The International Pharmacopoeia

Fourth Edition

First Supplement

World Health Organization

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The World Health Organization was established in 1948 as a specialized agency of the United Nations serving as the directing and coordinating authority for international health matters and public health. One of WHO's constitutional functions is to provide objective and reliable information and advice in the field of human health, a responsibility that it fulfils in part through its extensive programme of publications. The Organization seeks through its publications to support national health strategies and address the most pressing public health concerns of populations around the world. To respond to the needs of Member States at all levels of development, WHO publishes practical manuals, handbooks and training material for specific categories of health workers; internationally applicable guidelines and standards; reviews and analyses of health policies, programmes and research; and state-of-the-art consensus reports that offer technical advice and recommendations for decision-makers. These books are closely tied to the Organization's priority activities, encompassing disease prevention and control, the development of equitable health systems based on primary health care, and health promotion for individuals and communities. Progress towards better health for all also demands the global dissemination and exchange of information that draws on the knowledge and experience of all WHO's Member countries and the collaboration of world leaders in public health and the biomedical sciences. To ensure the widest possible availability of authoritative information and guidance on health matters, WHO secures the broad international distribution of its publications and encourages their translation and adaptation. By helping to promote and protect health and prevent and control disease throughout the world, WHO's books contribute to achieving the Organization's principal objective — the attainment by all people of the highest possible level of health.

SELECTED WHO PUBLICATIONS OF RELATED INTEREST

The International Pharmacopoeia, fourth edition.
Volume 1: general notices; monographs for pharmaceutical substances (A–O)
Volume 2: monographs for pharmaceutical substances (P–Z); monographs for dosage forms and radiopharmaceutical preparations; methods of analysis; reagents. 2006 (1500 pages), also available in CD-ROM format and online

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Also available on: WHO training modules on GMP. A resource and study pack for trainers, 2007 (CD-ROM).

WHO Expert Committee on Specifications for Pharmaceutical Preparations.
Forty-second report.
WHO Technical Report Series, No. 948, 2008 (138 pages)

International nonproprietary names (INN) for pharmaceutical substances. Cumulative list no. 12.
2007 (available in CD-ROM format only)

The use of essential medicines.
Report of the WHO Expert Committee (including the 15th Model List of Essential Medicines).
WHO Technical Report Series, No. 946, 2007 (163 pages)
First WHO Model List of Essential Medicines for Children (http://www.who.int/childmedicines/en/index.html)

WHO Expert Committee on Biological Standardization.
Fifty-fifth report.
WHO Technical Report Series, No. 941, 2008 (290 pages) (in press)

Further information on these and other WHO publications can be obtained from
WHO Press,
World Health Organization, 1211 Geneva 27, Switzerland.

Contents

Preface

This is the first supplement to the fourth edition of *The International Pharmacopoeia*. The fourth edition thus comprises the two main volumes published in 2006 and this supplement.

The International Pharmacopoeia[1] (Ph. Int.) comprises a collection of recommended procedures for analysis and specifications for the determination of pharmaceutical substances (active ingredients and excipients) and dosage forms that is intended to serve as source material for reference or adaptation by any WHO Member State wishing to establish pharmaceutical requirements. The pharmacopoeia, or any part of it, shall have legal status, whenever a national or regional authority expressly introduces it into appropriate legislation. Further explanation of the role of *The International Pharmacopoeia* is provided in the paragraphs entitled "Scope and function" at the end of the Preface in Volume 1.

This supplement to the fourth edition is published simultaneously both in print and electronically by means of incorporation into a replacement CD-ROM and on-line[2]. This provides the user of *The International Pharmacopoeia* with a choice of form in which to consult the publication depending on the circumstances and the type of enquiry.

New monographs. New monographs are included for five antiretroviral substances, for sixteen antiretroviral dosage forms including two fixed-dose combination preparations, for one antimalarial dosage form and for six antituberculosis dosage forms including 2-, 3-, and 4-component fixed-dose preparations. Such specifications support the joint UNICEF-WHO-UN Prequalification project[3], managed by WHO. In developing these monographs WHO has worked closely with manufacturers, national authorities and

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[1] Published in accordance with World Health Assembly resolution WHA3.10, *WHO Handbook of Resolutions and Decisions*, Vol. 1, 1977, p. 127.

[2] See link to "International Pharmacopoeia 4th edition" on Medicines web site (htpp://www.who.int/medicines/publications/pharmacopoeia).

[3] For current project information, consult the prequalification web site (http://mednet3.who.int/prequal/).

national quality control laboratories[4]. A list of new monographs is provided as an Annex to this Preface.

New general monographs for Liquid preparations for oral use and Oral powders are included to support the relevant specific dosage-form monographs. The monograph for Liquid preparations for oral use highlights that such preparations are often the dosage form of choice for paediatric use. This general monograph also includes a statement on Safety concerns in the section on Manufacture. This draws attention to the importance of ensuring the quality of starting materials. Failure to ensure that starting materials are of the required quality can have very serious consequences. The most documented incidents involve liquid preparations for oral use manufactured with excipients such as glycerol and propylene glycol that have been contaminated, adulterated or mixed up with diethylene glycol. Such incidents have been responsible for hundreds of deaths (through kidney failure) throughout the world.

As noted above, many of the new monographs introduced into *The International Pharmacopoeia* by means of this supplement are for specific dosage forms. An important function of these monographs is to provide an independent analyst with some means of demonstrating the quality of a product in relation to impurities. Guidance notes concerning the application of tests for related substances to dosage form monographs have been published[5] and are also provided within the section on Supplementary information. Developing suitable pharmacopoeial tests, especially for preparations containing several active ingredients or with complex formulations, can present challenges. This aspect of dosage form monographs continues to evolve and an approach to dealing with complex liquid formulations is illustrated by the test in the monograph for Zidovudine oral liquid.

Where a dosage form that is the subject of a new monograph in this Supplement is included in the first edition of the WHO Model list of medicines for children, an indication of the strength or strengths given in this new Model list is provided in the monograph. Such information is provided, where relevant, under the heading "Additional information" following the statement concerning the strength(s) given in the main Model list[6].

Revision. In parallel with the development of the new monograph for Doxycycline capsules, the published monographs for Doxycycline hyclate and Doxycycline tablets have been revised and replacement texts are included in this supplement.

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[4] For information on monograph development, consult the Medicines web site (http://www.who.int/medicines/publications/pharmacopoeia/mono_dev).

[5] Annex 1 to 41st Report of Expert Committee on Specifications for Pharmaceutical Preparations, WHO Technical Report Series, No. 943, 2007.

[6] For information on the current Model lists, consult the essential medicines web site (http://www.who.int/medicines/publications/essentialmedicines/en/index.html).

A requirement for dissolution has been included in the above monographs for Doxycycline capsules and tablets and added to a number of other monographs for tablets and capsules containing highly soluble drug substances, for example, Chloroquine sulfate tablets and Isoniazid tablets. A standardized dissolution test has been included in these monographs as an alternative to disintegration since, for pharmacopoeial purposes, the disintegration test is considered to be generally satisfactory for such products.

Revision of storage statements in monographs for substances and dosage forms has been carried out in order to remove references to in "in a cool place" or "at a temperature not exceeding 15°C", wherever possible. This has been done in recognition of the impracticality of continuing to recommend a maximum storage temperature of 15°C. In the past 'a cool place' was a term used fairly widely in pharmacopoeias. A cool place was normally understood to mean a temperature below 15°C — typically, in temperate regions, the unheated larder/pantry in a house built before the mid-20th century. Once storage in a refrigerator provided a temperature range of 2° to 8°, a cool place was usually taken to correspond to a temperature range of 8° to 15°C. The revised statements either make no reference to a storage temperature thereby implying, in accordance with the General Notices, that storage at room temperature is suitable or, where necessary (for example, for Colecalciferol), specify a temperature between 2° to 8°C.

Methods of analysis. General methods of analysis that are commonly used in carrying out the tests and assays included in the monographs of *The International Pharmacopoeia* are described in the section on Methods of Analysis. As was noted in the Preface to the main volumes published in 2006, in some cases a specific cross-reference to the method required was provided within the monograph text. However, in other cases, where the relevant method could be inferred from the title of the test (for example, Specific optical rotation, Sulfated ash) no explicit cross-reference was given. It was noted that a statement had been added to the General notice on General requirements to assist in the correct interpretation of the monograph requirements, especially in those cases where there is no cross-reference. This statement emphasizes that, whether or not a specific cross-reference is included, the requirements of the monographs of *The International Pharmacopoeia* are to be interpreted in relation to the relevant method of analysis. In the interests of improved transparency, a specific cross-reference has been given within the monographs published in this supplement in all cases where a general method text is available. Such cross-references are usually in the form of the number of the method text given in parentheses, for example "(1.13)" for the method text for "Determination of pH".

Infrared Reference spectra. Many monographs in *The International Pharmacopoeia* include an identification test using infrared spectroscopy; these tests usually allow comparison either with a spectrum obtained from the ICRS

or with a reference spectrum. Until now, these spectra were held by the WHO Collaborating Centre in Sweden and the user of the pharmacopoeia, who wished to make use of a reference spectrum rather than prepare a spectrum using the ICRS, had to obtain the required infrared reference spectrum from the Collaborating Centre. To avoid any such inconvenience the majority of the infrared reference spectra required are now published within this supplement. The remainder are in preparation and will be published in a future supplement. Meanwhile, they will be placed on the WHO Medicines website as soon as they are available.

Chromatographic tests. In chromatographic tests included within the monographs of *The International Pharmacopoeia*, the type of chromatographic column, column packing or TLC plate to be used is stated but reference to commercial sources of these supports is not given. When a draft monograph is circulated for comment, the particular column that was used during the development of a liquid chromatographic test is provided for information (usually in a footnote to the text). This information is now provided on the WHO Medicines website to assist analysts with respect to choice of column for those monographs recently introduced into the Pharmacopoeia.

It is emphasized that this information is intended to indicate a commercially available material that has been found to be suitable but does not imply that a different but equivalent commercial brand may not be used. Whatever column is chosen, the analyst is responsible for ensuring that the chromatographic system achieves the desired separation as defined by the system suitability/validity requirements of the monograph.

Annex

New monographs

Pharmaceutical substances

- Abacavir sulfate
- Efavirenz
- Lamivudine
- Stavudine
- Zidovudine

Dosage forms

General monographs

- Liquid preparations for oral use
- Oral powders

Specific monographs

- Abacavir oral solution
- Abacavir sulfate tablets
- Didanosine oral powder

- Didanosine liquid for oral use, paediatric
- Didanosine tablets
- Doxycycline capsules
- Isoniazid and ethambutol hydrochloride tablets
- Lamivudine oral solution
- Lamivudine tablets
- Nelfinavir Mesilate oral powder
- Nelfinavir Mesilate tablets
- Rifampicin capsules
- Rifampicin tablets
- Rifampicin and isoniazid tablets
- Rifampicin, isoniazid and pyrizinamide tablets
- Rifampicin, isoniazid, pyrizinamide and ethambutol hydrochloride tablets
- Saquinavir mesilate capsules
- Stavudine capsules
- Zidovudine capsules
- Zidovudine oral solution
- Zidovudine intravenous infusion
- Zidovudine and Lamivudine tablets
- Zidovudine, Lamivudine and Abacavir tablets

History

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Fourth edition
Change the entry to:

Fourth edition
Volumes 1 and 2 of the fourth edition were published together in 2006. Volume 1 contains the General Notices and many of the monographs for pharmaceutical substances and Volume 2 contains the remaining monographs for pharmaceutical substances together with those for dosage forms and radiopharmaceutical preparations, the methods of analysis and the reagents section and index. The main volumes of this edition consolidated and updated the texts of the five separate volumes of the third edition and included new monographs for antiretroviral substances.

The first supplement, published in 2008 contains new and revised monographs for pharmaceutical substances and dosage forms together with additions and amendments to the texts published in Volumes 1 and 2. As with the main volumes, the first supplement is published simultaneously in print, as a CD-ROM and online. The replacement CD-ROM contains the complete text of the current fourth edition comprising Volumes 1 and 2 as amended and augmented by the text of the first supplement.

The new monographs published in the first supplement include additional antiretroviral substances, antiretroviral dosage forms and antituberculosis dosage forms including 2-, 3-, and 4-component fixed-dose preparations.

Acknowledgements

The specifications published in the fourth edition, including the first supplement, were developed in collaboration with members of the WHO Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations, other specialists, and the WHO Collaborating Centres on quality control and quality assurance.

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The following specialists participated both in person and by correspondence in the preparation of this edition: Professor H.Y. Aboul-Enein, Bioanalytical and Drug Development Laboratory, Department of Biological and Medical Research, King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia; Professor I. Addae-Mensah, Department of Chemistry, University of Ghana, Legon, Ghana; Dr C. Ahlstich, Corporate Department, Drug Regulatory Affairs, RCC Management, Regulatory Intelligence Office, Ingelheim, Germany; Mrs S. Ahmed Jaffar, Directorate General of Pharma-ceutical Affairs and Drugs Control, Ministry of Health, Muscat, Oman; Professor J.-M. Aiache, Laboratory of Biopharmacy, Faculty of Pharmacy, University of Clermont-Ferrand, Clermont-Ferrand, France; Dr K. Akalin, Ministry of Health, Ankara, Turkey; Professor P.I. Akubue, Department of Pharmacology and Toxicology, University of Nigeria, Nsukka, Lagos, Nigeria; Dr H. Ali, Novartis Pharma Ltd, Basel, Switzerland; Dr S.L. Ali, Bad Vilbel, Germany; Professor H. Altorfer, Jona, Switzerland; Dr N. Anand, Lucknow, Uttar Pradesh, India; Dr P. Arends, Skagen Apotek, Skagen, Denmark; Dr A. Artiges, European Directorate for the Quality of Medicines and HealthCare, Council of Europe, Strasbourg, France; Dr K. Bailey, Bureau of Drug Research, Health and Welfare, Health Protection Branch, Health Canada, Ottawa, Ontario, Canada; Dr L. Bhattacharyya, Noncomplex Actives and Excipients, Department of Standards Development, United States Pharmacopeia, Rockville, MD, USA; Professor I. Bayer, Budapest, Hungary; Dr C. Becerril Martinez, Subdirección de Normalización y Farmacovigilancia, Mexico, DF, Mexico; Dr L. Bigger, Regulatory and Scientific Affairs, International Federation of Pharmaceutical Manufacturers Associations, Geneva, Switzerland; Mr J.Y. Binka, Accra, Ghana; Professor C.F. Bittencourt, Brazilian Pharmacopoeia Permanent

Revision Committee, Santa Maria RS, Brazil; Professor H. Blume, Bad Homburg, Germany; Dr Y. Boer, Laboratory of the Dutch Pharmaceutical Society, The Hague, Netherlands; Mr P.-A. Bonnet, Direction des Laboratoires et des Contrôles, Agence française de sécurité sanitaire des produits de santé, Montpellier-Vendargues Site, Vendargues, France; Dr L. Borka, Oslo, Norway; Dr R. Boudet-Dalbin, Paris, France; Professor D.D. Breimer, Center for Bio-Pharmaceutical Sciences, Sylvius Laboratories, Leiden, Netherlands; Dr Briskot, Bayer AG, Wuppertal, Germany; Mr W. Bukachi, International Affairs, United States Pharmacopeia, Rockville, MD, USA; Dr T. Burat, Drug and Cosmetics Research Department, Central Institute of Hygiene, Ankara, Turkey; Dr M.N. Caetano Pisciottano, Department of Pharmacy, Federal University of Pernambuco, Recife, Brazil; Dr D.H. Calam, Pewsey, Wiltshire, England; Dr R. Carter, Knoll AG, Basel, Switzerland; Dr B. Chapart, Global Analytical Development, Sanofi-Aventis Pharma, Anthony, France; Dr E. Charton, European Directorate for the Quality of Medicines and HealthCare, Council of Europe, Strasbourg, France; Ms Cheah Nuan Ping, Quality Assurance, Centre for Analytical Science, Health Sciences Authority, Singapore; Professor Y. Cherrah, Laboratoire National de Contrôle des Médicaments, Rabat, Morocco; Dr G.P. Chiu, The Upjohn Company, Kalamazoo, MI, USA; Dr Y. Chopra, International Regulatory Affairs, Ranbaxy Laboratories Limited, Mumbai, India; Dr J.A. Clements, Scientific and Technical Services Division, Royal Pharmaceutical Society of Great Britain, London, England; Mrs E.M. Cortes Montejano, Agencia Española de Medicamentos y Productos Sanitarios, Madrid, Spain; Professor P.F. Coville, School of Pharmacy, University of Otago, Dunedin, New Zealand; Dr R. Cox, Corporate Compendia and Standards, Abbott Laboratories, Abbott Park, Illinois, USA; Dr J.C. Craft, Member of International Health Expert Committee, United States Pharmacopeia, Rockville, MD, USA; Dr P. Christen, Pharmaceutical Analytical Chemistry Laboratory, Faculty of Sciences, Pharmacy Section, University of Geneva, Geneva, Switzerland; Dr B. Davani, Department of Standards Development, United States Pharmacopeia, Rockville, MD, USA; Professor T.G. Dekker, Research Institute for Industrial Pharmacy, North-West University, Potchefstroom, South Africa; Dr E. Demant, Pharmaceutical Division, Bayer, West Haven, CT, USA; Mrs Ding Lixia, National Institute for the Control of Pharmaceutical and Biological Products, Beijing, People's Republic of China; Dr P. Dikshit, Member of International Health Expert Committee, United States Pharmacopeia, Rockville, MD, USA; Dr A. Dobrotvorsky, Ministry of Health and Medical Industry, State Pharmacopoeia Committee, Moscow, Russian Federation; Professor E. Doelker, Department of Pharmaceutics, University of Geneva, Geneva, Switzerland; Dr Doll, Aventis Pharma Gmbh, Frankfurt am Main, Germany; Professor J.B. Dressman, Institute for Pharmaceutical Technology, Johann Wolfgang Goethe University, Frankfurt am Main, Germany; Dr P.O. Emafo, Benin City, Nigeria; Dr R.R. Engle, Fort Myers, FL,

USA; Dr E. Ehrin, Central Laboratory, Apotek AB, Kungens Kurva, Sweden; Dr K. Florey, Princeton, NJ, USA; Dr H. Fukuda, Society of Japanese Pharmacopoeia, Tokyo, Japan; Professor D. Ganderton, Cheriton Bishop, England; Mr C. Ghilardi, Novartis Pharma Ltd, Basel, Switzerland; Ms E. Gomez, Quality Assurance, Phibro Animal Health Corporation, Ridgefield Park, NJ, USA; Dr K. Goode, GlaxoSmithKline, Ware, Hertfordshire, England; Dr L.T. Grady, Drug Standards Division, United States Pharmacopeia, Rockville, MD, USA; Dr S.A. Hanna, Bristol-Myers Squibb, New Brunswick, NJ, USA; Dr H. Hauth, Novartis Pharma Ltd, Basel, Switzerland; Dr P. Hayes, School of Pharmacy, University of Otago, Dunedin, New Zealand; Dr W. Hecker, Novartis Pharma Ltd, Basel, Switzerland; Dr H. Heimbach, Bayer AG, Wuppertal, Germany; Mr J.-P. Helenport, Rhône-Poulenc Rorer Doma, Antony Cedex, France; Dr M. Hessel, Messer Griesheim GmbH, Duisburg, Germany; Mr A. Holbrook, Zeneca Pharmaceuticals, Macclesfield, Cheshire, England; Professor J. Hoogmartens, Laboratory for Pharmaceutical Chemistry and Drug Analysis, Leuven, Belgium; Mr R.K. Howard, Therapeutic Goods Administration Laboratories, Department of Community Services and Health, Woden, ACT, Australia; Dr Hyung Kook Kim, Division of Drug Standardization, National Institute of Health, Seoul, Republic of Korea; Dr R. Ilyas, National Agency of Drug and Food Control, Jakarta, Indonesia; Dr InKyu Kim, Korean Food and Drug Administration, Seoul, Republic of Korea; Professor R. Jachowicz, Department of Pharmaceutical Technology and Biopharmaceutics, Jagiellonian University, Krakow, Poland; Ms V. Jerd-Amphai, Quality Assurance Department, The Government Pharmaceutical Organization, Bangkok, Thailand; Professor Jin Shaohong, National Institute for the Control of Pharmaceutical and Biological Products, Ministry of Health, Beijing, People's Republic of China; Dr P. Kashemsant, Department of Medical Sciences, Ministry of Public Health, Nonthaburi, Thailand; Dr A. Kaukinen, Helsinki, Finland; Dr E. Keller, Novartis Pharma Ltd, Basel, Switzerland; Dr L. Kelly, Therapeutic Goods Administration Laboratories, Department of Community Services and Health, Woden, ACT, Australia; Mr I. Keuser, Novartis Pharma Ltd, Basel, Switzerland; Dr J. Kincaid, Manufacturing Division, Merck, Westpoint, PA, USA; Mr R.H. King, Division of Standards Development, United States Pharmacopeia, Rockville, MD, USA; Mr M. Krummen, Mepha AG, Aesch, Basel, Switzerland; Dr P. Kucera, Warwick, NY, USA; Dr C.S. Kumkumian, Center for Drug Evaluation and Research, Food and Drug Administration, Rockville, MD, USA; Dr S. Kuttatharmmakul, Inspection Control Section, The Government Pharmaceutical Organization, Bangkok, Thailand; Dr T. Layloff, Quality Assurance, Supply Chain Management System, Arlington, VA, USA; Mr M.A. Lee, Analytical Sciences Development, SmithKline Beecham Pharmaceuticals, Worthing, England; Dr P. Lim, Palo Alto, CA, USA; Professor J. Lípták, Budapest, Hungary; Dr H. Lomská, Head, Pharmacopoeia Department, State Institute for Drug Control,

Czech Republic; Ms Low Min Yong, Pharmaceutical Laboratory, Centre for Analytical Science, Health Sciences Authority, Singapore; Dr H. Ludwig, Novartis Pharma Ltd, Basel, Switzerland; Dr C.B. Lugt, Artecef BV, Maarssen, Netherlands; Dr G. Maillard, The French Pharmaceutical Manufacturers Association, Paris, France; Dr M.K. Majumdar, Jadavpur, Calcutta, India; Dr G. Maldener, Bayer AG, Wuppertal, Germany; Associate Professor L. Martinec, State Institute for Control of Drugs, Bratislava, Slovakia; Dr I.N. Matondo, Scientific Liaison Office, Harare, Zimbabwe; Mr F. Maxl, Novartis Pharma Ltd, Basel, Switzerland; Dr I.J. McGilveray, Biopharmaceutics Section, Health Protection Branch, Ottawa, Ontario, Canada; Dr J.H. McB. Miller, European Directorate for the Quality of Medicines and HealthCare, Council of Europe, Strasbourg, France; Dr S. Messner, Corporate Compendial Liaison, Abbott Laboratories, Abbott Park, Illinois, USA; Dr N. Miyata, Faculty of Pharmaceutical Sciences and Chemistry, Graduate School, Nagoya City University, Nagoya, Japan; Mr M.G. Moester, Inspectorate of Health Care, Ministry of Health, Welfare and Sport, Rijswijk, Netherlands; Dr H. Möller, Aventis Pharma GmbH, Frankfurt am Main, Germany; Mr G. Mondain-Monval, Air Liquide Santé France, Paris, France; Mrs Z.J. Montbrun de Reinfeld, National Institute of Hygiene Rafael Rangel, Caracas, Venezuela; Mrs A.B. Moraes da Silva, Escola Nacional de Saúde Publica-Fiocruz, Manguinhos, Rio de Janeiro, Brazil; Dr K. Morimoto, Office of Review Management, Review Planning Division, Pharmaceuticals and Medical Devices Agency, Tokyo, Japan; Dr O. Morin, Director, Regulatory and Scientific Affairs, International Federation of Pharmaceutical Manufacturers Associations, Geneva, Switzerland; Dr H. Müller, Messer Griesheim GmbH, Duisburg, Germany; Mr R.D. Munro, Therapeutic Goods Administration, Woden, ACT, Australia; Dr M. Negwer, Berlin, Germany; Dr Ng Tju Lik, Singapore; Dr J.D. Nicholson, Medicines Testing Laboratory, Department of Pharmaceutical Sciences, Royal Pharmaceutical Society of Great Britain, Edinburgh, Scotland; Dr E. Njau, Arusha, United Republic of Tanzania; Professor L. Ogunlana, Lanpharm Laboratories, Lagos, Nigeria; Professor A.A. Olaniyi, Department of Pharmaceutical Chemistry, College of Medicine, University of Ibadan, Ibadan, Nigeria; Professor T.L. Paál, National Institute of Pharmacy, Budapest, Hungary; Dr P.R. Pabrai, New Delhi, India; Dr H. Partenheimer, Novartis Pharma Ltd, Basel, Switzerland; Professor X. Perlia, Pharmaceutical Institute, Swiss Federal Institute of Technology, Zurich, Switzerland; Dr Pham Hoang Ngoc, National Center for Scientific Research, Institute of Chemistry, Hanoi, Viet Nam; Dr J. Pogány, Budapest, Hungary; Ms A. Poompanich, Division of Drug Analysis, Department of Medical Sciences, Ministry of Public Health, Nonthaburi, Thailand; Dr J. Posti, Associate Director and Regulatory Affairs Pharmaceutical Adviser, Schering Oy, Helsinki, Finland; Professor M. Rafiee-Tehrani, Industrial Pharmacy Research Laboratory, Tehran University of Medical Sciences, Tehran, Islamic

Republic of Iran; Dr S. Reddy, Head, Analytical Services Department, Strides Arcolab Ltd, Bangalore, India; Dr M. Riklin Lauper, F. Hoffmann-La Roche Ltd, Basel, Switzerland; Dr J.-L. Robert, National Health Laboratory, Luxembourg; Dr E.A. Roberts, GlaxoSmithKline, Ware, Hertfordshire, England; Dr S. Roenninger, F. Hoffmann-La Roche Ltd, Basel, Switzerland; Dr L. M. Santos, Scientific Liaison, International Health Expert Committee, United States Pharmacopeia, Rockville, MD, USA; Dr K. Satiadarma, Bandung, Indonesia; Dr M. Scheiwe, Mepha AG, Aesch, Basel, Switzerland; Dr B. Schmauser, Federal Institute for Drugs and Medical Devices, Department of Pharmaceutical Quality, Bonn, Germany; Dr P.J. Schorn, Offenburg, Germany; Dr A. Schuchmann da Silva, Quality Assurance, Microbiologica Química e Farmacêutica, Rio de Janeiro, Brazil; Dr G. Schwartzman, Sarasota, FL, USA; Dr W. Sherwin, Chief Chemist, Therapeutic Goods Administration Laboratories, Canberra, Australia; Dr P.G. Shrotriya, New Mumbai, India; Dr P. Sidhu, Therapeutic Goods Administration Laboratories, Department of Community Services and Health, Woden, ACT, Australia; Dr G. N. Singh, Indian Pharma-copoeia Commission, Central Indian Pharmacopoeia Laboratory, Ghaziabad, India; Dr S. Siiskonen, International Pharmaceutical Federation, The Hague, Netherlands; Dr K. Sinivuo, National Agency for Medicines, Helsinki, Finland; Dr C.J.P. Siregar, National Quality Control Laboratory of Drug and Food, Ministry of Health, Jakarta, Indonesia; Dr N. Sittichai, Bureau of Drug and Narcotic, Department of Medical Sciences, Nonthaburi, Thailand; Dr L. Slamet, Deputy for Therapeutic Product, Narcotic, Psychotropic and Addictive Substance Control, National Agency of Drug and Food Control, Jakarta, Indonesia; Dr R. Soliman, Alexandria, Egypt; Dr J.-M. Spieser, European Directorate for the Quality of Medicines and HealthCare, Council of Europe, Strasbourg, France; Dr H.D. Spitz, International Product Support, The R.W. Johnson Pharmaceutical Research Institute, Raritan, NJ, USA; Dr L. Stefanini-Orešić, Croatian Institute for Medicines Control, Zagreb, Croatia; Dr A. Sulistiowati, National Quality Control Laboratory of Drug and Food, Ministry of Health, Jakarta, Indonesia; Dr S. Sur, Director, Research and Development, Arterium Corporation, Kiev, Ukraine; Dr Y. Takeda, Society of Japanese Pharmacopoeia, Tokyo, Japan; Professor Tang Lin-hua, Institute of Parasitic Diseases, Chinese Academy of Preventive Medicine, Shanghai, People's Republic of China; Dr D. Teitz, Bristol-Myers Squibb Company, New Brunswick, NJ, USA; Dr B. B. Thapa, Chief Drug Administrator, Department of Drug Administration, Ministry of Health and Population, Kathmandu, Nepal; Professor K. Thoma, University of Munich, Munich, Germany; Dr K. M. Thomas, APL Research Centre, Hyderabad, India; Dr H.G. Tölle, F. Hoffman-La Roche Ltd, Basel, Switzerland; Dr H. Tomankova, International Pharmacopoeia Department, State Institute for Drug Control, Prague, Czech Republic; Dr I. Török, Quality Control Division, National Institute of Pharmacy, Budapest, Hungary; Dr R. Torano, Pharmacopoeia Intelligence and Advocacy