administered in loose combination: model protocol.</i>	1999



Table 1 (continued)

Title	Date
Quality assurance: protocol for assessing the rifampicin bioavailability of combined formulations in healthy volunteers: WHO/IUTLD joint statement. <i>International Journal of Tuberculosis and Lung Disease</i> , 3, S284–S285.	1999
Guidelines for good clinical practice (GCP) for trials on pharmaceutical products. In: <i>The use of essential drugs</i> . WHO Technical Report Series, No. 850.	1995

^a These publications are being further updated.

Table 2

International guidelines that relate directly to fixed-dose combination finished pharmaceutical products

Title, publisher and date	Notes
<i>Fixed dose combination and co-packaged drug products for treatment of HIV</i> . Washington, DC, Food and Drug Administration, May 2004, DRAFT	21 pages
<i>Scientific and technical principles for fixed dose combination drug products</i> . Botswana, 22 April 2004, DRAFT	21 pages
<i>Part 7. Report on bioavailability of oral dosage formulations of drugs used for systemic effects. Report C. Report on bioavailability of oral dosage formulations, not in modified release form, of drugs used for systemic effects, having complicated or variable pharmacokinetics</i> . Canada, Health Protection Branch, December 1992.	Approximately 400 words. Discusses the reporting, statistical analysis and decision criteria for bioequivalence studies on combination drug products. A notice to industry in June 2004 confirmed the decision criteria.
<i>Fixed-combination prescription drugs for humans FDA, 2003</i> 21CFR300.50	Approximately 250 words. In terms of safety and efficacy, describes the circumstances in which actives may be combined in an FDC.
<i>Estrogen estrogen/progestin drug products to treat vasomotor symptoms and vulvar vaginal atrophy symptoms recommendations for clinical evaluation</i> . FDA, Jan 2003 DRAFT	Ten pages. This guideline is not restricted to estrogens from a biological source. Approval will be based on two criteria: <ul style="list-style-type: none"> • that each component contributes to safety and efficacy as defined in 21CFR300.50 and • the FDC contains the lowest effective dose of each of the actives for their respective labelled indication.
Conjugated estrogens, USP-LC-MS method for both qualitative chemical characterization	Seven pages. This guideline relates only to conjugated estrogens from a



Table 2 (continued)

Title, publisher and date	Notes
<p>and documentation of qualitative pharmaceutical equivalence. FDA June 2000 DRAFT</p>	<p>biological source, normally urine from gestating mares, which contains multiple estrogens. There have been difficulties in preparing generic equivalents of this type of product. The guideline specifies how chemical equivalence can be demonstrated.</p>
<p><i>Fixed-combination medicinal products.</i> CPMP Apr 1996 — CPMP/EWP/240/95, III/5773/94 (formerly known as <i>Testing and licensing criteria for fixed combination medicinal products</i>)</p>	<p>Four pages that:</p> <ul style="list-style-type: none"> • require justification of the particular combination; • give examples of circumstances (safety and efficacy) in which FDCs may be acceptable; • describe principles that define acceptable indications; • require consideration of possible pharmacokinetic and pharmacodynamic interactions; • require evidence as to safety and efficacy (allowing bibliographical data as supportive evidence in certain circumstances); and • require evidence as to safety and efficacy of the doses selected. <p>“This guideline is also applicable to a new chemical substance which dissociates in vivo into two well known active substances.”</p> <p>“Substances having a critical dosage range or a narrow therapeutic index are unlikely to be suitable for inclusion in fixed combinations.”</p>
<p><i>Part 7. Fixed combinations in Note for guidance on clinical investigation of medicinal products in the treatment of hypertension.</i> CPMP Nov 1997 — CPMP/EWP/238/96 Rev1</p>	<p>Three pages that:</p> <ul style="list-style-type: none"> • describe the circumstances (in terms of safety and efficacy) in which FDCs may be acceptable in the therapy of hypertension; and • provide advice on their clinical development as first- or second-line therapy.
<p>IV.3. The ratio and/or fixed content of one component of a combination drug product. In: <i>Points to consider on pharmacokinetics and pharmacodynamics in the development of antibacterial medicinal products.</i> CPMP Jul 2000 — CPMP/EWP/2655/99</p>	<p>Seven pages. This guideline discusses the relationship between plasma concentration/time profiles and clinical efficacy. Selection of a suitable ratio of doses for FDCs is discussed in Part IV.3 (approx. 100 words).</p>



Table 2 (continued)

Title, publisher and date	Notes
5.1.5 Fixed combination products. In <i>Note for guidance on the investigation of bioavailability bioequivalence</i> CPMP July 2001 — CPMP/EWP/QWP/1401/98	Approximately 50 words. States that FDCs should in general be assessed as to the bioavailability and bioequivalence of the individual actives administered either as single entity products given concurrently (in the case of a new combination) or as an existing combination. Studies should be designed to detect any pharmacokinetic drug–drug interaction.
<i>Part 6. Fixed combination products in ICH principles document for clinical evaluation of new antihypertensive drugs.</i> ICH/CPMP/541/00, DRAFT Also issued by CPMP as CPMP/ICH/541/00, DRAFT	Approximately 250 words. Describes two experimental designs for safety and efficacy studies on FDCs of antihypertensives, namely: <ul style="list-style-type: none"> • factorial studies; and • studies in patients who have failed to respond adequately to each of the drugs given alone.
5.2.1 <i>Fixed-combination products in Australian Guidelines for the Registration of Drugs</i> , Volume 1. Australia, TGA, July 1994.	Approximately 250 words. Discusses justification of the combination in terms of either pharmacodynamics or demonstrated therapeutic effect.

- 2.2.1 Scientific developments allow alternative means of achieving the same goals.
- 2.2.2 A circumstance unique to the product in question can be demonstrated.
- 2.2.3 An original but acceptable approach is devised.
- 2.2.4 Sufficient alternative studies have been conducted which, although not exactly what the guidelines seek, nevertheless satisfy the criteria of quality, safety and efficacy.

When these guidelines (or others referred to herein) describe evidence that is required, applicants may either: provide the requested evidence, or provide an alternative form of evidence that addresses the same issues. In this case, the application should include an explanation and justification of the approach taken.

2.3 It is not always necessary to generate new (original) data. Evidence may be obtained from the scientific literature, subject to its being of adequate quality (see Appendix 2 entitled *Principles for determining whether data from the scientific literature are acceptable*).



Table 3

Other guidelines consulted in preparing these guidelines

Title	Publisher	Date
<i>Consort E-checklist</i> . Available at: www.consort-statement.org		2004
<i>The Cochrane Collaboration</i> . Available at: http://www.cochrane.org/index0.htm		2004
<i>Literature-based submissions: points to consider</i> . Available at: http://www.tga.gov.au/docs/html/litbsubs.htm	TGA, Australia	2003
<i>Bioanalytical method validation</i> . Available at: http://www.fda.gov/cder/guidance/index.htm .	FDA	2001
<i>Waiver of in vivo bioavailability and bioequivalence studies for immediate-release solid oral dosage forms based on a biopharmaceutics classification system</i> . Washington, DC, US Food and Drug Administration. Available at: http://www.fda.gov/cder/guidance/index.htm	FDA	2000
<i>Specifications: test procedures and acceptance criteria for new drug substances and new drug products: Chemical substances</i> . Available at: http://www.ich.org/UrlGrpServer.jserv?@_ID=276&@_TEMPLATE=254	ICH	1999
<i>Points to consider on switching between superiority and non-inferiority</i> . CPMP/EWP/482/99	CPMP	1999
<i>Points to consider on the choice of non-inferiority margins</i> . EMEA, CPMP/EWP/2158/99, DRAFT	CPMP	1999
<i>Statistical principles for clinical trials</i> . EMEA, CPMP/ICH/363/99, DRAFT	CPMP	1998
<i>Development pharmaceuticals and process validation</i> , Eudralex 3AQ1a, http://pharmacos.eudra.org/	CPMP	1988
<i>Impurities in new drug products (revised)</i> . Q3B(R)	ICH	2003

An application for a marketing authorization may comprise:

- 2.3.1 Entirely original data.
- 2.3.2 Entirely data from the literature.
- 2.3.3 Both original data and data from the literature (a “hybrid” submission).

For FDC-FPPs, it is likely that hybrid submissions will be the most common type.

The scientific literature rarely contains enough adequately validated information on quality to allow the full quality data set to be based solely on data from the literature. In particular, the complete formulation and method of manufacture are rarely

E





Table 4

Preclinical guidelines from the International Conference on Harmonisation that may be a source of guidance

Available at: www.ich.org (last accessed 03/09/04)

Carcinogenicity studies

- S1A Guideline on the need for carcinogenicity studies of pharmaceuticals
- S1B Testing for carcinogenicity of pharmaceuticals
- S1C Dose selection for carcinogenicity studies of pharmaceuticals
- S1C(R) Addendum to S1C: addition of a limit dose and related notes

Genotoxicity studies

- S2A Guidance on specific aspects of regulatory tests for pharmaceuticals
- S2B A standard battery for genotoxicity testing for pharmaceuticals

Toxicokinetics and pharmacokinetics

- S3A Note for guidance on toxicokinetics: the assessment of systemic exposure in toxicity studies
- S3B Pharmacokinetics: guidance for repeated dose tissue distribution studies

Toxicity testing

- S4 **Single dose toxicity tests**
Agreement was reached, at the time of ICH 1, in 1991, that the determination of the median lethal dose (LD₅₀) should be abandoned for pharmaceuticals. The recommendation was published in the *Proceedings of the First International Conference on Harmonisation*, p. 184.
- S4A Duration of chronic toxicity testing in animals (rodent and non-rodent)

Reproductive toxicology

- S5A Detection of toxicity to reproduction for medicinal products
- S5B(M) An addendum on toxicity to male fertility (amended guideline)

Pharmacology studies

- S7A Safety pharmacology studies for human pharmaceuticals
- S7B Safety pharmacology studies for assessing the potential for delayed ventricular repolarization (QT interval prolongation) by human pharmaceuticals

Joint safety/efficacy (multidisciplinary) topic

- M3(M) Maintenance of the ICH guideline on non-clinical safety studies for the conduct of human clinical trials for pharmaceuticals
-

specified. Consequently the quality data set is almost always either totally original or hybrid.

2.4 When these guidelines request that an applicant explain and/or justify non-conformity with requirements, a suitable argument should be included in the section that discusses the advantages and disadvantages of the combination (see below), together with cross-references to data elsewhere in the submission.

2.5 When an applicant is unsure of registration requirements or wishes to deviate from these guidelines, prior consultation with the relevant regulatory authority may be advantageous. How-



Table 5

Clinical guidelines from the International Conference on Harmonisation that may be a source of guidance

Available at: www.ich.org (last accessed: 03/09/04)

Clinical safety

- E1* The extent of population exposure to assess clinical safety for drugs intended for long-term treatment of non-life-threatening conditions
- E2A* Clinical safety data management: definitions and standards for expedited reporting
- E2B/ M2* Maintenance of the clinical safety data management including the maintenance of the electronic transmission of individual case safety reports message specification
- E2C* Clinical safety data management: periodic safety update reports for marketed drugs
- E2CA* Addendum to E2C: periodic safety update reports for marketed drugs
- E2D* Post-approval safety data management: definitions and standards for expedited reporting
- E2E* Pharmacovigilance planning

Clinical study reports

- E3* Structure and content of clinical study reports

Dose–response studies

- E4* Dose–response information to support drug registration

Ethnic factors

- E5* Ethnic factors in the acceptability of foreign clinical data

Good clinical practice

- E6* Good clinical practice: consolidated guideline

Clinical trials

- E7* Studies in support of special populations: geriatrics
- E8* General considerations for clinical trials
- E9* Statistical principles for clinical trials
- E10* Choice of control group and related issues in clinical trials
- E11* Clinical investigation of medicinal products in the paediatric population

Guidelines for clinical evaluation by therapeutic category

- E12A* Principles for clinical evaluation of new antihypertensive drugs (consensus draft principle)

Clinical evaluation

- E14* The clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs

ever, applicants should not request advice until they have read all relevant guidelines and WHO's *Marketing authorization of pharmaceutical products with special reference to multisource (generic) products: a manual for a drug regulatory authority* (1999) or updates thereof. Not all of the guidelines in Tables 1–5 are necessarily relevant to a particular enquiry; the particulars of each case should be considered.

E



2.6 Risk–benefit assessments for FDCs should take into consideration any differences in anticipated patient populations. Consequently decisions on the same data set may vary between different national drug regulatory authorities.

3. Definitions

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

Active pharmaceutical ingredient (API)

Any substance or mixture of substances intended to be used in the manufacture of a pharmaceutical dosage form. When so used the API becomes the *active moiety* as defined below, often termed simply the *active*. The API may be a salt, hydrate or other form of the active moiety, or may be the active moiety itself. Active moieties 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 moiety

The term used for the therapeutically active entity in the final formulation of therapeutic goods, irrespective of the form of the API. The *active* is alternative terminology with the same meaning. For example, if the API is propranolol hydrochloride, the active moiety (the active) is propranolol.

applicant

The person or company who submits an application for marketing authorization of a new pharmaceutical product, an update to an existing marketing authorization or a variation to an existing market authorization.

certificate of pharmaceutical product

A WHO-type certificate of the form described in *Guidelines for implementation of the WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce*. Geneva, World Health Organization, 1998.

comparator

The finished pharmaceutical product with which an FDC-FPP is to be compared. The comparison may be by means of bioequivalence studies or clinical studies of safety and/or effectiveness. A single study



may use more than one comparator, for example several single entity FPPs. A comparator may be a placebo.

co-packaged product

A product consisting of two or more separate pharmaceutical products in their final dosage form that are packaged together for distribution to patients in the co-packaging.

drug

Any substance or product for human or veterinary use that is intended to modify or explore physiological states for the benefit of the recipient.

finished pharmaceutical product (FPP)

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

fixed-dose combination (FDC)

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

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

A finished pharmaceutical product that contains two or more actives.

generic products

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



microbiology

A branch of science that refers to microbes of all of types, including bacteria, viruses, rickettsia, protozoa, fungi and prions. Derived words (such as microbiological) have a similar meaning.

multisource (generic) pharmaceutical product

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

new chemical (or biological) entities

Actives that have not previously been authorized for marketing as a drug for use in humans in the country in question.

pharmaceutical equivalents

Products are pharmaceutical equivalents if they contain the same amount of the same actives 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 manufacturing process and some other variables can lead to differences in product performance.

pivotal clinical trials

Those clinical studies that provide the significant evidence that is the basis for the decision as to the risk–benefit assessment for a particular FDC.

product information

The information provided by the supplier of an FPP that allows prescribers and consumers to ensure the safe and effective use of drugs. If it is written especially for prescribers, it may be termed *prescribing information*.

reference product

A pharmaceutical product with which the new product is intended to be interchangeable in clinical practice. The reference product will normally be the innovator product for which efficacy, safety and quality have been established. Where the innovator product is not available, the product that is the market leader may be used as a reference product, provided that it has been authorized for marketing and its efficacy, safety and quality have been established and documented.



summary of product characteristics (SPC)

A term used in the European Union. Product information or data sheets in the European Union should be based on the approved SPC.

well-established drugs

Actives that:

- have been marketed for at least 5 years in countries that undertake active postmarket monitoring;
- have been widely used in a sufficiently large number of subjects to permit the assumption that safety and efficacy are well known; and
- have the same route of administration and strength and the same or similar indications as in those countries.

4. Scenarios

An application to register an FDC-FPP may fall into any one of the following four scenarios. These guidelines are intended to address the different requirements for each scenario.

4.1 *Scenario 1.* The new FDC-FPP contains the same actives in the same doses as an existing FDC-FPP; that is it is a “generic” of the existing FDC-FPP; they are “multisource” products. The quality, safety and efficacy of the existing product have been established.

4.2 *Scenario 2.* The new FDC-FPP contains the same actives in the same doses as an established regime of single entity products, and the dosage regimen is the same. Alternatively the established regime may involve combinations of single entities and FDCs, for example, a single entity FPP combined with an FDC-FPP that contains two actives. In all cases, the established regime has a well-characterized safety and efficacy profile, and all of the FPPs used in obtaining clinical evidence have been shown to be of good quality.

4.3 *Scenario 3*

- The new FDC-FPP combines actives that are of established safety and efficacy but have not previously been used in combination for this indication.
- The new FDC-FPP comprises a combination for which safety and efficacy have been established, but that will be used in a different dosage regimen.

4.4 *Scenario 4.* The new FDC-FPP contains one or more new chemical entities.

E



5. **Balancing the advantages and disadvantages of a new fixed-dose combination**

5.1 In determining whether it is rational to combine actives into a single product, there are medical, quality and bioavailability considerations.

5.1.1 *Quality* issues may be addressed by much the same criteria that apply to single-component products and it is difficult to imagine a case in which essentially the same standards would not apply.

5.1.2 *Medical* considerations are more complex and sometimes contradictory, for example, when increased efficacy is accompanied by increased toxicity. The decision as to whether to give marketing approval for a new FDC-FPP in scenarios 3 and 4 is often based on a consideration of the balance of advantages and disadvantages from the medical perspective.

5.1.3 Interpretation of the results of *bioavailability and bioequivalence* tests involves both quality and medical considerations. For example it is not acceptable that bioavailability is reduced or variable, when compared with that of single entity products, because of poor formulation, but an interaction between two actives that leads to an increased bioavailability may be one of the advantages that is taken into account when balancing advantages and disadvantages.

Balancing the advantages and disadvantages of a new FDC-FPP should form a major component of submissions pursuant to this guideline.

5.2 Submissions for marketing approval of a new FDC in scenarios 2, 3 and 4 should include a section in which the advantages of the new combination are weighed against the disadvantages. All the possible advantages and disadvantages of the combination should be listed and discussed. The discussion should be based on the available data and on scientific and medical principles. In less well-developed nations, and particularly where there are difficulties with transport and the logistics of distribution, other matters may need to be taken into account, such as:

5.2.1 The cost of the combination as compared with the cost of individual components.



5.2.2 Evidence as to whether the new FDC will improve the reliability of supply as a result of simplified distribution procedures. Improved patient adherence may result from more reliable (continuing) availability of the FDC-FPP than of all of the components as loose combinations of single entity products.

However, issues of cost and procurement alone are not sufficient reason to approve an FDC if it has not been justified by appropriate data and on scientific and medical principles.

5.3 From a scientific or medical perspective, FDCs are more likely to be useful when several of the following factors apply:

5.3.1 There is a medical rationale for combining the actives.

5.3.2 There is an identifiable patient group for which this combination of actives and doses is suitable therapy. The larger the patient group in question, the more significant is this factor. It is not appropriate to combine actives that separately treat conditions that do not commonly coexist.

5.3.3 The combination has a greater efficacy than any of the component actives given alone at the same dose.

5.3.4 The incidence of adverse reactions in response to treatment with the combination is lower than in that response to any of the component actives given alone, for example as a result of a lower dose of one component or a protective effect of one component, and particularly when the adverse reactions are serious.

5.3.5 For antimicrobials, the combination results in a reduced incidence of resistance.

5.3.6 One drug acts as a booster for another (for example in the case of some antiviral drugs).

5.3.7 The component actives have compatible pharmacokinetics and/or pharmacodynamics. See comments under Pharmacokinetics and pharmacodynamics below (section 6.6.2).

5.3.8 Therapy is simplified, particularly when the existing therapy is complex or onerous (e.g. because of a “high tablet load”).

5.3.9 One of the ingredients is intended to minimize abuse of the other ingredient (e.g. the combination of diphenoxylate with atropine, or buprenorphine with naloxone).

E





5.3.10 The active pharmaceutical ingredients are chemically and physicochemically compatible, or special formulation techniques have been used that adequately address any incompatibility.

5.3.11 Other potential advantages of FDCs over single entity products given concurrently in the same dose may include:

5.3.11.1 Convenience for prescribers and patients.

5.3.11.2 Better patient adherence (but the evidence for this is largely anecdotal) (*I*, and Haynes, RB, personal communication, 2003).

5.3.11.3 Simplified logistics of procurement and distribution.

5.3.11.4 Lower cost.

These factors are important, but there may not necessarily be evidence to support them; they may be more significant when there is specific evidence available to support a particular case.

5.4 From a scientific or medical perspective, FDCs are less likely to be useful when one or more of the following factors apply:

5.4.1 The component actives are normally separately titrated to meet the patient's needs. Consequently:

5.4.1.1 Either the doses of the components, and/or the ratio of doses, typically differ from patient to patient, and/or

5.4.1.2 Patients are likely to be taking different doses at different stages of treatment (for example initial treatment compared with long-term treatment).

These two factors are particularly significant when one or more of the actives has a narrow therapeutic index and/or a steep dose-response curve in the therapeutic range.

5.4.2 There is a higher incidence or greater severity of adverse reactions to the combination than with any of the ingredients given alone, or there are adverse reactions not seen in response to treatment with any of the individual ingredients.

5.4.3 There are unfavourable pharmacokinetic interactions between the ingredients, for example when one drug alters the



metabolism, absorption or excretion of another. However, see comments under Pharmacokinetics and pharmacodynamics below (section 6.6.2) concerning circumstances in which such interaction is intended.

- 5.4.4 Dose adjustment is necessary in special populations, such as in people with renal or hepatic impairment.
- 5.4.5 The product (tablets or capsules), is so large that patients find it difficult to swallow.

6. Data requirements for marketing authorization of fixed-dose combination finished pharmaceutical products

6.1 General

- 6.1.1 The framework for issuing a marketing authorization for an FDC-FPP is the same as that for single entity FPPs and is summarized in WHO's *Marketing authorization of pharmaceutical products with special reference to multisource (generic) products: a manual for a drug regulatory authority* (1999) — the “Blue book”, or updates thereof. Information on the pharmaceutical development of a new product is planned for inclusion in the next edition of the Blue book and is summarized in Appendix 3.
- 6.1.2 Data requirements for marketing authorization of FDC-FPPs depend broadly on the scenario into which the application falls (see sections 4.1–4.4 above). Table 6 summarizes these differences. However, each application should be considered on its own merits using scientific judgement and logical argument.
- 6.1.3 Data requirements for marketing authorization do not differ when the combination is in the *WHO Model list of essential medicines*, i.e. data requirements are the same whether or not the combination or its components are in the *Model list of essential medicines*.
- 6.1.4 Submissions should include a statement of the marketing status of the FDC-FPP in other countries.
- 6.1.5 All applications to register an FDC-FPP should include a draft “product information” or “summary of product characteristics” for indicated diseases, and any package information leaflet or patient information. See the more detailed discussion below (section 7).



6.1.6 A full quality data set is required in all scenarios (see 6.3 below).

6.1.7 In general, preclinical or clinical safety and efficacy data are not required in *scenario 1*. If the risk–benefit assessment has been found to be acceptable for an FDC, then new brands may be

Table 6

Summary of requirements for the various scenarios

This table is a list of the most likely set of requirements for marketing authorization of an FDC-FPP in each scenario. However each application should be considered on its own merits in relation to data requirements, using scientific judgement and logical argument. Some of the data may be provided in the form of literature studies, subject to the guidance given in the main text and Appendix 2.

Requirement	Scenario 1	Scenario 2	Scenario 3	Scenario 4
Rationale for the combination	Not usually	Not usually	√	√
Balancing advantages and disadvantages of the combination	Not usually	Not usually	√	√
Marketing status in other countries	√	√	√	√
Analysis of literature data in the submission	Possibly for pharmaceutical development	Possibly for pharmaceutical development	√	√
Pharmaceutical development studies	√	√	√	√
GMP certification of sites of manufacture	√	√	√	√
A full quality data set	√	√	√	√
Bioavailability data ^a	Not usually	Not usually	Sometimes	√
Bioequivalence data	√	√	Sometimes	Sometimes
Preclinical pharmacology and safety	Not usually	Not usually	Sometimes	√
Clinical safety and efficacy	Not usually	Not usually	√	√
Product information	√	√	√	√
Plan for passive post-marketing surveillance	√	√	√	√
Plan for active post-marketing surveillance	Not usually	Not usually	√	√
Assurances ^b	√	√	√	√

√ This is a requirement.

^a Normally absolute bioavailability for a new chemical entity, or comparative bioavailability for a new dosage form.

^b The applicant should provide assurances that:

- “The Product Information will not be altered without prior approval from [*name of regulatory authority*], except for safety updates that further restrict use of the product. Any such safety-related changes should be notified to [*name of regulatory authority*] within five days of making the change”; and
- “No changes will be made to the product without prior approval, except for changes of the type listed in [*name of regulatory authority*]’s policy on ‘Changes to pharmaceutical aspects which may be made without prior approval’ and subject to the conditions in that policy.”





approved on the basis of bioequivalence with the brand(s) used in pivotal clinical trials.

The applicant may, however, be asked to establish that a risk–benefit assessment has been conducted and found acceptable if, for example the drug regulatory authority to which the application is submitted is not convinced that this is the case or does not have access to the data.

- 6.1.8 If the FDC directly substitutes for an established regimen of single entity products, in relation to both actives and doses and for the same indication(s), a bioequivalence study may provide adequate evidence of safety and efficacy. This is *scenario 2*. The established regimen should have well-characterized safety and efficacy, and all of the FPPs should have been shown to be of good quality, including compliance with a suitable code of good manufacturing practice (GMP) during manufacture. Again the applicant may have to establish that this is the case.

6.2 Good manufacturing practice

- 6.2.1 Application of a suitable and relevant code of GMP is a critical element in assuring the current and continuing quality of medicines. Certification of GMP should be provided for all sites of manufacture of finished products, and preferably also for the sites of manufacture of active pharmaceutical ingredients (APIs). A suitable code of GMP would be the WHO Good manufacturing practices (GMP): main principles for pharmaceutical products, and for Inspection, both in: *Quality assurance of pharmaceuticals. A compendium of guidelines and related materials*, Volume 2, updated edition. Geneva, World Health Organization, 2004, and subsequent additions and revisions (e.g. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-ninth report*. Geneva, World Health Organization, 2005 (WHO Technical Report Series, No. 929), Annex 2).

Assurance as to certification of GMP may conveniently be obtained using the WHO Certification Scheme — Guidelines for implementation of the WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce, and WHO pharmaceutical starting materials Certification Scheme (SMACS) (*WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-eighth report*. Geneva, World Health Organization, 2004 (WHO Technical Report Series, No. 917), Annex 3).

E





6.2.2 Sites of storage and distribution, including company storage facilities, should also be subject to ongoing audits of GMP. Relevant guidelines include: Guide to good storage practices for pharmaceuticals (*WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-seventh report*. Geneva, World Health Organization, 2003 (WHO Technical Report Series, No. 908), Annex 9); and Good trade and distribution practices for pharmaceutical starting materials (*WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-eighth report*. Geneva, World Health Organization, 2004 (WHO Technical Report Series, No. 917), Annex 2).

6.3 Quality

6.3.1 In relation to quality, very similar principles apply to FDC-FPPs as apply to single entity products. However there are additional complexities arising from the need to consider two or more actives instead of one. These complexities are principally, but not exclusively, related to assay, stability, physicochemical properties (for example dissolution rate) and bioavailability/bioequivalence. Consequently the following considerations (and others) may be pertinent.

6.3.2 Appendix 3, entitled *Development (or preformulation) studies*, makes some general points about this type of study. Pharmaceutical development studies are especially important for FDC-FPPs because they are technically more demanding than single-component products. Issues that are specific to the development of FDC-FPPs include:

6.3.2.1 Chemical and physicochemical compatibility of the APIs in an FDC with one another as well as with possible excipients.

6.3.2.2 The degradability of each API under stress conditions in the presence of the others.

6.3.2.3 Uniformity of content of each active prior to compression (tablets) or filling (for instance capsules, sachets and suspension dosage forms). This study determines whether mixing during manufacture is adequate.

6.3.2.4 Analytical procedures. These should be validated for each active in the presence of the others during development of analytical methods for quality control of the finished product, stability testing and dissolution testing. Validation should be conducted for each active in the



presence of the others and in the presence of related synthesis (process) impurities and potential degradation products. In the case of high-performance liquid chromatography (HPLC) (a common analytical technique), possible interference by degradation products in the assay of the active can usually be controlled by peak purity testing.

6.3.2.5 The dissolution rate of each active in pilot formulations. Multipoint limits should normally be established for routine quality control of each active. For some FDC-FPPs, different dissolution media may be acceptable for the different actives.

6.3.2.6 Different assay procedures may be necessary for the different actives in the finished product, and for different purposes (e.g. dissolution testing may be needed rather than stability testing).

6.3.3 For solid dosage forms a test and limit for content uniformity should be applied to any active that is present at a weight of ≤ 25 mg or when the API comprises 25% or less of a dosage unit. Some authorities permit an exception for soft gelatin capsules that contain a solution of the API. Typically, when any one API is present at less than 25 mg or less than 25% of the weight of a dosage unit, all of the actives are subjected to content uniformity testing.

If a solid dosage form is not subject to content uniformity testing, for example because all of the actives are present at a weight of greater than 25 mg and greater than 25% of the weight of a dosage unit, there should be a test and limit for mass variation.

6.3.4 Acceptance criteria for impurities in FDC-FPPs should be expressed with reference to the parent API (and not with reference to the total content of APIs). If an impurity results from reaction between two APIs, its acceptance limits should be expressed in terms of the API that represents the worst case. If available, a reference standard should be used to quantify the degradation product in percentage mass/mass with respect to the parent API. Alternatively, and if justified, other quantitative techniques that are described in *Impurities in new drug products* (revised) ICH-Q3B(R) (2003), may be applied.

Note: there should be an approximate mass balance. Together with the remaining active, degradants expressed with reference

E





to the parent compound should sum to approximately 100% of initial strength.

- 6.3.5 The specifications and defining characteristics of the product should be based on the most vulnerable active. For example expiry dates should be based on the stability of the least stable active.
- 6.3.6 In setting specifications, relevant pharmacopoeial monographs, WHO guidelines and ICH guidelines should be taken into account. For example in the absence of a relevant WHO guideline, the ICH guideline *Specifications: test procedures and acceptance criteria for new drug substances and new drug products: chemical substances* (1999) is a suitable source of guidance.
- 6.3.7 Specifications in addition to those in pharmacopoeias may be necessary for APIs in some cases, for example for particle size, residual solvents and synthesis-related impurities that are not covered by relevant monographs.

6.4 **Bioavailability and bioequivalence**

- 6.4.1 Data on bioequivalence provide a bridge between two *pharmaceutical equivalents* (see Glossary) when safety and efficacy data are available for one of the FPPs, but not for the other. By demonstrating that the two products lead to the same profile for plasma concentration over time, available safety and efficacy data for one of the products can be extrapolated to the other. The two products being compared may be different brands, or different batches of the same brand, for example when manufactured by different methods, at different sites or according to different formulations.
- 6.4.2 Data on bioequivalence may also be important when the same FPP is administered under different circumstances, for example before or after food, in different patient populations (such as children versus adults), or by different routes of administration (such as subcutaneous versus intramuscular injection).
- 6.4.3 In the context of these guidelines, an additional application of bioequivalence studies is in scenario 2 in which safety and efficacy data on single entity products given concurrently may be extrapolated to an FDC-FPP, provided that all of the conditions described elsewhere in these guidelines are met.
- 6.4.3 There are two common circumstances in which data on bioequivalence are likely to be generated for *pharmaceutical equivalents*:



6.4.3.1 Pivotal clinical trials were generated on one formulation and another is to be marketed by the same company (for example because the second formulation is more stable or more marketable than the first); or

6.4.3.2 A relevant patent has expired and a multisource pharmaceutical equivalent has been developed.

6.4.4 Evidence as to bioequivalence is required for *scenarios 1* and *2*, and sometimes for *scenarios 3* and *4*, for example when there are major differences between the formulation and/or method of manufacture of the product to be registered and that used in pivotal clinical trials.

6.4.5 If a study of bioequivalence finds that the two treatments are bioequivalent, it may be assumed that any pharmacokinetic interactions between the actives were the same, even if one treatment comprised an FDC-FPP and the other comprised separate products.

6.4.6 Data on absolute bioavailability are usually required in scenario 4, i.e. comparison of the area under the curve for plasma concentration over time after an intravenous injection with that after administration of the dosage form to be marketed, for example a tablet given orally.¹

6.4.7 A decision as to whether it is necessary to conduct a study of the effect of food on the bioavailability of an FDC-FPP should be based on what is known of the effect of food on the individual actives, and any relevant recommendations in the product information for the single entity products.

The effect of food should normally be studied in scenario 4.

6.4.8 Recommendations as to the conduct and analysis of bioequivalence studies are provided in the WHO guidelines, *Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability* (1996, or later updates). Other guidelines may be relevant depending on the jurisdiction in which the application is submitted.

6.4.9 In demonstrating bioequivalence it may not always be necessary to provide in vivo data. The nature of suitable evidence as

¹ See the WHO guidelines on *Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability* (1996, or later updates) for options to be employed when an intravenous solution cannot be prepared or is unsafe.



to bioequivalence differs according to the type of application and the remainder of the data set.¹

6.4.10 During analysis of the results of a bioavailability or bioequivalence study for an FDC-FPP, the parameters to be reported and assessed are those that would normally be required of each active if it were present as a single entity and the same statistical confidence intervals and decision criteria should be applied.

6.4.11 An additional scientific consideration that has been elaborated in recent years is the option for biowaivers based on the Biopharmaceutics Classification Scheme (BCS). This is an area in which further developments are expected. The main relevant publication to date is *Waiver of in vivo bioavailability and bioequivalence studies for immediate-release solid oral dosage forms based on a biopharmaceutics classification system*. US Food and Drug Administration (2000). At present, and in the absence of clear guidance for FDCs, it is recommended that biowaivers based on the BCS classification as the sole criterion for a decision be handled cautiously because there is at present no guidance as to how to consider the possibility of a chemical or pharmacokinetic interaction between actives that may affect bioequivalence. However there are circumstances in which the BCS classification may nevertheless be relevant to FDCs. In such a case the BCS classification of all the actives in the FDC should be taken into account. For example:

6.4.11.1 For a new multisource product, if all the actives are in the most favourable biopharmaceutics classification of high solubility and high gastrointestinal permeability (i.e. BCS #1), and the criterion of dissolution of not less than 85% in 30 minutes is met for each active in the requisite media, a biowaiver may be considered.

6.4.11.2 For approval of new strengths when all actives are in BCS #1.

In addition, the BCS classification and in vitro dissolution rates may be factors in marginal cases, for example when considering whether a new study is required in support of a change in site or method of manufacture, or another change that might be considered minor.

¹ See the WHO guidelines on *Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability* (1996, or later updates) for options to be employed when an intravenous solution cannot be prepared or is unsafe.



Even if one or more of the actives is not in BCS #1, if an in vitro/in vivo correlation has been established, then in vitro comparison of dissolution performance in various media may be an option.

- 6.4.12 Validation of assays of actives in biological media is crucial in order to generate a meaningful bioavailability and bioequivalence study. See, for example, the guidelines *Bioanalytical method validation*. US Food and Drug Administration (2001).
- 6.4.13 Selection of a suitable comparator for the purpose of bioequivalence is described in *Guidance on the selection of comparator pharmaceutical products for equivalence assessment of interchangeable multisource (generic) products*. World Health Organization (2002). Some additional comments follow.
- 6.4.13.1 The comparator should be of known quality, safety and efficacy.
- 6.4.13.2 For applications in scenario 1, the decision as to the comparator depends on whether there is more than one existing brand of the combination whose safety and efficacy is known to be acceptable. If only one brand is known to have acceptable safety and efficacy, this should be used as comparator. In other circumstances, the decision is more difficult and should be justified by cogent argument and data. The WHO *Guidance on the selection of comparator pharmaceutical products for equivalence assessment of interchangeable multisource (generic) products* (2002) may be of assistance.
- 6.4.13.3 For applications in scenario 2, single entity products will have been used in the majority of pivotal clinical trials. The same brands of those single entity FPPs should be the comparator and should be given concurrently as was the case in the pivotal clinical trials.
- 6.4.13.4 For applications in scenarios 3 and 4 (with which evidence as to safety and efficacy will be submitted), the new product should be shown to be bioequivalent to the product(s) that was (were) used in pivotal clinical trials.
- 6.4.13.4.1 If an FDC-FPP was used in the majority of pivotal clinical trials, then that brand should be the comparator.





6.4.13.4.2 If single entity products were used in the majority of pivotal clinical trials, then they should be the comparator, but should be given as (1) the same brands and (2) concurrently, as in the pivotal clinical trials.

6.4.13.4.3 If approximately equal numbers of pivotal clinical trials used an FDC and single entity products, then in principle either may be used as comparator. However judgement should be applied in deciding which to use, for example if one group of studies was more rigorous than another, or if the conclusions were more definitive in relation to one group.

6.4.13.5 If in any of the scenarios, the selection of comparator cannot be made according to the suggestions above (for example because the brand in question is no longer available), the decision is more difficult and should be justified by cogent argument and supporting data. It may be necessary to conduct bridging clinical studies. See the WHO *Guidance on the selection of comparator pharmaceutical products for equivalence assessment of interchangeable multisource (generic) products* (2002).

6.5 Preclinical pharmacology and safety

6.5.1 Preclinical data are not normally required in scenarios 1 and 2. Data may, however, be required in some circumstances, for example if an unusual excipient is included in the formulation or if the impurity profile differs significantly from that of reference products.

6.5.2 Preclinical data will be required in scenario 4 as for any new chemical entity. The standard of evidence should be the same as for any new chemical entity.

6.5.3 In scenario 3, preclinical studies may not be required if all the actives have been extensively used in humans in the same combination for a long period and the safety of the combination has been well demonstrated. Bridging studies may be appropriate in some cases, for example for a new ratio of doses.



- 6.5.4 If the safety of the combination in humans has not already been demonstrated (i.e. in scenarios 3 and 4), preclinical studies should be conducted on the actives administered in combination in order to investigate possible additive or synergistic toxicological effects.

The preclinical data that are required in scenarios 3 and 4 will vary according to the data that are already available. For example, by definition in scenario 3, the safety and efficacy of each active will have already been established, but that of the combination will not. In scenario 4, the safety and efficacy of one or more of the actives may already have been established, but not those of all the actives or of the combination.

- 6.5.5 When preclinical data are required, the studies should aim to determine both the pharmacological and the adverse effects that may be expected from the combination of actives during clinical use.
- 6.5.6 As a general rule, preclinical studies on the combination should be performed with the actives in same the ratio as in the FDC-FPP in question. If this is not the case, the applicant should explain and justify the proportions used. A comparison of the systemic exposures in animals and humans will be relevant.
- 6.5.7 In the absence of relevant WHO guidelines, the ICH preclinical guidelines in Table 4 may be used as source of guidance.
- 6.5.8 Preclinical studies should comply with a suitable code of good laboratory practice (GLP); see, for example *Handbook: Good laboratory practice: Quality practices for regulated non-clinical research and development*. World Health Organization (2001).
- 6.5.9 Microbiological preclinical studies

In general this section is applicable to scenarios 3 and 4, but not to scenarios 1 and 2. There may be some exceptions, for example microbiological data may be appropriate in scenarios 1 and 2 if a different pathogen or resistance pattern is encountered.

- 6.5.9.1 In scenarios 3 and 4, when a new combination is proposed for an antimicrobial indication, microbiological studies may be needed to determine the advantage of the FDC over the individual active moieties against relevant pathogen(s), and especially when





clinical trials of monotherapy are inappropriate or unethical.

6.5.9.2 Data from microbiological preclinical studies of FDCs are particularly useful when clinical trials of monotherapy are inappropriate or unethical.

6.5.9.3 Data from the following types of study should normally be available for the combination:

6.5.9.3.1 Characterization of microbiological activity *in vitro* and *in vivo* against laboratory strains and clinical isolates of the targeted pathogen(s), including those strains in the relevant geographical regions.

6.5.9.3.2 Characterization of microbiological activity in appropriate animal models of infection with the targeted pathogen(s).

6.5.9.3.3 If possible, characterization of the mechanism by which the actives exhibit additive or synergistic microbiological activity against the targeted pathogen(s).

6.5.9.3.4 The potential for antagonistic effects between the actives.

6.5.9.3.5 The potential for development of resistance by target pathogens.

6.6 Clinical efficacy and safety

This section is in general applicable to *scenarios 3* and *4* but not to *scenarios 1* and *2*. Bridging studies may sometimes be appropriate in scenario 3, for example for a new ratio of doses or a longer duration of treatment.

6.6.1 General principles

6.6.1.1 The risk–benefit assessment for a new combination may be based on data generated using *either* the components given as single entity products concurrently *or* the FDC as a single FPP.

6.6.1.2 Any theoretical advantages of a particular combination should be confirmed by means of efficacy studies. The risk–benefit assessment should not be based on theoretical considerations only, or on extrapolation from other data.



6.6.1.3 If the actives in an FDC are intended to relieve different symptoms of a disease state, it is a prerequisite that these symptoms commonly occur simultaneously at a clinically relevant intensity and for a period of time such that simultaneous treatment is appropriate. Occurrence of the individual symptoms in isolation should not be indications for the FDC.

6.6.1.4 Clinical studies should be designed to determine whether the combination has an advantage over the component actives given alone in a substantial patient population. The data should demonstrate that each active contributes to the therapeutic effect of the combination.

It may not be essential to show that all of the components have efficacy when administered as single entities; for example clavulanic acid has little or no antimicrobial activity when given alone, but it enhances the efficacy of beta-lactam antibiotics.

6.6.1.5 In situations where comparative clinical trials are not feasible, for example when monotherapy is inappropriate or is unethical, an aggregate of clinical and preclinical data may be substituted. Such data may include:

6.6.1.5.1 Historical clinical data, preferably at an exposure comparable to that for the proposed FDC.

6.6.1.5.2 Bridging pharmacokinetic data.

6.6.1.5.3 Preclinical pharmacology and/or toxicology data.

6.6.1.5.4 In vitro data (e.g. microbiological studies).

6.6.1.6 If the FDC is available in more than one strength or ratio of doses, there should be a risk-benefit assessment for each combination.

6.6.1.7 The choice of comparators for the purposes of safety and efficacy studies should be justified. They should normally represent the recognized treatment for the indication in question. As far as possible, comparators should be licensed products with well-established safety and efficacy profiles and of established quality. Unapproved or novel combinations should be avoided as comparators as they may introduce new efficacy or toxicity characteristics and thus complicate assessment of the combination under test.

E





- 6.6.1.8 If the combination is intended for long-term use, data on safety in patients will normally be required for 6 months or longer.
- 6.6.1.9 If one or more of the component actives has an established use and dosage regimen in indications unrelated to the indications of the FDC, existing experience as to its safety may nevertheless be taken into account, bearing in mind the relative doses for the two sets of indications.
- 6.6.1.10 End-points in clinical trials should be such as to characterize the advantages and disadvantages of the combination. For example, for a combination designed to reduce the development of drug resistance, end-points might include the frequency of new drug resistance as well as the overall clinical outcome.
- 6.6.1.11 Parallel group comparisons are one means of demonstrating a therapeutic effect. A parallel placebo group should be included if feasible and if consistent with the indications under treatment. Multifactorial designs are another means by which it may be possible to demonstrate that a combination is superior to the individual actives.
- 6.6.1.12 In some cases, studies have to be specifically designed to confirm the minimal effective dose and the usual effective dose of the combination. Multiple dose-effect studies may be necessary.
- 6.6.1.13 The design and analysis of studies of efficacy and safety should consider (among other things) whether the combination is indicated as first- or second-line therapy.
- 6.6.1.14 In general, all of the actives in a combination should have a similar duration of action. If this is not the case, the applicant should explain and justify the combination.
- 6.6.1.15 In general, the actives in a combination should have similar pharmacokinetics. If this is not the case, the applicant should explain and justify the combination.
- 6.6.1.16 If there is an increase in the number or severity of adverse reactions to the FDC as compared with those in response to the individual actives given alone, evidence and argument should be presented showing that the advantages of the combination outweigh the disadvantages. These should be included in the section of the submission entitled “Balancing the advantages and disadvantages of a new FDC”.



6.6.1.17 Data generated in clinical safety and efficacy studies should comply with the WHO *Guidelines for good clinical practice (GCP) for trials on pharmaceutical products* (1995).

6.6.2 **Pharmacokinetics and pharmacodynamics**

This section is generally applicable to scenarios 3 and 4, but not to scenarios 1 and 2. In scenarios 1 and 2, the information described below will usually already be available.

6.6.2.1 In general, it is desirable that there be no pharmacokinetic or pharmacodynamic interactions between the components of a combination. However, there are circumstances in which such an interaction is intentional and may even contribute to the therapeutic outcome. For example:

6.6.2.1.1 Ritonavir boosts the activity of protease inhibitors.

6.6.2.1.2 Carbidopa and benserazide both reduce decarboxylation of levodopa in the gut wall, and consequently reduce the dose of levodopa that should be administered.

6.6.2.1.3 Clavulanic acid reduces bacterial hydrolysis of beta lactam antibiotics and consequently both increases the concentration and prolongs the duration of effectiveness.

6.6.2.2 Tests should be conducted to elucidate any pharmacokinetic or pharmacodynamic interaction between the actives in a combination. Some interactions may be predictable from pharmacokinetic and enzyme profiles, but should be confirmed by experiment. Any interaction should be quantified so that its effect on safety and efficacy is either predictable or (preferably) has been tested in a clinical study. This includes competing metabolic effects and effects on gastrointestinal efflux mechanisms or on renal excretion or reabsorption. Interactions may be additive, synergistic or antagonistic.

6.6.2.3 If there is an unintended pharmacokinetic interaction between the actives, it should be demonstrated that the therapeutic advantages of the combination outweigh any disadvantages resulting from the interaction. Relevant argument and cross-references to data should be included in the section that discusses the balance between the advantages and disadvantages of the combination.

E



6.6.3 **Additional guidelines for scenario 3**

- 6.6.3.1 The risk–benefit assessment for a new combination may be based (at least in part) on a demonstration of the clinical non-inferiority of the combination to another product licensed for the same indication. See Appendix 4, entitled *Superiority, equivalence and non-inferiority clinical trials*, for more information.
- 6.6.3.2 Pharmacodynamic studies for new combinations should normally be conducted at several dose ratios of the actives unless the applicant can provide justification for not doing so.

6.6.4 **Additional guidelines for scenario 4**

- 6.6.4.1 When an FDC-FPP contains an active that is a new chemical entity, data requirements are the same as for any new chemical entity. In some circumstances, some of the preclinical and clinical data on safety and/or efficacy may have been generated from studies on the combination rather than on single entities, for example when one active confers a protective effect in relation to adverse reactions or when the actives act synergistically.
- 6.6.4.2 Dose-finding monotherapy studies should normally be conducted for the new chemical entity before commencing studies of combination therapy, unless the new chemical entity is not intended to have activity when used alone (such as clavulanic acid). Alternative approaches may be acceptable if they can be justified.
- 6.6.4.3 The pharmacokinetics and enzyme profile of any new chemical entity should be fully characterized, including prediction of possible interactions and pharmacokinetics in children if the new chemical entity could be used in that population (see also section 7.6.6 on *Paediatric dosage forms*).

6.6.5 **Superiority, equivalence and non-inferiority trials and fixed-dose combinations**

Appendix 4 defines superiority, equivalence and non-inferiority trials and makes some general points concerning different types of study. More information can be found in the Committee for Medicinal Products for Human Use (CHMP) guidelines in Table 3.

- 6.6.5.1 In the context of FDCs, equivalence trials are largely confined to bioequivalence studies.



6.6.5.2 An FDC-FPP should be shown, directly or indirectly, to be superior to the component actives given as single entity treatments. Only a superiority trial can give the necessary statistical confidence. Submissions should discuss both the statistical significance and clinical relevance of the results. Any alternative form of evidence that purports to address the same issues, for example one that concerns a dose–response surface, must be explained and justified with appropriate statistical confidence.

6.6.5.3 In clinical trials that are intended to test for superiority and/or non-inferiority, the choice of comparator should be carefully considered and will depend in part on the medical and ethical circumstances. The comparator may be:

6.6.5.3.1 The treatment whose risk–benefit profile is best supported by evidence or is at least well established.

6.6.5.3.2 One or more of the actives in the FDC given as a single treatment.

6.6.5.3.3 A placebo.

6.6.5.4 Depending on the claim, superiority or non-inferiority should be demonstrated for each specified clinical outcome. For example if the claim is less bone marrow depression, but similar efficacy, a non-inferiority outcome should be demonstrated for efficacy and a superiority outcome for safety.

6.6.6 **Paediatric dosage forms**

6.6.6.1 Different FDC-FPPs may be needed in paediatric populations from those needed in adults because of differences in pharmacokinetic and pharmacodynamic profiles of the actives, and for reasons of palatability. The doses of each active may need to be lower or higher, and the appropriate dose ratio may be different.

Scenarios 1 and 2

6.6.6.2 In scenarios 1 and 2, when the combination of actives and doses has already been shown to be safe and effective in the paediatric population, a bioequivalence study in adults may be extrapolated to the paediatric population provided that the pharmacokinetics of all actives are well-established in both populations and it is known that there are no differences that could affect the outcome of the bioequivalence study. Extrapolation of bioequivalence data between age groups should be justified in these terms.

E



Scenarios 3 and 4

6.6.6.3 If the FDC is indicated in a paediatric population, but the combination of actives and doses has not been shown to be safe and effective in this population, suitable doses of the actives given in combination should be established. In some cases, it may be necessary to do this in more than one age group (see the table below).

Paediatric populations

Neonate	Birth to under 1 month
Infant	1 month to under 2 years
Children	2 years to under 12 years
Adolescent	12 years to under 16 years

From the age of 16 years, individuals are considered to be adults in the context of these guidelines.

6.6.6.4 The pharmacokinetic profile of each active should be established in the age groups for which the FDC is indicated.

6.6.6.5 If it is possible to define target plasma concentrations in both adults and the paediatric population for an FDC that has established safety and efficacy in adults, then it may be possible to define suitable doses in the paediatric population on the basis of pharmacokinetics. The task is easier for actives that have the same target concentrations in adults and the paediatric population, such as antimicrobials that have established minimum inhibitory concentrations (MICs) and established safety at these concentrations.

6.6.6.6 When defining target plasma concentrations in the paediatric population, possible differences in the concentration–effect relationship should be taken into account.

6.6.6.7 If safe and effective use of the FDC has not been established in any age group, and extrapolation between groups is not possible based on pharmacokinetic data, then new clinical, and possibly also preclinical, safety and efficacy data should be obtained.





7. **Product information (or summary of product characteristics) for fixed-dose combination finished pharmaceutical products**

The product information is the information provided by the supplier of an FPP that allows prescribers and consumers to ensure the safe and effective use of drugs. If it is written especially for prescribers, it may be termed prescribing information. The summary of product characteristics (SPC) is a term used in the European Union (EU). Product information or data sheets in the EU should be based on the approved SPC.

This section of the guideline applies to all scenarios.

- 7.1 The product information should contain all of the information listed in the Appendix to WHO's Ethical criteria for medicinal drug promotion (see Table 1) in addition to the information mentioned below.
- 7.2 The product information should be an integrated evaluation of the FDC, and not a summation of the product information for each of the actives.
- 7.3 The rationale for use of the product should be presented in terms of the combination rather than in terms of the individual actives.
- 7.4 Only those indications for which each active in the FDC makes a useful contribution should be included in the product information. Each indication should be a well-recognized disease state, modification of a physiological state, dysfunctional state, syndrome or pathological entity.
- 7.5 For each indication there should be a statement as to whether the FDC is recommended for first- or second-line therapy.
- 7.6 Any pharmacokinetic and pharmacodynamic interactions between the actives should be described in qualitative and, as far as possible, in quantitative terms.
- 7.7 All clinically relevant interactions between the FDC and other drugs should be described, together with the resulting contraindications and precautions. Any deviations from expected interactions known for the single components should be highlighted.
- 7.8 When safety experience with the FDC is limited in comparison with that for the individual components, safety experience from

E



clinical trials and postmarketing experience should be presented for both the FDC and the individual components, and should be identified as such.

- 7.9 If the safety profile for the combination is different to that for the individual actives, this should be highlighted. For example a combination of a fibrate and a statin might carry a risk of more frequent or more severe rhabdomyolysis than for either individual active.

8. Postmarketing studies and variations

8.1 Postmarket monitoring of safety is an important part of the role of both drug regulatory authorities and manufacturers. It is especially important when there are unresolved concerns regarding safety, and when a new product is intended for wide community use, as for example a new antimicrobial FDC-FPP for use in the treatment of tuberculosis, malaria or HIV/AIDS. See WHO's *The importance of pharmacovigilance: safety monitoring of medicinal products* (2002). Manufacturers should have (and use) written operating procedures for continuous assessment of the safety and utilization of their products following marketing authorization; SOPs can be examined during a GMP inspection. For antimicrobials, monitoring of patterns of resistance is an important component of pharmacovigilance. Note also that pharmacovigilance outcomes can differ with diet, ethnicity, comorbidity and other factors.

8.2 For scenarios 1 and 2, passive surveillance (spontaneous reporting) would usually be acceptable. For scenarios 3 and 4, additional active (prospective) surveillance should be considered, especially when there is an outstanding safety concern. For more information, see the draft ICH guideline *Pharmacovigilance planning* (Table 5), or later updates thereof.

8.3 Once the product information has been approved, any proposed changes should be validated according to principles similar to those for the initial application.

To ensure that drug regulatory authorities are aware of proposed changes to product information, it is recommended that marketing approval letters contain this statement:

"The product information may not be altered without prior approval, except for safety updates that further restrict use of the product. Any such safety-related changes should be notified to [*name of regulatory authority*] within five days of making the change."



From Annex 9 of *Marketing authorization of pharmaceutical products with special reference to multisource (generic) products: a manual for a drug regulatory authority* (WHO, 1999).

- 8.4 Variations to pharmaceutical aspects of registered FDC-FPPs are subject to similar considerations to those described in Section IV and Annex 10 of *Marketing authorization of pharmaceutical products with special reference to multisource (generic) products: a manual for a drug regulatory authority* (WHO, 1999). As outlined in that text, some changes may be made without prior approval (“self-assessable” changes), and some require prior consideration by the drug regulatory authority.

To ensure that drug regulatory authorities are aware of proposed variations, it is recommended that marketing approval letters contain this statement:

“No changes may be made to the product without prior approval, except for changes of the type listed in [name of regulatory authority]’s policy on ‘Changes to pharmaceutical aspects which may be made without prior approval’. Conditions in that policy apply.”

From Annex 9 of *Marketing authorization of pharmaceutical products with special reference to multisource (generic) products: a manual for a drug regulatory authority* (WHO, 1999).

Reference

1. Haynes RB, McDonald HP, Garg AX. *Interventions for helping patients to follow prescriptions for medications*. Cochrane Library: Update software Issue #2, 2002.



Appendix 1

Guidelines for co-packaged fixed-dose combinations

A *co-packaged product* consists of two or more separate pharmaceutical products in their final dosage form that are packaged together for distribution to patients in the co-packaging.

1. Co-packaged products may fall into any of scenarios 1 to 4. The data requirements for each scenario are the same as those listed in Table 6 of this Annex.
2. A full quality data set is required for all components of co-packaged pharmaceutical products, except for any component that already has marketing authorization in which case more limited requirements apply (see below).
3. If one or more of the pharmaceutical products already has marketing authorization, then the additional quality information to support co-packaging of those pharmaceutical products will typically be limited to data on stability of the products in the co-packaging. However the manufacturer of each component pharmaceutical product should provide an assurance that the product as used in co-packaging will be identical in formulation and method of manufacture to the one that already has marketing authorization. This is especially important when the manufacturer of a component is not the manufacturer of the co-packaged product.
4. Submissions concerning co-packaged pharmaceutical products should take into account the Guidelines on packaging for pharmaceutical products. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-sixth report*. Geneva, World Health Organization, 2002 (WHO Technical Report Series, No. 902), Annex 9.



Appendix 2

Principles for determining whether data from the scientific literature are acceptable

Literature-based data concerning FDCs may be acceptable, subject to the principles below.

1. Bibliographical data should not replace the source data (i.e. original study reports) if they are available.
2. The overall strength of literature-based evidence will depend on its quality, quantity and consistency of outcomes.
3. Unless otherwise justified by the applicant, literature-based data concern actives that have an extensive marketing history.
4. All documents that are directly relevant to the application should be provided.
5. Literature-based submissions should include:
 - 5.1 Details of the search strategy, including a list of the databases searched and the service provider.
 - 5.2 The date on which the search was performed.
 - 5.3 The rationale for the search strategy, including an explanation of and reasons for the inclusion and exclusion criteria.
 - 5.4 An unedited search strategy and the outcome thereof.
 - 5.5 An analysis of the data collected, including both favourable and unfavourable results; this is a critical component of a submission that includes data from the scientific literature.
6. The applicant's analysis of literature-based data should:
 - 6.1 Include an appraisal of:
 - 6.1.1 The quality of the data.
 - 6.1.2 Relevance to the application being made (including a comparison of formulations and methods of manufacture of products used in clinical studies reported in the literature with those proposed for marketing).
 - 6.1.3 Consistency and compatibility of the data from the literature with any original data submitted.
 - 6.1.4 The impact of the literature-based data on the risk-benefit assessment for the FDC.
 - 6.1.5 Any contradictions between favourable and unfavourable results.
 - 6.2 Include cross-references to appended copies of publications and to any original data submitted.
 - 6.3 Include separate sections for clinical, preclinical and quality data.



- 6.4 Include an appraisal of the sources of information, in particular whether the data come from an independently refereed source or from other sources.
7. If a literature search and/or the analysis of data from the literature is more than 6 months old, the submission should justify using this search and analysis and should indicate why more recent publications and data have not been used. Alternatively a supplementary review of the more recent literature may be appended to the report that brings it to within 6 months of the date of submission.
8. Copies of all documents referred to in the submission or in the data analysis should be appended to the submission. If a document is not written in a language that is acceptable in the jurisdiction, a certified translation should also be attached (in addition to the original).
9. Review articles are acceptable in principle, but should be judged on their quality.
10. “Consensus” publications are acceptable in principle, but should be judged on their quality and on whether the original data and documentation are attached.
11. Searches of company or in-house databases (including post-marketing surveillance reports) are acceptable, provided that they are identified as such. If possible, these searches should be stratified according to patient groups such as age and ethnicity.
12. The relative strength of clinical publications is generally in this order:
 - 12.1 Controlled clinical trials.
 - 12.2 Cohort/case-control studies.
 - 12.3 Uncontrolled studies.
 - 12.4 Case descriptions.
 - 12.5 Expert opinion.
13. Clinical studies published according to accepted protocol guidelines (for example Consort, Cochrane and others) generally carry more weight than studies that fail to report all pertinent data (e.g. safety data). Although a good reporting format facilitates evaluation, it is not in itself a criterion for the quality of the data set.
14. Papers from peer-reviewed journals carry more weight in the regulatory decision than papers from non-peer-reviewed publications.
15. Clinical studies carry more weight if they meet current standards of design and control, including compliance with a code of good clinical practice.



16. Reports of preclinical studies carry more weight in the regulatory decision if they:
 - 16.1. Include individual animal reports.
 - 16.2. Are reported according to internationally accepted guidelines.
 - 16.3. Are in compliance with the principles of good laboratory practice (GLP). See, for example WHO's *Handbook: Good laboratory practice* (2001).



Appendix 3

Pharmaceutical development (or preformulation) studies

Pharmaceutical development studies identify, document and control those attributes of the ingredients of the formulation and critical parameters of the manufacturing process that influence final product quality. If a manufacturer fails to conduct such studies or to obtain the information from the literature, and consequently develops a poor formulation, there is a temptation to continue with that formulation and method of manufacture rather than lose time and possibly competitiveness. Consequently it is in the interests of product quality that a drug regulatory authority seek the results of preformulation studies with applications to register new products.

Consequently a section on pharmaceutical development is an integral part of an application for marketing authorization. A thorough literature search may provide some of the information and commonly this part of a submission will be a hybrid of new data and reports from the literature.

Systematic studies should be conducted on APIs, on pilot formulations of the finished product and on manufacturing processes. For each API, there should be studies of:

- physicochemical properties;
- chemical and physicochemical stability, including stability under stress conditions (see below);
- impurity profile and batch-to-batch variation thereof;
- chemical and physicochemical compatibility of the API with possible excipients under stress conditions;
- the manufacturing process, and definition and control of its critical parameters;
- dissolution rate of the API in pilot formulations; and
- stability of pilot formulations under accelerated stability testing conditions and under the maximum recommended conditions of storage.

With this information there is a greater likelihood that the finished product will:

- meet specifications, including for assay, impurities and dissolution rate;
- be of consistent quality within and between batches;
- have optimum chemical and physicochemical stability;



- be manufacturable for the minimum cost that is consistent with acceptable quality; and
- be found acceptable in stability and bioequivalence studies.

A typical set of studies of the degradation paths of an active pharmaceutical ingredient

Degradation paths for APIs are typically reactions of hydrolysis, oxidation, photolysis and/or acid–base chemistry. To force these reactions, the API is placed in solution under stress conditions such as those shown in Table A.1 below. For well-established drugs, some of this information may already be available in the literature.

The objective is not to completely degrade the API, but to cause degradation to occur to a small extent, typically 10–30% loss of active by assay when compared with non-degraded API. This target is chosen so that some degradation occurs, but not enough to generate secondary products. For this reason, the conditions and duration may need to be varied when the API is especially susceptible to a particular stress factor.

If no degradation products are detectable after 10 days under the conditions in Table A.1, the API is considered stable. If degradation is detectable, but its extent is significantly less than 10%, then the stress factors, stress conditions or duration may need to be increased to identify and monitor degradation products.

Table A.1
Typical stress conditions in preformulation stability studies

Stress factor	Conditions	Concentration of API ^a	Time
Heat	60°C	1:1 with diluent ^b	1–10 days
Humidity	75% relative humidity or greater	Solid state	1–10 days
Acid	0.1 N hydrochloric acid	2:1 in 0.1 N hydrochloric acid	1–10 days
Base	0.1 N sodium hydroxide	2:1 in 0.1 N sodium hydroxide	1–10 days
Oxidation	3% hydrogen peroxide	1:1 in 3% hydrogen peroxide	1–3 hours
Photolysis	Metal halide, mercury, xenon or ultraviolet-B fluorescent lamp	1:1 with diluent ^b	1–10 days
Metal ions (optional)	0.05 M Fe ₂₊ or Cu ₂₊	1:1 with solution of metal ions	1–10 days

^a When testing degradability of APIs in combination, the APIs should be in the same ratio as in the FDC-FPP.

^b In each case, the diluent is either an excipient or all excipients in the formulation in the same ratios as in the formulation. Other ratios of diluent may also be appropriate, for example the approximate ratio in which the drug and excipients will be used in a formulation.





Solid-state degradation can also be considered. For APIs, exposing a solid sample to elevated temperatures such as 60–120 °C, or 5–10 °C below the melting point, can generate a different degradation profile. This approach usually generates degradation products that can be used as a worst case to assess the performance of the analytical method.



Appendix 4

Superiority, equivalence and non-inferiority clinical trials

Definitions

Equivalence trial

A trial that has the primary objective of testing whether the difference in quantitative response to two or more treatments is clinically unimportant. This is usually demonstrated by showing that the true treatment difference is likely to lie between a lower and an upper equivalence margin of clinically acceptable differences.

Non-inferiority trial

A trial that has the primary objective of testing whether the response to the investigational product is clinically inferior to that of a comparator product. The comparator may be an active or a placebo control. The aim is to test whether the new product is inferior to the comparator by more than a specified small margin (the non-inferiority margin).

Superiority trial

A trial that has the primary objective of testing whether the response to the investigational product is superior to that to a comparator. The comparator agent may be an active or a placebo control.

Points to note

1. Protocols should clearly state whether the demonstration of non-inferiority, equivalence or superiority is the objective of the study.
2. If superiority is demonstrated in a non-inferiority trial, the results can generally be considered to show superiority, but the analysis should be based mainly on the intention-to-treat analysis.
3. If superiority cannot be demonstrated in a superiority trial, non-inferiority can generally not be claimed unless the lower margin of the confidence interval for the treatment difference is above a level that had been defined in the planning of the study. If non-inferiority is an acceptable outcome, it is, therefore, prudent to specify a non-inferiority margin in the protocol before the study is conducted. A non-inferiority margin may not be specified after the trial has commenced.

E



4. In a non-inferiority trial, the intention-to-treat analysis and the per-protocol analysis have equal importance for interpretation of the results.
5. In therapeutic areas where there is a problem of lack of assay sensitivity (e.g. allergy or depression), a non-inferiority trial that does not also include a placebo arm is not possible.
6. If the comparator has only modest efficacy, it may not be possible to define a non-inferiority margin. Therefore, if a placebo arm is not permissible, the only other alternative for demonstrating efficacy is a superiority trial.

Further reading

See these CHMP guidelines.

Points to consider on switching between superiority and non-inferiority. CPMP/EWP/482/99.

DRAFT Points to consider on the choice of non-inferiority margins. EMEA, CPMP/EWP/2158/99.

DRAFT Statistical principles for clinical trials. EMEA, CPMP/ICH/363/99.