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WHO Expert Committee on Specifications for Pharmaceutical Preparations

Fifty-seventh report

World Health Organization

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Dr S. Azatyan, Team Lead, Regulatory Convergence and Networks; Dr R. Balocco, Unit Head, International Nonproprietary Names and Classification of Medical Products; Dr D. Catsoulacos, Inspection Services; Mr M. Chafai, Laboratory Networks and Services; Mr A. Chemwolo, Medicines Assessment; Dr X. Chen, Inspection Services; Mr R. Corrin, Consultant; Ms S. Croft, Inspection Services; Professor T. Dekker, Consultant; Dr S. Estevão Cordeiro, Norms and Standards for Pharmaceuticals; Dr A. Fake, Medicines Assessment; Dr I. Fradi, Tunisia Country Office; Mr M. Freitas, WHO Regional Office for the Americas; Ms A. Geyer, Inspection Services; Ms N. Guerra Simões, Laboratory Networks and Services; Dr L. Gwaza, Secretary of the Expert Committee, Team Lead, Norms and Standards for Pharmaceuticals; Mr N. Hudroge, Incidents and Substandard/Falsified Medical Products; Dr B. Huttner, Team Lead, Essential Medicines; Dr M. Ismail, Team Lead, Medicines Supply Health Infrastructure; Ms S. Jones, Norms and Standards for Pharmaceuticals; Ms B. Kibret, Norms and Standards for Pharmaceuticals; Dr I. Knezevic, Team Lead, Norms and Standards for Biological Products; Mr R. Kuwana, Team Lead, Technnical Officer, Incidents and Substandard/Falsified Medical Products; Dr D. Lei, Norms and Standards for Biological Products; Dr S. Lewis, Consultant; Ms H. Martin-Ballestero, Medicines Assessment; Ms L. Megias Lastra, Incidents and Substandard/Falsified Medical Products; Mr D. Mubangizi, Unit Head, Prequalification; Dr Y. Nakatani, Assistant Director-General, Access to Medicines and Health Products; Mr L. Nzumbu, Medicines Assessment; Dr C. Ondari, Director, Health Product Policy and Standards; Dr D. Pirgari, WHO Regional Office for Europe; Mr S. Pujari, Be Healthy, Be Mobile; Dr M. Refaat, Regulatory System Strengthening; Dr A. Romeo, International Nonproprietary Names and Classification of Medical Products; Mr V. Sachdeva, Inspection Services; Ms A. Sands, Incidents and Substandard/Falsified Medical Products; Dr H. Schmidt, Norms and Standards for Pharmaceuticals; Dr M. Shridhar, WHO Regional Office for South-East Asia; Mr H. Sillo, Unit Head, Regulation and Safety; Dr M. Stahl, Medicines Assessment; Mr P. Steyn, Contraception and Fertility Care; Mr F. Takanashi, Pharmacovigilance; Mr D. Thela, WHO Regional Office for Africa; Ms L.A. Velez Ruiz Gaitan, Health Care Readiness; Mr W.Z. Worku, Medicines Assessment; Ms H. Yin, Medicines Assessment.

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Mr H. Abboud, International University of Science and Technology, Damascus, Syrian Arab Republic; Dr M. Abdallah, Head of Central Administration of Drug Control, Egyptian Drug Authority, Cairo, Egypt; Dr S. Almeling, European Directorate for the Quality of Medicines and HealthCare, Council of Europe, Strasbourg, France; Dr N. Al Saqer, Saudi Food and Drugs Administration, Saudi Arabia; Ms S. Anwar, Ministry of Health, Malaysia; Ms M.I. Assalone, Technical Secretariat, Farmacopoea Argentina, Administración Nacional de Medicamentos Alimentos y Tecnología Médica, Buenos Aires, Argentina; Ms H. Bahaa, Egyptian Drugs Authority, Chair of the GMP Subcommittee on Vaccines, African Medicines Regulatory Harmonisation Initiative, African Union Development Agency, Cairo, Egypt; Ms H. Baião, Coordinator, Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme, Geneva, Switzerland; Dr J. Bennett, Therapeutic Goods Administration, Australian Government Department of Health, Chemistry Section/ Laboratories Branch, Woden ACT, Australia; Professor M.D.V. Bermejo Sanz, Universidad Miguel Hernández, Valencia, Spain; Ms J. Bernat, Director, Scientific & Regulatory Affairs, International Federation of Pharmaceutical Manufacturers and Associations, Geneva, Switzerland; Dr R. Bose, Deputy Drugs Controller, Ministry of Health & Family Welfare, Government of India, FDA Bhavan, New Delhi, India; Mr Y. Cao, Deputy Director of the 4th Inspection Division Centre for Food and Drug Inspection, Department of Science and Technology and International Cooperation of NMPA, Xicheng, Beijing, China; Mr N. Cappuccino, Chair of the Science Committee, International Generic and Biosimilar Medicines Association, New Jersey, United States of America; Ms S. Cloëz, Specialist, Pharmaceutical Products Quality Assurance, Geneva, Switzerland; Mr I. Colmagne-Poulard, Head of International Global Regulatory Affairs & Scientific Policy, Merck, Eysins, Switzerland; Mr R. Conocchia, GMP Inspector, European Medicines Agency, Netherlands (Kingdom of the); Mr L. Corbett, Ex Pharmaceutical Inspectors Consortium Ltd, Co. Durham, United Kingdom of Great Britain and Northern Ireland; Ms H. Corns, Head of BP and Labs Team 1, British Pharmacopoeia Commission, Medicines and Healthcare Products Regulatory Agency, London, United Kingdom of Great Britain and Northern Ireland; Ms T. Corrêa Rocha, Coordinator, Farmacopéia Brasileira, Agência Nacional de Vigilância Sanitária, Brasília, Brazil; Mr P. Crowley, Head of BP and Labs, British Pharmacopoeia Commission, Medicines and Healthcare Products Regulatory Agency, London, United Kingdom of Great Britain and Northern Ireland; Ms C. De Angelis, Technical Secretariat, Farmacopea Argentina, Administración Nacional de Medicamentos Alimentos y Tecnología Médica, Buenos Aires, Argentina; Dr A. De Negri Filho, Advisor on Health Services and Systems, Pan American Health Organization/World Health Organization, Mexico City, Mexico; Dr M.A. Desouky, Senior Inspector Pharmacist and Quality Coordinator, Biological Products Inspectorate, Central Administration of Pharmaceutical Affairs, Ministry of Health, Cairo, Egypt; Dr P. Doerr, Director, European Directorate of Quality of Medicines & HealthCare, Strasbourg, France; Mr E. Elias, Government & Regulatory Affairs Director, Latin America, United States Pharmacopeia, United States of America; Mr J.C. Gallegos Ortega, Manager of Editions and Publications,

Mexican Pharmacopoeia, Comisión Permanente de la Farmacopea de los Estados Unidos Mexicanos, Mexico City, Mexico; Dr A. García Arieta, Agencia Española De Medicamentos y Productos Sanitarios, Madrid, Spain; Ms A. Garnier, Scientific Program Manager, European Pharmacopoeia Department, European Directorate of Quality of Medicines & HealthCare, Strasbourg, France; Mr K. Ghasemi, Quality Assurance Specialist, Copenhagen, Denmark; Mr G. Giancaspro, Distinguished Scientific Fellow, Documentary Standards & Compendia Policy, United States Pharmacopeia, Rockville, United States of America; Ms L.S. Giorgis, Senior GMP Inspector, Acting Manager Assistant, Agência Nacional de Vigilância Sanitária, Brasília-DF, Brazil; Mr A.I. Haryani, Senior Food and Drug Control Officer, Indonesian Food and Drug Administration, Jakarta, Indonesia; Dr M. Hassan, Egyptian Pharmacopoeia Proofreading Group Team Leader, Egyptian Drug Authority, Cairo, Egypt; Ms M.d.C. Hernández Alonso, Manager of Committees Coordination, Mexican Pharmacopoeia, Comisión Permanente de la Farmacopea de los Estados Unidos Mexicanos, Mexico City, Mexico; Mr N. Hidayati, Senior Food and Drug Control Officer, Indonesian Food and Drugs Administration, Jakarta, Indonesia; Dr D. Hipolite, Head of the National Quality Control Laboratory at Tanzania Medicines and Medical Devices Authority, United Republic of Tanzania; Mr S. Hoare, Head of Standards and Regulatory Governance, Secretary & Scientific Director, British Pharmacopoeia Commission, London, United Kingdom of Great Britain and Northern Ireland; Dr F. Hoeper, Laboratory Manager, Institut für Pharmaceutische und Angewandte Analytik, Bremen, Germany; Mr G. Huerta, Scientific Affairs Manager, United States Pharmacopeia, United States of America; Mr A. Iarutkin, Deputy Head of the Institute of Pharmacopoeia and Standardisation, Federal State Budgetary Institution "Scientific Centre for Expert Evaluation of Medicinal Products" of the Ministry of Health of Russia, Moscow, Russian Federation; Dr P.M. Ikamati, Technical Specialist-Pharmaceuticals, Technical Unit/MNC, Supply Division, United Nations Children's Fund, Copenhagen, Denmark; Professor S. Jin, National Institutes for Food and Drug Control, Beijing, China; Dr U. Juárez Sevilla, Executive Sub-Director of Pharmacopoeia, Mexican Pharmacopoeia, Comisión Permanente de la Farmacopea de los Estados Unidos Mexicanos, Mexico City, Mexico; Professor E. Kaale, Professor in Quality Assurance and Regulatory Affairs Pharm R&D Lab, Head SoP-TDA NEPAD-RCORE Coordinator, School of Pharmacy, Muhimbili University of Health and Allied Sciences, Dar es Salaam, United Republic of Tanzania; Mr G. Kaddu, United States Pharmacopeia, Maryland, United States of America; Mr D.K. Karimovich, Chief Editor of the State Pharmacopoeia, State Institution Center for Pharmaceutical Products Safety, Medical Devices and Medical Equipment under Agency on Development of the Pharmaceutical Industry under Ministry of Health of the Republic of Uzbekistan, Tashkent, Uzbekistan; Ms R. Khomenko, State Expert, Center of the Ministry of Health of Ukraine, Ukraine; Mr J. Kim, Scientific Officer, Pharmaceutical Standardization Division, Research Division of National Institute of Food and Drug Safety Evaluation, Ministry of Food and Drug Safety, Chungbuk, Republic of Korea; Dr M. Kim, Scientific Officer, Drug Research Division, Research Division of National Institute of Food and Drug Safety Evaluation,

Ministry of Food and Drug Safety, Chungbuk, Republic of Korea; Dr A. Korde, Radiopharmaceutical Scientist, International Atomic Energy Agency, Vienna, Austria; Dr E. Kovaleva, Deputy Director, State Pharmacopoeia of the Russian Federation, Federal State Budgetary Institution of the Ministry of Health of the Russian Federation, Moscow, Russian Federation; Ms A. Kravchuk, Deputy Head, Section for Coordination of the Circulation of Medicines and Medical Devices, Eurasian Economic Commission, Moscow, Russian Federation; Dr R. Kumar, Principal Scientific Officer, Indian Pharmacopoeia Commission, Ministry of Health and Family Welfare, Ghaziabad, India; Ms Z. Kusynová, Lead for Policy, Practice and Compliance, International Pharmaceutical Federation, The Hague, Netherlands (Kingdom of the); Ms C. Laverty, Director, Communications and Policy, Global Self-Care Federation, Nyon, Switzerland; Ms R. Lima e Silva, Health Regulation Specialist, Farmacopéia Brasileira, Agência Nacional de Vigilância Sanitária, Brasília, Brazil; Ms M.J. Loera Rosales, Commissioner of Evidence and Risk Management of the Health Secretary of Mexico, COFEPRIS, Mexico City, Mexico; Dr A. López Sotelo, Permanent Commission of FEUM Member, Mexican Pharmacopoiea, Comisión Permanente de la Farmacopea de los Estados Unidos Mexicanos, Mexico City, Mexico; Ms T.T.H. Luc, Head of Vietnamese Pharmacopoeia and Formulary Center, National Institute of Drug Quality Control, Ministry of Health of Viet Nam, Hanoi, Viet Nam; Dr H. Maegawa, Division Director, Division of Pharmacopoeia and Standards for Drugs, Japanese Pharmacopoeia, National Institute of Health Sciences, Kanagawa, Japan; Dr O. Malik, Drug Regulatory Authority of Pakistan, Pakistan; Dr E. Mamdouh, Member of the General Administration of Public Relations and International Cooperation, Egyptian Drug Authority, Cairo, Egypt; Mr F. Masekela, Medicines Control Authority of Zimbabwe, Zimbabwe; Ms G. Matimba, Medicines Control Authority of Zimbabwe, Zimbabwe; Ms R. Matos Gonçalves, Specialist in Health Regulation and Surveillance, Farmacopéia Brasileira, Agência Nacional de Vigilância Sanitária, Brasília, Brazil; Mr J. Mehta, Deputy General Manager, Zydus Lifesciences Ltd., Gujarat, India; Mr F. Meyer, Senior Principal Scientist, NEXT Innovation & Tech Development, Global Pharmaceutical Commercialization Development, Rahway, United States of America; Professor J. Miller, Scotland, United Kingdom of Great Britain and Northern Ireland; Ms D. Monserrat Vázquez García, Internal Coordinator of Committees and International Affairs, Mexican Pharmacopoiea, Comisión Permanente de la Farmacopea de los Estados Unidos Mexicanos, Mexico City, Mexico; Dr K. Moore, Senior Manager, Pharmacopoieal Collaboration, Rockville MD, United States of America; Mr W. Muller, GMP Inspector, South African Health Products Regulatory Authority, Pretoria, South Africa; Mr I. Mwila, Laboratory Analyst, Zambia Medicines Regulatory Authority, Republic of Zambia; Dr M. Nagar, Vice President and Head, Technical Services & New Product Launch, Dr Reddy's Laboratories, Inc., United States of America; Professor G. Navas, Pharmaceutical Analysis, School of Pharmacy, University of Panama, Panama City, Panama; Ms N.K. Negmatilloevna, Chairwoman of the Pharmacopoeia Committee, State Institution Center for Pharmaceutical Products Safety, Medical Devices and Medical Equipment, Agency on Development of the Pharmaceutical Industry under Ministry of

Health of the Republic of Uzbekistan, Tashkent, Uzbekistan; Ms D. Nel, Medicines Control Officer, South African Health Products Regulatory Authority, Pretoria, South Africa; Ms M.A. Ojoo, Technical Manager, Medicines and Nutrition Center, United Nations Children's Fund, Copenhagen, Denmark; Mr S. Onen, National Drug Authority, Kampala, Uganda; Mr Z.A. Oskarkhodjaevich, Scientific Secretary of the Editorial Board of the State Pharmacopoeia, State Institution Center for Pharmaceutical Products Safety, Medical Devices and Medical Equipment, Agency on Development of the Pharmaceutical Industry under Ministry of Health of the Republic of Uzbekistan, Tashkent, Uzbekistan; Ms E. Pandova, Head of Unit, Department for Assessment of Drug Documentation; Agency of Medicines and Medical Devices, Skopje, North Macedonia; Dr S. Park, Director, Advanced Drug Quality Division, Drug Evaluation Department, National Institute of Food and Drug Safety Evaluation, Ministry of Food and Drug Safety, Republic of Korea; Professor G.M. Pauletti, University of Health Sciences & Pharmacy, St Louis, United States of America; Dr W. Potter, United Nations Population Fund, Copenhagen, Denmark; Dr S. Ramakrishnan, Dr Reddy's Laboratories, Inc, Telangana, India; Dr S. Rastogi, Scientific Assistant, Indian Pharmacopoeia Commission, Ministry of Health and Family Welfare, Government of India, Ghaziabad, India; Ms L. Rodriguez, Director, Regulatory Affairs, Policy and Innovation, Bayer U.S. LLC, United States of America; Mr P. Rolandi, Executive Director, Head of Department, Digital Integration & Predictive Technologies, Functional Digital Lead, Process Development, Amgen Massachusetts, United States of America; Ms N.K. Said-Akhmedovna, Leading Specialist of the Pharmacopoeia Committee, State Institution Center for Pharmaceutical Products Safety, Medical Devices and Medical Equipment, Agency on Development of the Pharmaceutical Industry under Ministry of Health of the Republic of Uzbekistan, Tashkent, Uzbekistan; Dr P. Saini, Senior Scientific Officer, Indian Pharmacopoeia Commission, Ministry of Health and Family Welfare, Ghaziabad, India; Dr Y. Saito, Deputy Director-General, Japanese Pharmacopoeia, National Institute of Health Sciences, Kanagawa, Japan; Dr L. Sallam, Egyptian Pharmacopoeia Preparation Group Team Leader, Egyptian Drug Authority, Cairo, Egypt; Dr S. Sanuki, Technical Officer, Division of Pharmacopoeia and Standards for Drugs, Office of Review Management, PMDA, National Institute of Health Sciences, Kanagawa, Japan; Professor G.K.E. Scriba, Professor for Pharmaceutical Chemistry, Friedrich-Schiller-University Jena, Department of Pharmaceutical Chemistry, Jena, Germany; Ms L. Serwaa, Head, Product Quality Assurance, Supply Chain Management Unit, United Nations Population Fund, Copenhagen, Denmark; Mr L. Shabani, Director, Agency of Medicines and Medical Devices, Skopje, North Macedonia; Mr C. Shamhuyarira, Chief of Party, United States Pharmacopeial Convention PQM Plus, Kigali, Rwanda; Ms F. Smidt Lara Resende, Health Regulation Specialist, Farmacopéia Brasileira, Agência Nacional de Vigilância Sanitária, Brasília, Brazil; Dr V.G. Somani, Drug Controller General of India, Central Drugs Standard Control Organization, FDA Bhavan, New Delhi, India; Dr L. Stoppa, GMP Inspections & Certification Department, Italian Medicines Agency, Rome, Italy; Dr C. Sun, Deputy Laboratory Director, Health Sciences Authority, Pharmaceutical Laboratory Pharmaceutical Division, Applied Sciences

Group, Singapore; Dr Alejandro Svarch Pérez, Federal Commissioner of the Protection of Sanitary Risk of the Health Ministry of Mexico, COFEPRIS, Mexico City, Mexico; Mr P. Svarrer Jacobsen, Quality Assurance Specialist, United Nations Children's Fund, Copenhagen, Denmark; Dr G. Thurau, Head of Manufacturing Technology Innovation in CMC Regulatory Policy, Roche, Basel, Switzerland; Mr S.C. Todde, Tecnomed-Fondazione dell' Universita di Milano-Bicocca, Monza, Italy; Mr A. Tolmachev, Leading Specialist of the International Cooperation Department, State Pharmacopoeia of the Russian Federation, Federal State Budgetary Institution of the Ministry of Health of the Russian Federation, Moscow, Russian Federation; Ms M. Trajchuleski, Head of Sector for Evaluation of the Documentation for Marketing Authorization for Medicines and Medical Devices, Agency of Medicines and Medical Devices, Skopje, North Macedonia; Dr R. Van Der Werf, Study Director, European Pharmacopoeia Commission, Council of Europe, Strasbourg, France; Ms C. Vielle, Head of European Pharmacopoeia Department, European Directorate of Quality of Medicines & HealthCare, Strasbourg, France; Dr N. Volovyk, Senior Researcher/ Deputy Director for Quality, Quality Management Representative at Ukrainian Scientific Pharmacopoeial Center for Quality of Medicines, State Pharmacopoeia of Ukraine, Kharkiv, Ukraine; Dr T. Vu, Federal Institute for Drugs and Medical Devices, Bonn, Germany; Dr J. Welink, Medicines Evaluation Board, Utrecht, Netherlands (Kingdom of the); Dr G. Westman, Head of Artificial Intelligence, Swedish Medical Products Agency, Uppsala, Sweden; Mr M. Whaley, Head of BP and Labs Team 2, British Pharmacopoeia Commission, London, United Kingdom; Ms K. Wilson, Head, Regulatory Affairs Intelligence, Policy & Training, VIATRIS, Pennsylvania, United States of America; Mr D. Wotton, Assistant Director, Emerging Technologies & Diagnostics, Australian Government Department of Health and Aged Care, Woden ACT, Australia; Mr A. Yeboah, Ghana Food and Drugs Administration, Ghana; Ms M. Yeomans, Ex Pharmaceutical Inspectors Consortium Ltd, Co. Durham, United Kingdom of Great Britain and Northern Ireland; Ms S. Yuen, Department of Health, Hong Kong Special Administrative Region, China; Ms M. G. Zilli, Senior Digital & Data Management Regulatory Intelligence Expert, Merck, Aubonne, Switzerland.

Agencia Estatal de Medicamentos y Tecnologías en Salud, La Paz, Bolivia; Agência Nacional de Vigilância Sanitária, Brasília, Brazil; Asia Industrial Gases Association; Directorate General of Pharmaceutical Affairs and Drug Control, Ministry of Health, Muscat, Oman; European Commission, Brussels, Belgium; European Directorate for the Quality of Medicines and HealthCare, Council of Europe, Strasbourg, France; European Industrial Gases Association, European Medicines Agency, Amsterdam, Netherlands (Kingdom of the); Global Self-Care Federation (formerly World Self Medication Industry), Nyon, Switzerland; International Atomic Energy Agency, Vienna, Austria; International Federation of Pharmaceutical Manufacturers and Associations, Geneva, Switzerland; International Generic and Biosimilar Medicines Association, Brussels, Belgium; International Pharmaceutical Excipients Council Federation ASBL, Brussels, Belgium; International Pharmaceutical Federation, The Hague, Netherlands (Kingdom

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Professor M. McIntosh, Monash Institute of Pharmaceutical Sciences, Monash University, Australia; Therapeutic Goods Administration, Woden, Australia; Directorate General of Drug Administration, Dhaka, Bangladesh; K.U. Leuven, Leuven, Belgium; Professor K. Rezende, Universidade Federal de Goias, Brazil; Chengdu Institute for Food and Drug Control, Sichuan, China; Chongqing Institute for Food and Drug Control, Chongqing City, China; Dalian Drug Quality Control Institute, Dalian City, China; Guangzhou Municipal Institute for Drug Control, Guangzhou, China; Hubei Institute For Drug Control, Wuhan, China; Jiangsu Institute for Food and Drug Control, Nanjing, China; National Institutes for Food and Drug Control, Beijing, China; Shandong Institute for Food and Drug Control, Shandong, China; Shenzhen Institute for Drug Control, Jiangsu Province, Shenzhen, China; Sichuan Institute for Food and Drug Control, Sichuan, China; Suzhou Institute for Drug Control, Jiangsu, China; Tianjin Institute for Drug Control, Tianjin, China; Wuxi Institute For Drug Control, Jiangsu, China; Xiamen Institute for Food and Drug Control, Xiamen, China; Zhejiang Institute for Drug and Food Control, Zhejiang, China; Medicamentos y Productos Biológicos, Instituto Nacional de Vigilancia de Medicamentos y Alimentos, Bogotá, Colombia; Laboratorio de Análisis y Asesoría Farmacéutica, Facultad de Farmacia, Universidad de Costa Rica, San José, Costa Rica; Laboratorio de Normas y Calidad de Medicamentos, Caja Costarricense de Seguro Social, Universidad de Costa Rica, Alajuela, Costa Rica; Agency for Medicinal Products and Medical Devices of Croatia, Official Medicines Control Laboratory Division, Zagreb, Croatia; Mekelle University, School of Pharmacy, Pharmaceutical Analysis and Quality Assurance, Mekelle, Ethiopia; Federal Institute for Drugs and Medical Devices, Bonn, Germany; Institut für Pharmazeutische und Angewandte Analytik, Bremen, Germany; United States Pharmacopeia, Accra, Ghana; Central Drugs Laboratory, Ministry of Health and Family Welfare, Kolkata, India; National Quality Control Laboratory of Drug and Food, National Agency for Food and Drug Control, Yogyakarta, Indonesia; Mission for Essential Drugs and Supplies, Nairobi, Kenya; Arwan Pharmaceutical Industries Lebanon s.a.l., Jadra, Lebanon; Laboratoire de Contrôle de Qualité des Médicaments, Agence du Médicament de Madagascar, Antananarivo, Madagascar; Laboratoire National de Contrôle de Qualité des Médicaments, Nouakchott, Mauritania; Quality Surveillance Laboratory, Windhoek, Namibia; Instituto Especializado

de Análisis, Universidad de Panamá, Panama; Centro Nacional de Control de Calidad, Instituto Nacional de Salud, Lima, Peru; Professor J.J. Sousa, Faculdade de Farmácia, Universidade de Coimbra, Portugal; Professor B.J. Lee, College of Pharmacy, Ajou University, Republic of Korea; Professor J. Ladutko, St Petersburg State Chemical Pharmaceutical University, Russian Federation; Laboratoire National de Contrôle des Médicaments, Dakar Etoile, Senegal; Drug Quality Control Laboratory, Ministry of Health, Victoria, Seychelles; Professor A. Wessels, North West University, South Africa; Professor V. Merino Sanjuán, Facultad de Farmacia, Spain; National Drug Quality Assurance Laboratory, Ministry of Health, Colombo, Sri Lanka; National Drug Quality Control Laboratory, Directorate General of Pharmacy, Federal Ministry of Health, Khartoum, Sudan; Bureau of Drug and Narcotic, Department of Medical Sciences, Ministry of Public Health, Nonthaburi, Thailand; National Drug Quality Control Laboratory, National Drug Authority, Kampala, Uganda; Laboratory of Pharmaceutical Analysis, State Pharmacological Centre, Ministry of Health, Kyiv, Ukraine; School of Pharmacy, Muhimbili University of Health and Allied Sciences, Dar es Salaam, United Republic of Tanzania; Professor H. Fadda, Professor of Pharmaceutics, College of Pharmacy and Health Sciences, Butler University, Indianapolis, United States of America; Laboratorio Control de Productos Ministerio de Salud Pública, Comisión Para El Control de Calidad de Medicamentos, Montevideo, Uruguay; National Institute of Drug Quality Control, Hanoi, Viet Nam; Zambia Medicines Regulatory Authority, Lusaka, Zambia; Medicines Control Authority of Zimbabwe, Harare, Zimbabwe.

Farmacopea Argentina, Buenos Aires, Argentina; Farmacopeia Brasileíra, Brasilía DF, Brazil; British Pharmacopoeia Commission, Medicines and Healthcare Products Regulatory Agency, London, United Kingdom of Great Britain and Northern Ireland; Chinese Pharmacopoeia Commission, Beijing, China; Pharmacopoeial Committee of the Eurasian Economic Union, Moscow, Russian Federation; Egyptian Pharmacopoeia, Egyptian Drug Authority, Cairo, Egypt; European Pharmacopoeia, European Directorate for the Quality of Medicines and HealthCare, Council of Europe, Strasbourg, France; German Pharmacopoeia Commission, Bonn, Germany; Indian Pharmacopoeia Commission, Ghaziabad, India; Indonesian Pharmacopoeia Commission, Jakarta Pusat, Indonesia; The International Pharmacopoeia, World Health Organization, Geneva, Switzerland; Committee of the Japanese Pharmacopoeia, Tokyo, Japan; Mexican Pharmacopoeia, México DF, Mexico; North Macedonia Pharmacopoeia, Agency of Medicines and Medical Devices, Skopje, North Macedonia; Pharmacopoeia of the Republic of Korea, Chuncheongbuk-do, Republic of Korea; Federal State Budgetary Institution "Scientific Centre for Expert Evaluation of Medicinal Products" of the Ministry of Health of Russia, Moscow, Russian Federation; Swiss Pharmacopoeia, Bern, Switzerland; Turkish Medicines and Medical Devices Agency, Department of Analysis and Control Laboratories, Vice Presidency of Economic Assessments and Laboratory Services, Pharmacopoeia Division, T.C. Ministry of Health, Ankara, Türkiye; State Pharmacopoeia of Ukraine, Ukrainian Scientific Pharmacopoeial Center for Quality of Medicines, Kharkiv, Ukraine; United

States Pharmacopeia, Rockville (MD), United States of America; State Institution Center for Pharmaceutical Products Safety, Medical Devices and Medical Equipment, Agency on Development of the Pharmaceutical Industry under Ministry of Health of the Republi of Uzbekistan, Tashkent, Uzbekistan.

Therapeutic Goods Administration Laboratories, Woden, ACT, Australia; WHO Collaborating Centre for Drug Quality Assurance, National Institutes for Food and Drug Control, Beijing, China; WHO Collaborating Centre for Drug Quality Assurance, Pharmaceutical Laboratory, Centre for Analytical Science, Health Sciences Authority, Singapore; WHO Collaborating Centre for Quality Assurance of Drugs, North-West University, Potchefstroom, South Africa; WHO Collaborating Centre for Quality Assurance of Essential Drugs, Bureau of Drug and Narcotic, Department of Medical Sciences, Ministry of Public Health, Nonthaburi, Thailand.

Antimicrobial Resistance Division, WHO, Geneva, Switzerland; Regulation and Prequalification, WHO, Geneva, Switzerland; Global Malaria Programme, Universal Health Coverage/Communicable and Noncommunicable Diseases, WHO, Geneva, Switzerland; Global Tuberculosis Programme, WHO, Geneva, Switzerland; HIV/AIDS, WHO, Geneva, Switzerland; International Nonproprietary Names and Classification of Medical Products, WHO, Geneva, Switzerland; Office of the Legal Counsel, WHO, Geneva, Switzerland; Prequalification, WHO, Geneva, Switzerland; Prevention and Control of Noncommunicable Diseases, WHO, Geneva, Switzerland; Regulation and Prequalification, WHO, Geneva, Switzerland; Technologies, Standards and Norms, WHO, Geneva, Switzerland.

WHO Regional Office for Africa, Brazzaville, Congo; WHO Regional Office for the Americas, Washington, DC, United States of America; WHO Regional Office for South-East Asia, New Delhi, India; WHO Regional Office for Europe, Copenhagen, Denmark; WHO Regional Office for the Eastern Mediterranean, Cairo, Egypt; WHO Regional Office for the Western Pacific, Manila, Philippines.

Abbreviations

API	active pharmaceutical ingredient
CMIC	chloromethyl isopropyl carbonate
COVID-19	coronavirus disease
DEG	diethylene glycol
ECBS	Expert Committee on Biological Standardization
ECSPP	Expert Committee on Specifications for Pharmaceutical Preparations
EDQM	European Directorate for the Quality of Medicines and HealthCare
EG	ethylene glycol
EML	WHO Model List of Essential Medicines
EMLc	WHO Model List of Essential Medicines for Children
ePQS	electronic prequalification system
EQAAS	External Quality Assurance Assessment Scheme
GMP	good manufacturing practices
GSMS	Global Surveillance and Monitoring System (WHO)
IAEA	International Atomic Energy Agency
ICDRA	International Conference of Drug Regulatory Authorities
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICRS	International Chemical Reference Substance(s)
IMWP	International Meeting of World Pharmacopoeias
INN	international nonproprietary name
MeNP	1-methyl-4-nitrosopiperazine
mRNA	messenger ribonucleic acid
PDG	Pharmacopoeial Discussion Group
PQT/INS	Prequalification Team – Inspection Services (WHO)
PQT/MED	Prequalification Team for Medicines Assessment (WHO)
TRS	Technical Report Series

UNFPA	United Nations Population Fund
WHO	World Health Organization

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Dr Adriaan J. Van Zyl, George, South Africa

Dr Mingzhe Xu, Beijing, China (Co-Chair)

Professor Kaouther Zribi, Monastir, Tunisia

Temporary advisers

Mr Habib Abboud, Damascus, Syrian Arab Republic

Ms Melina I. Assalone, Buenos Aires, Argentina

Professor Maria Del Val Bermejo Sanz, Valencia, Spain

Dr Rubina Bose, New Delhi, India

Dr Alfredo García Arieta, Madrid, Spain

Professor Shaohong Jin, Beijing, China

Professor Eliangiringa Kaale, Dar es Salaam, United Republic of Tanzania

Mr Gabriel Kaddu, Kampala, Uganda

Professor Giovanni M. Pauletti, St Louis, United States of America

Dr Luisa Stoppa, Rome, Italy

Mr Sergio Camillo Todde, Monza, Italy

Dr Jan Welink, Utrecht, Netherlands (Kingdom of the)

Representation from intergovernmental organizations[1]

Council of Europe, European Directorate for the Quality of Medicines and HealthCare (EDQM)
represented by the European Pharmacopoeia Commission

International Atomic Energy Agency (IAEA)
Dr Aruna Korde, Radiopharmaceutical Scientist, Vienna, Austria

United Nations Children's Fund (UNICEF)
Mr Peter Svarrer Jakobsen, Quality Assurance Specialist, Copenhagen, Denmark

United Nations Population Fund (UNFPA)
Ms Linda Serwaa, Technical Specialist, Copenhagen, Denmark; and Dr William Potter, Consultant to UNFPA

State actors (pharmacopoeias)[2]

Farmacopeia Argentina
Ms Celeste de Angelis, Administración Nacional de Medicamentos Alimentos y Tecnología Médica (ANMAT), Buenos Aires, Argentina

Farmacopéia Brasileira
Ms Thaís Corrêa Rocha and Ms Riviane Matos Gonçalves, Brazilian Health Regulatory Agency (ANVISA), Brasília, Brazil

British Pharmacopoeia
Mr Peter Crowley and Ms Helen Corns, Medicines and Healthcare products Regulatory Agency (MHRA), London, United Kingdom of Great Britain and Northern Ireland

Egyptian Pharmacopoeia
Dr Mohamed Abdallah, Dr Lobna Sallam, Dr Marwa Hassan and Dr Eman Mamdouh, Egyptian Drug Authority, Cairo, Egypt

European Pharmacopoeia Commission (also representing EDQM, Council of Europe)
Dr Remmelt van der Werf, European Directorate for the Quality of Medicines and HealthCare (EDQM), Strasbourg, France

Indian Pharmacopoeia Commission
Dr Pawan Kumar Saini, Ministry of Health and Family Welfare, Ghaziabad, India

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[1] Unable to participate: European Commission (EC), European Medicines Agency (EMA), United Nations Development Programme (UNDP), United Nations Industrial Development Organization (UNIDO), World Customs Organization (WCO), World Bank Group, World Intellectual Property Organization (WIPO), World Trade Organization (WTO).

[2] Unable to participate: Chinese Pharmacopoeia Commission, Indonesian Pharmacopoeia.

Japanese Pharmacopoeia
Dr Yoshiro Saito and Dr Hikoichiro Maegawa, National Institute of Health Sciences, Tokyo, Japan

Pharmacopoeia of the Eurasian Economic Union
Ms Anna Kravchuk, Eurasian Economic Commission, Moscow, Russian Federation

Pharmacopoeia of the Republic of Korea
Mr Jayoung Kim, Ministry of Food and Drug Safety Evaluation, Chungcheongbuk-do, Republic of Korea

Mexican Pharmacopoeia
Ms Daniel Monserrat Vázquez García, Comisión Permanente de la Farmacopea de los Estados Unidos Mexicanos, Mexico City, Mexico

*State Pharmacopoeia of the Russian Fed*eration
Dr Elena Kovaleva and Mr Alexander Tolmachev, Federal State Budgetary Institution, Moscow, Russian Federation

State Pharmacopoeia of Ukraine
Dr Natalia Volovyk, State Service of Ukraine on Medicinal Products, Kharkov, Ukraine

State Pharmacopoeia of Uzbekistan
Mr Khabibulla Karimovich Dzhalilov and Mr Akmalkhodja Oskarkhodjaevich Zaynidinov, State Center for Expertise and Standardization of Medicines, Medical Devices and Medical Equipment, Tashkent, Uzbekistan

Representation from non-State actors[3]

Global Self-Care Federation, Nyon, Switzerland
Ms Catherine Laverty, Director, Communications and Policy, and Mr Hezron Munyakin, Communications and Policy Coordinator

International Federation of Pharmaceutical Manufacturers and Associations (IFPMA), Geneva, Switzerland
Ms Janis Bernat, Director, Scientific and Regulatory Affairs

International Generic and Biosimilar Medicines Association, Geneva, Switzerland
Dr Nick Cappuccino, Chair, Science Committee

International Pharmaceutical Federation (FIP), The Hague, Netherlands (Kingdom of the)
Ms Zuzana Kusynová, Lead, Policy, Practice and Compliance

United States Pharmacopoeia, Rockville, United States of America
Dr Kevin Moore, Senior Manager, Pharmacopoeial Collaboration

[3] Unable to attend: World Federation of Societies of Anaesthesiologists, London, United Kingdom.

Partnerships[4]

Global Fund to Fight AIDS, Tuberculosis and Malaria, Geneva, Switzerland
Ms Sandrine Cloëz, Specialist, Pharmaceutical Products Quality Assurance

Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S), Geneva, Switzerland
Ms Helena Baião, Coordinator

World Health Organization

Access to Medicines and Health Products (MHA)
Dr Yukiko Nakatani, Assistant Director-General

Health Products Policy and Standards (HPS)
Dr Clive Ondari, Director

Norms and Standards for Pharmaceuticals (NSP)
Dr Luther Gwaza, Team Lead and Secretary of the Expert Committee
Dr Herbert Schmidt, Technical Officer
Dr Steve Estevão Cordeiro, Technical Officer
Ms Sinéad Jones, Administrative Assistant
Ms Bezawit Kibret, Administrative Assistant
Dr Sian Lewis, Consultant

Health Care Readiness (HCR)
Ms Laura Alejandra Velez Ruiz Gaitan, Technical Officer

International Nonproprietary Names and Classification of Medical Products (INN)
Dr Raffaella Balocco, Unit Head
Dr Antonio Romeo, Technical Officer

Norms and Standards for Biological Products (NSB)
Dr Ivana Knezevic, Team Lead
Dr Dianliang Lei, Scientist

Essential Medicines (EML)
Dr Benedikt Huttner, Team Lead

Prequalification (PQT)
Mr Deus Mubangizi, Unit Lead

Prequalification Inspection Services (PQT/INS)
Mr Mustapha Chafai, Technical Officer
Dr Xingyu Chen, Technical Officer
Ms Stephanie Croft, Technical Officer
Mr Vimal Sachdeva, Technical Officer

[4] Unable to attend: Stop TB Partnership, Unitaid.

Prequalification Medicines Assessment (PQT/MED)
Mr Lawrence Nzumbu, Technical Officer

Regulation and Safety (REG)
Mr Hiiti B. Sillo, Unit Head

Incidents and SF (REG/ISF)
Mr Rutendo Kuwana, Team Lead
Ms Leticia Megias Lastra, Technical Officer

Laboratory Networks and Services (LNS)
Ms Natércia Guerra Simões, Technical Officer

Pharmacovigilance (PVG)
Dr Fumihito Takanashi, Technical Officer

Regulatory Convergence and Networks (RCN)
Dr Samvel Azatyan, Team Lead

Regulatory Systems Strengthening (RSS)
Dr Mohamed Refaat, Technical Officer

Representation from WHO regional offices

Regional Office for Europe
Dr Dorina Pirgari, Technical Officer

Representation from WHO country offices

Country Office of Tunisia
Dr Ines Fradi, National Professional Officer

Declarations of interest

Declarations of interest made by members of the WHO Expert Committee on Specifications for Pharmaceutical Preparations and temporary advisers are listed below.

Ms Melina Assalone declared that she worked for the Argentinian national regulatory agency, Administración Nacional de Medicamentos, Alimentos y Tecnología Médica (ANMAT). She prepared technical reports on documentation of pharmaceutical preparations from laboratories in the course of her duties. She also declared that her spouse worked for a national laboratory of pharmaceutical products, Lab Mat. That disclosure did not constitute a conflict of interest as the discussion and decisions of the meeting did not include product-specific or manufacturer-specific products.

Professor Maria del Val Bermejo Sanz declared that she received research funding from a university and the Ministry of Science in Spain, and that she provided consulting to pharmaceutical companies. That disclosure did not constitute a conflict of interest as the discussion and decisions of the meeting did not include product-specific or manufacturer-specific products.

Dr Adriaan J. Van Zyl declared previously working as an independent consultant and auditor to assess compliance with good manufacturing practices for the pharmaceutical industry and organizing training workshops. That disclosure did not constitute a conflict of interest as the discussion and decisions of the meeting did not include product-specific or manufacturer-specific products.

All other members of the WHO Expert Committee on Specifications for Pharmaceutical Preparations and temporary advisers declared no conflict of interest.

CLOSED SESSION

The closed session was attended by members of the Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP), temporary advisers, international organizations and State actors.

Opening

The fifty-seventh meeting of the ECSPP was held in hybrid format (with in-person and virtual attendance) from 9 to 13 October 2023. To maximize the meeting's efficiency, some agenda items were covered by correspondence beforehand.

The meeting was opened by Dr Yukiko Nakatani, Assistant Director-General of Access to Medicines and Health Products, on behalf of the World Health Organization (WHO) Director-General, Dr Tedros Ghebreyesus.

After welcoming all participants to the meeting, Dr Nakatani gave recognition to the Expert Committee's work on priority health issues, including development of quality standards for new and existing therapeutics relevant to coronavirus disease (COVID-19) and their publication in *The International Pharmacopoeia* (*1*). Dr Nakatani emphasized the importance of quality international standards to combat substandard and falsified medicines, as illustrated by the recent preventable deaths of more than 300 children across several countries due to substandard cough syrups that had been contaminated with diethylene glycol and ethylene glycol.

Dr Nakatani reminded participants that WHO was planning its 2025–2028 Programme of Work and reaffirmed the importance of the ECSPP's work in ensuring that WHO standards remained timely, relevant, inclusive and science driven.

Election of chairpersons and rapporteurs

The ECSPP appointed Dr Petra Doerr as Chair and Dr Mingzhe Xu as Co-Chair of the meeting. The ECSPP further appointed Dr Sawsan Barrou and Professor Erwin Adams as rapporteurs.

1. General policy

1.1 Process for development of WHO norms and standards

Developing, establishing and promoting international standards for food, biological, pharmaceutical and similar products were part of WHO's core mandate (Article 2, WHO Constitution) (*2*). WHO achieved that through expert committees that were established by the World Health Assembly or Executive Board, and that were governed through set regulations and rules of procedure.

The ECSPP was responsible for WHO's guidance for medicines quality assurance, as well as regulatory standards, across the full life cycle of medicines from development to post-marketing. That included taking responsibility for more than 130 official WHO guidance texts and guidelines. The ECSPP worked in close collaboration with a wide range of partners, including national and regional authorities and groupings, international organizations, professional and other associations, non-State actors, quality assurance and regulatory experts, WHO collaborating centres, and pharmacopoeial authorities and secretariats.

Dr Luther Gwaza, Team Lead of Norms and Standards for Pharmaceuticals and Secretary of the Expert Committee, described the process used to develop norms and standards through the ECSPP. All Expert Committee members and temporary advisers that attended the fifty-seventh ECSPP were selected from WHO's established expert advisory panels, based on the meeting's agenda, and were invited to participate in their personal capacities.

Dr Gwaza informed the meeting that all monographs, guidance texts, good practices, model schemes and guidelines adopted by the ECSPP were developed in response to recommendations and requests from WHO governing bodies and programmes or in response to major public health needs. They were widely circulated for public comment, reviewed by expert groups and discussed in at least one ECSPP meeting before being adopted by consensus for use. All monographs were also subjected to robust laboratory investigations. In all cases, the norms and standards adopted by the ECSPP were:

- based on science and publicly available evidence;
- designed to reflect WHO's core value of the "right to health";
- developed using a multidisciplinary process that considered all relevant perspectives and minimized risk of bias;
- relevant to all WHO Member States and adaptable to local settings and context.

Dr Gwaza gave an overview of a new online review system, PleaseReview, which was being used to manage the consultation and revision processes during a guideline's development. He explained how to use the new system, highlighted

some of its key features, and emphasized its benefits for all stakeholders, especially in improving transparency of the process.

The Expert Committee congratulated the team on its achievement in introducing the new PleaseReview tool and suggested that it might be beneficial to arrange regular trainings for new users to learn how to use it.

The Expert Committee noted the process.

OPEN SESSION

The open session was attended by ECSPP members, temporary advisers, international organizations, State actors, Member States' mission representatives and non-State actors.

Introduction and welcome

Dr Yukiko Nakatani welcomed all participants – including non-State actors – to the open part of the meeting. She gave recognition to the ECSPP's efforts to support the global response to the COVID-19 pandemic, which had been ongoing for the previous three years. During that time, the ECSPP had not only continued to work on other priority health issues but had also striven to issue quality standards for new and existing COVID-19 therapeutics, some of which had already been published in *The International Pharmacopoeia* (*1*).

Dr Nakatani emphasized the collaborative nature of WHO's work and highlighted the value of in-person interactions that were achieved through open sessions. She applauded the ECSPP's ongoing collaboration with other United Nations agencies, including the International Atomic Energy Agency (IAEA) and the United Nations Population Fund (UNFPA), to develop standards in areas that were often overlooked, including radiopharmaceuticals and female condoms.

Dr Nakatani also praised the continuous contributions of global experts in the periods between ECSPP meetings. She noted that preparatory working groups had been working all year to support the Secretariat in preparing technical documents for the ECSPP's consideration and she thanked all the experts, temporary advisers, collaborating partners, institutions and the WHO Secretariat for their dedicated work and commitment to improving global health.

Update on norms and standards for pharmaceuticals

Dr Gwaza gave a brief overview of the work of the Norms and Standards for Pharmaceuticals Team to develop and establish norms and standards for pharmaceuticals. That work included promoting the implementation and use of WHO norms and standards across all WHO Member States. Norms and Standards for Pharmaceuticals also served as the Secretariat to the ECSPP, whose scope covered quality assurance of medicines, regulatory guidance, good practices, the WHO model scheme and quality control specifications.

Dr Gwaza underscored the critical value of the ECSPP's work, particularly given the importance of ensuring patients' access to safe and quality-assured medicines, not only to WHO but also to the broader United Nations group. He noted that the Expert Committee's work made considerable contribution to attainment of the United Nations Sustainable Development Goals, for example.

Dr Gwaza described five key areas of work that were supported by the Norms and Standards for Pharmaceuticals Team:

- *The International Pharmacopoeia* (see subsection 6.1);
- International Chemical Reference Substances (see section 7);
- the External Quality Assurance Assessment Scheme (see section 5);
- WHO recommendations for pharmaceuticals in the *Quality assurance of pharmaceuticals* compendium (see subsection 8.5);
- standards for generic product development and regulatory approval, including the WHO Biowaiver Project (see subsection 10.1) and the WHO list of international comparator pharmaceutical products (see subsection 10.2).

Dr Gwaza summarized the latest guidelines, norms and standards adopted by the ECSPP, which had been published in the Expert Committee's fifty-sixth meeting report (*3*). Those included:

- 10 new and revised general medicines quality assurance and regulatory guidance texts;
- 17 new and revised specifications for active pharmaceutical ingredients (APIs) and specific dosage forms in *The International Pharmacopoeia*;
- one revised general chapter in *The International Pharmacopoeia*;
- 11 new International Chemical Reference Substances (ICRS).

Dr Gwaza informed participants that all the latest guidelines – as adopted by the fifty-fourth, fifty-fifth and fifty-sixth meetings of the ECSPP – would be available in the 10th edition of the WHO *Quality assurance of pharmaceuticals: a compendium of guidelines and related materials, Volume 2* (*4*).

The Expert Committee noted the update.

2. General updates and matters for information

2.1 Expert Committee on Biological Standardization

Dr Ivana Knezevic, Team Lead for WHO Norms and Standards for Biological Products, spoke about the recent work of the Expert Committee on Biological Standardization (ECBS). The ECBS was responsible for establishing evidence-based international norms and standards for biological products, which included vaccines and related substances, biotherapeutics, blood products and related substances, in vitro diagnostics, and cell and gene therapies. She emphasized the collaborative nature of that work, highlighting the contribution of WHO's eight collaborating centres and four custodian laboratories in establishing measurement standards and written standards and supporting implementation workshops for biologicals.

The previous ECBS meeting (its seventy-seventh meeting) had been held virtually in March 2023. At that meeting, the ECBS had recommended adopting two WHO written standards: guidelines on the nonclinical and clinical evaluation of monoclonal antibodies and related products intended for the prevention or treatment of infectious diseases; and considerations in developing a regulatory framework for human cells and tissues and for advanced therapy medicinal products.

The seventy-seventh ECBS had recommended establishing eight new and three replacement WHO international reference preparations. It had also endorsed 12 proposals for new standards.

Dr Knezevic informed the ECSPP that the ECBS had increased the frequency of its meetings from once to twice a year – a change that had been adopted in response to the increased need for standards for biologicals as a consequence of the COVID-19 pandemic. The next two ECBS meetings were scheduled for October 2023 and March 2024.

Dr Knezevic provided an overview of written standards for biologicals that were under development, including a revision of *Guidelines on procedures and data requirements for changes to approved vaccines* (*5*). She informed the ECSPP that a meeting on the revised guideline had taken place in September 2023, where experts had agreed various changes to the text and had recommended an expedited review, given the annual strain changes for influenza and COVID-19 vaccines.

Dr Knezevic updated the ECSPP on various other ECBS activities, including a series of informal consultations and implementation workshops held in 2022 and 2023, case studies on small molecules (insulins) and large molecules (monoclonal antibodies) to support implementation, and a review of WHO guidelines, which had been undertaken from 2020 to 2023. The review had aimed to identify all documents that were outdated and would need either

updating or archiving. The final report of the review would be presented to the ECBS in October 2023, following which decisions would be made on how to proceed with updating or archiving.

Find out more about the ECBS at https://www.who.int/groups/expert-committee-on-biological-standardization.

The Expert Committee noted the update.

2.2 Expert Committee on the Selection and Use of Essential Medicines

Dr Benedikt Huttner, Secretary of the Expert Committee on the Selection and Use of Essential Medicines, briefed participants on the work of the Expert Committee on the Selection and Use of Essential Medicines, which met every two years to update the WHO Model List of Essential Medicines (EML), including the WHO Model List of Essential Medicines for Children (EMLc). Dr Huttner explained that there were three broad criteria for including a medicine on the list: public health relevance; evidence of efficacy and safety; and a consideration of comparative cost-effectiveness.

The twenty-fourth meeting of the Expert Committee on the Selection and Use of Essential Medicines, in April 2023, had reviewed 85 applications for the latest update of the EML. In total, 24 new medicines and 19 new formulations had been added to the EML, and 12 new medicines and 48 new formulations had been added to the EMLc. At the same time, three medicines and 12 formulations had been deleted from the EML, and three medicines and 23 formulations had been deleted from the EMLc. The Expert Committee on the Selection and Use of Essential Medicines had rejected proposals for inclusion, change or deletion for 32 medicines, medicine classes or formulations.

In previous years the EML had seen an increased emphasis on cancer medicines. The 2023 update had included two new cancer medicines and new indications of already listed medicines for children. Several applications for cancer medicines had been rejected because of concerns about immature data, high prices and feasibility.

Four other areas of change in the latest EML were highlighted by Dr Huttner.

- **Medicines for multiple sclerosis**. A new subsection on medicines for multiple sclerosis had been added to the EML, with three individual medicines listed in it: cladribine, glatiramer acetate and rituximab. Dr Huttner noted that the EML had never before included any medicines for the treatment of multiple sclerosis.
- **Cardiovascular medicines**. Three fixed-dose combinations of cardiovascular medicines (sometimes called cardiovascular

"polypills") had been added to the EML for use in primary and secondary prevention of atherosclerotic cardiovascular diseases. Applications for those medicines had been previously rejected three times because of a lack of mature data.

- **Antimicrobials**. Several new medicines and formulations had been added to the EML. New guidance – *The WHO AWaRe (Access, Watch, Reserve) antibiotic book* (*6*) – had also been published on the choice of essential antibiotics, dose, route of administration, and duration of treatment for more than 30 of the most common clinical infections in children and adults in both primary health care and hospital settings.
- **Medicines for COVID-19**. The Expert Committee on the Selection and Use of Essential Medicines had recommended that effective and safe therapeutics for COVID-19 should be considered as essential medicines. It had further recommended that a new section for COVID-19 therapeutics should be added to both the EML and EMLc (but that no individual medicines should be added at that time and that countries should rather refer to the WHO living guidelines).

Other additions to the 2023 EML had included medicines for alcohol use disorder and smoking cessation, monoclonal antibodies for treating Ebola virus disease and medicines for diseases of the nervous system. Some medicines for mental and behavioural disorders had also been added to the 2023 EML, specifically to align with recommendations in the WHO Mental Health Gap Action Programme.

Dr Huttner informed the ECSPP that in November 2023 the first Technical Advisory Group on Pricing Policies for Medicines would convene to advise WHO on methods for implementing medicine pricing policies, emerging evidence, and good practices for improving the affordability of essential medicines.

The ECSPP discussed the latest EML, noting that the recommendation to include fixed-dose combinations of cardiovascular medicine had been made in recognition of the fact that the evidence base for those medicines had recently changed and their price had also reduced. The ECSPP noted that WHO guidance on how to use those medicines (which combination to use and in what context) had still not been developed.

Find out more about the Expert Committee on the Selection and Use of Essential Medicines at https://www.who.int/groups/expert-committee-on-selection-and-use-of-essential-medicines.

The Expert Committee noted the update.

2.3 Prequalification of medicines

Mr Lawrence Nzumbu, Technical Officer, WHO Prequalification Team for Medicines Assessment (PQT/MED), updated meeting participants on the latest activities of PQT/MED, which worked to facilitate access to medicines that met unified standards of quality, safety and efficacy for HIV/AIDS, malaria and tuberculosis.

Since May 2022, 60 products had been prequalified, including six insulin products, four COVID-19 medicines and the first benzathine benzylpenicillin for maternal syphilis. Applications had continued to be received for recently added therapeutic areas, such as Ebola virus disease. New expressions of interest had also been published for the treatment of disorders caused by the use of tobacco and multidrug-resistant bacterial infections. Other existing expressions of interest had been updated, including those for malaria and hepatitis B and C.

WHO's prequalification processes had continued to speed up, and the overall median time taken for finished pharmaceutical products to achieve prequalification had decreased compared with the previous year. Many other key performance targets had also been met in 2022. To support further improvement, a new electronic prequalification system (ePQS) was in the final stages of development. Its internal database had been in use for more than a year and the external ePQS portal would be launched by January 2024.

Mr Nzumbu informed the Expert Committee of other activities undertaken by PQT/MED over the previous year. Those included publishing an update on N-nitrosamine impurities in September 2023, presenting new approaches to define acceptable intakes of N-nitrosamine impurities in medicines and updates to various guidelines. In 2022 and 2023 PQT/MED had also undertaken capacity-building activities, including two workshops per year for manufacturers and two trainings per year for regulators.

The Expert Committee congratulated Mr Nzumbu on the progress in developing ePQS and looked forward to the launch of the new portal.

Find out more about WHO prequalification at https://extranet.who.int/prequal.

The Expert Committee noted the update.

2.4 Member State Mechanism and post-market surveillance

Mr Rutendo Kuwana, Team Lead for WHO Incidents and Substandard and Falsified Medical Products, summarized the Member State Mechanism, which was the political response to substandard and falsified medical products. He also updated the Expert Committee on WHO's latest post-market surveillance activities.

The Member State Mechanism had focused on a range of prioritized activities, including responding to recent events of contaminated paediatric

liquid formulations, and updating or developing new guidance to improve market surveillance and control in WHO Member States.

The latest post-market surveillance activities had been designed to support countries in preventing, detecting and effectively responding to substandard and falsified medical products. Mr Kuwana presented data from the WHO Global Surveillance and Monitoring System (GSMS) – a voluntary reporting system covering records of global incidents of substandard and falsified medical products. He described the different categories of medicines captured in the GSMS and noted the relatively poor reporting by Member States. Over the past year, surveys had been undertaken to identify reporting barriers, which had been found to include lack of reporting mechanisms or training available, heavy workloads and insufficient coordination. A literature review had also been undertaken to better understand the informal markets through which medicines were sold.

Other activities undertaken over the previous year had included developing an appropriate dissolution testing method for benzathine benzylpenicillin.

Mr Kuwana updated the ECSPP on risk-based post-market surveillance activities, past and future. A survey of the quality of five antibiotics had been completed in the United Republic of Tanzania, and surveys on reproductive health commodities had been completed in Côte d'Ivoire and Senegal. Plans for future surveys would focus on two types of medicines: antibiotics that were likely to contribute to antimicrobial resistance; and antituberculosis medicines with risk of nitrosamine impurities (rifampicin and rifapentine).

For all surveys, past and future, the importance of using WHO norms and standards and appropriate pharmacopoeial methods was emphasized.

Finally, Mr Kuwana summarized the WHO Incidents and Substandard and Falsified Medical Products Team's plans for 2024, which included:

- promoting standardized country data collection and analysis of GSMS and risk-based post-market surveillance data;
- conducting enhanced risk-based post-market surveillance surveys, as described above;
- supporting countries to implement market surveillance, control and vigilance-related institutional development plans;
- supporting the development and roll-out of national action plans to support the prevention of, detection of and response to substandard and falsified medicines and antimicrobial resistance.

Find out more about the Member State Mechanism at https://www.who.int/teams/regulation-prequalification/incidents-and-SF/mechanism.

The Expert Committee noted the update.

2.5 International Conference of Drug Regulatory Authorities

Dr Samvel Azatyan, Team Lead of WHO Regulatory Convergence and Networks, presented the latest news from the International Conference of Drug Regulatory Authorities (ICDRA). ICDRA had held biennial conferences since 1980 for regulatory authorities to share information and strengthen collaboration. Dr Azatyan said ICDRA was an important tool for WHO and regulatory authorities to discuss and achieve consensus on issues of international relevance, harmonize regulation, and improve the safety, efficacy, and quality of medicines.

Each conference lasted three days (with two preconference days) and covered topics such as quality, biosimilars, regulatory reform, medicines safety, counterfeiting, access, regulation of clinical trials, harmonization, new technologies and e-commerce.

In September 2021, WHO had held an extraordinary (virtual) ICDRA on smart regulation – timely delivery of quality-assured medical products for all during a global pandemic. It had been attended by more than 500 people from all over the world. The meeting had made several recommendations to Member States, WHO, industry and regulatory authorities. Those recommendations had included the following:

- continue using the Global Benchmarking Tool to enhance regulatory capacity;
- adopt regulatory flexibilities and reliance best practices introduced during the pandemic to speed up regulatory procedures, including emergency approval, rolling application submissions, remote inspections and digital submissions;
- integrate the principles of good regulatory practices and good reliance practices in their regulatory systems;
- identify and use new tools and techniques to support emergency response during the pandemic and beyond.

Dr Azatyan confirmed that the 19th ICDRA would be hosted by the Central Drugs Standard Control Organization in New Delhi, India, in September or October 2024.

Find out more about ICDRA at https://www.who.int/teams/regulation-prequalification/regulation-and-safety/regulatory-convergence-networks/icdra.

The Expert Committee noted the update.

3. Collaboration initiatives

3.1 International Meeting of World Pharmacopoeias

Dr Luther Gwaza updated ECSPP members on the latest International Meeting of World Pharmacopoeias (IMWP), which had been held virtually in September 2022, co-hosted by the Pharmacopoeia of the United Mexican States and WHO. The meeting had been attended by 38 participants from 51 pharmacopoeial authorities around the world. Each of the world pharmacopoeias covered a different country or region, but all worked to protect public health by creating and making available public standards to help ensure the quality of medicines. They met every year at the IMWP to share their experience and expertise and to find ways of working together to synchronize their efforts.

Key discussions during the 2022 IMWP had focused on lessons learned during COVID-19, for example considering how to respond to challenges posed using herbal medicines during a health crisis. The Pharmacopoeial Discussion Group (PDG), which aimed to harmonize general chapters and excipient monographs, had also provided an update of its work.

Dr Gwaza shared key outcomes from the 2022 IMWP, which included:

- knowledge exchange on the activities of pharmacopoeias to support national and global public health;
- agreement to gather feedback on the IMWP's COVID-19-related activities through a stakeholder consultation to inform the IMWP's future approach to public health emergencies and other crises;
- agreement to review information-sharing mechanisms to improve the communication and engagement of pharmacopoeias during public health emergencies and other crises;
- agreement to use the results of a survey on scientific priorities to identify potential topics for bilateral and multilateral collaboration.

Dr Gwaza confirmed that the next IMWP would be hosted by the Mexican Pharmacopoeia in Mexico City in November 2023 (in hybrid format, with virtual and in person attendance).

Following a question from the floor, Dr Gwaza confirmed the interest of the IMWP in considering and addressing the environmental impact of chemicals described in world pharmacopoeias. He clarified that proposals on how to proceed should be driven by the IMWP and brought to the Expert Committee for discussion.

The Expert Committee also noted that the PDG had met the previous week and had confirmed its expansion to include the Indian Pharmacopoeia.

Find out more about IMWP at https://www.who.int/teams/health-product-policy-and-standards/standards-and-specifications/norms-and-standards-for-pharmaceuticals/international-pharmacopoeia/IMWP.

The Expert Committee noted the update and expressed its support for the IMWP. It encouraged WHO to continue serving as the Secretariat for those events.

4. Nomenclature, terminology and databases

4.1 International nonproprietary names for pharmaceutical substances

Dr Raffaella Balocco, Unit Head of the WHO International Nonproprietary Names Programme and Classification of Medical Products, updated ECSPP members on WHO's latest work to support the development of international nonproprietary names (INNs), which were used to identify APIs. She explained how WHO collaborated closely with INN experts, national nomenclature committees and many other stakeholders to choose a single name of worldwide acceptability for each API that is marketed as a pharmaceutical.

Since the turn of the century, increasing globalization and rapid scientific and technical development had fuelled a rapid rise in the number of new biological products developed and approved for use. That trend had been reflected in a growing number of INN requests each year, rising from around 150 in 2000 to more than 1200 in 2021–2022. Dr Balocco described how the pharmaceuticals landscape was increasing in scope and complexity, and underscored the need to ensure that each element in that landscape was named and classified.

Dr Balocco highlighted four major activities in the INN update.

- **School of INN**. The virtual school, available at https://extranet.who.int/soinn, promoted INNs as a central teaching and learning theme for all health professionals. The school had held online webinars and courses in the science of nomenclature and naming of pharmaceutical substances in English, French, Spanish and Arabic.
- **COVID-19 vaccine substances**. Recent approaches to vaccine development had involved messenger ribonucleic acids (mRNAs), which were well defined and so fell within the scope of the INN nomenclature system. Many mRNAs containing anti-SARS-CoV-2 vaccine substances had already been assigned INNs.
- **New INN stems for monoclonal antibodies**. In 2021, the WHO INN Expert Group had adopted a new INN nomenclature scheme for monoclonal antibody-based drugs, which would replace the well known stem *-mab*. The new scheme divided substances with an immunoglobulin variable domain into four groups and used the following stems: *-tug*, *-bart*, *-mig* and *-ment*.
- **WHO INN open database for proteins (INN ODP)**. The new project aimed to develop a structured database for protein sequences, post-translational modifications and metadata. The database would consolidate information that had previously been scattered across various file formats. As the first of its kind in the world, the new

database was expected to be very useful in supporting INN experts and other stakeholders to analyse existing INNs and make well informed decisions about new ones.

Find out more about INNs at https://www.who.int/teams/health-product-and-policy-standards/inn.

The Expert Committee noted the update.

4.2 Quality assurance terminology

Dr Steve Estevão Cordeiro, Technical Officer, Norms and Standards for Pharmaceuticals, reminded meeting participants that all terms and definitions used in ECSPP norms, standards, guidelines and reports were published in the Quality Assurance of Medicines Terminology Database.

The database, which was initially established in 2005, was designed to help harmonize terminology and avoid misunderstandings that might arise from different interpretations of individual terms.

Dr Estevão Cordeiro informed the ECSPP that the database had been updated from the previous year.

Find out more at https://www.who.int/publications/m/item/quality-assurance-of-medicines-terminology-database.

The Expert Committee noted the latest update of the database and encouraged the WHO Secretariat to continue updating it on an annual basis.

4.3 Guidelines and guidance texts adopted by the ECSPP

ECSPP members were updated by correspondence on the guidelines and guidance texts adopted by the ECSPP. A full and updated list of WHO norms and standards for medicines, quality assurance and regulatory guidance adopted by the Expert Committee, and published in the WHO Technical Report Series, had been drawn up. It included 139 texts, categorized into broad topic areas: development, distribution, inspection, production, quality control, regulatory standards, and prequalification.

The Expert Committee recommended that the list of WHO norms and standards for medicines quality assurance guidelines and guidance texts be integrated into the ECSPP meeting report (Annex 1). It further invited WHO to establish a searchable database of those documents, including links to the full texts; and in that context to review the categorization of individual documents.

5. Quality control: national laboratories

5.1 External Quality Assurance Assessment Scheme

Dr Luther Gwaza updated ECSPP members on ongoing activities in the External Quality Assurance Assessment Scheme (EQAAS) platform for pharmaceutical quality control laboratories to measure their performance through a confidential system of blind testing.

Organized by WHO with the assistance of the European Directorate for the Quality of Medicines and HealthCare (EDQM), EQAAS had evaluated the technical performance of pharmaceutical quality control laboratories since 2000. The proficiency testing scheme served to demonstrate the reliability of laboratory analytical results by objective means; independently verify a laboratory's competence; establish mutual confidence with collaborating networks; and support continuous improvement in performance. Dr Gwaza reminded participants that proficiency testing was mandatory according to WHO's good practices for pharmaceutical quality control laboratories and for ISO 17025 accreditation.

EQAAS was run according to international standards for proficiency testing set by the International Organization for Standardization and the International Electrotechnical Commission. Since the scheme started, laboratories from across WHO's six regions had participated in more than 1200 studies, involving 36 different tests.

Update on EQAAS phase 11

Five procedures had been proposed for EQAAS phase 11 using test samples of metronidazole injection and two strengths of metronidazole tablets:

- pH of the injectable product – injection
- assay of the finished product – injection
- related substances of the finished product – injection
- dissolution test of the finished product – two tablet strengths
- disintegration test of the finished product – two tablet strengths.

The protocols for carrying out those procedures would be based on the corresponding provisions of *The International Pharmacopoeia*. EQAAS phase 11 had been due for completion in 2023 but had been delayed due to challenges in procuring samples. At the time of the fifty-seventh ECSPP meeting, the feasibility study for assay and dissolution test and the quality control of all the samples manufactured was ongoing. Laboratories were expected to participate in the proficiency testing between February and April 2024.

The Expert Committee discussed various aspects of EQAAS, including timelines, reference substances and the cost of participation, which was raised as a concern by some countries. Some participants highlighted the need to increase the number of prequalified pharmaceutical quality control laboratories as a means of reducing the burden of testing, but also stressed the importance of strengthening existing prequalified laboratories to provide testing services to other countries. The WHO Secretariat confirmed its support for the latter approach, pointing to the tiered approach to testing for diethylene glycol and ethylene glycol as an example of how to enable regional centres to support broader testing in their regions (see subsection 6.2.4).

The Expert Committee noted the update and encouraged WHO to continue EQAAS in support of national and regional pharmaceutical quality control laboratories.

CLOSED SESSION

The closed session was attended by ECSPP members, temporary advisers, international organizations and State actors.

6. Quality control: specifications and tests

6.1 The International Pharmacopoeia

Dr Herbert Schmidt, Technical Officer, Norms and Standards for Pharmaceuticals, presented an overview of the 11th edition of *The International Pharmacopoeia* (*1*). *The International Pharmacopoeia* was a freely available collection of quality specifications for pharmaceutical substances and dosage forms, together with supporting general methods of analysis. Updated every year, *The International Pharmacopoeia* offered source material for reference or adaptation by any WHO Member State wishing to establish pharmaceutical requirements. It provided quality requirements for essential medicines used by regulatory authorities, manufacturers, national quality control laboratories, procurement agencies and public pharmacies to check and evaluate the quality of a medicine.

The 11th edition of *The International Pharmacopoeia* reflected the decisions of the fifty-fifth and fifty-sixth ECSPP meetings. It continued to focus on providing standards for essential medicines that met global public health priorities and, as such, was primarily based on medicines that were included in the EML; were the subject of invitations to submit an expression of interest for prequalification; or were recommended by WHO or United Nations specific disease programmes.

The 11th edition of *The International Pharmacopoeia* had been aligned with other major pharmacopoeias as far as possible. It had been developed in collaboration with laboratories and expert groups and in consultation with stakeholders. The monograph development process had been governed by publicly available rules and procedures, and designed to ensure complete transparency and the participation of all interested parties. Before being included in the collection, every monograph had been formally adopted by the ECSPP.

The 11th edition of *The International Pharmacopoeia* included new and revised texts for 16 monographs on pharmaceutical substances, 10 monographs on dosage forms, three methods of analysis and three general monographs on dosage forms.

Dr Schmidt drew attention to a scientific publication on *The International Pharmacopoeia*'s response to the COVID-19 pandemic, which had been published in the *Bulletin of the Scientific Centre for Expert Evaluation of Medicinal Products: Regulatory Research and Medicine Evaluation* in 2023 (*7*).

The Expert Committee noted the update.

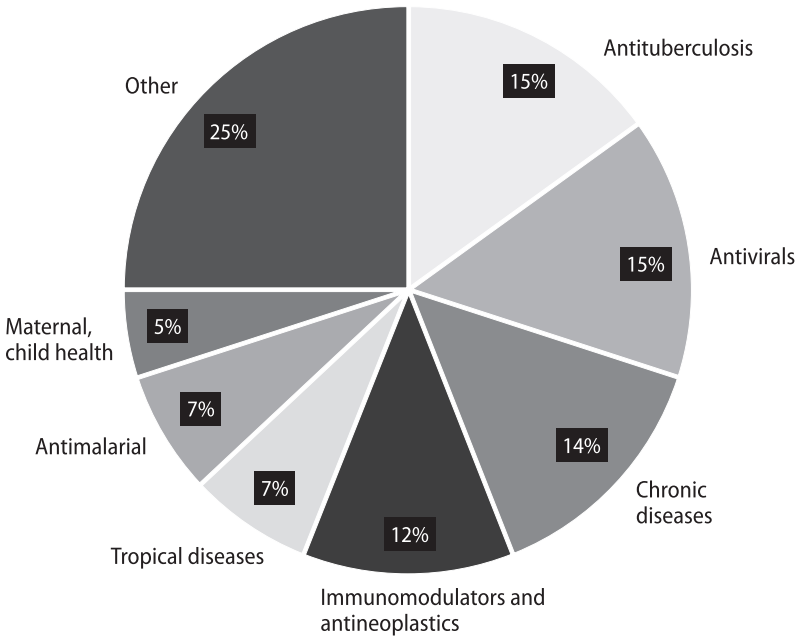
6.1.1 Workplan 2024–2025

Professor Kaouther Zribi, Expert Committee member, presented a proposed workplan for *The International Pharmacopoeia* for 2024–2025. The workplan included a listing of 210 medicines proposed for development based on a survey to identify medicines that were listed in the EML or that had been subject to an invitation to submit an expression of interest for prequalification of medicines but were not covered by other pharmacopoeias.

The list of medicines proposed for development had been divided into three levels of priority: 40 would be developed with priority A (medicines mentioned in the EML and expressions of interest, but not in other pharmacopoeias); 44 would be developed with priority B (medicines mentioned in expressions of interest, but not in the EML and not in other pharmacopoeias); and 126 would be developed with priority C (medicines mentioned in the EML but not in expressions of interest and not in other pharmacopoeias).

Of the proposed priority medicines, 15% were antiviral medicines, 15% were antituberculosis medicines, 14% were medicines for chronic diseases, and 12% were immunomodulators and antineoplastic medicines (Fig. 1). They included medicines that were relevant to various areas of WHO work, including specific disease programmes and the Prequalification of Medicines Programme. They also included medical products relevant to COVID-19, such as alcohol-based handrub solution and remdesivir powder for injection.

Fig. 1
Types of medical products proposed for priority development



In practice, the monographs from the priority list that would be developed would depend largely on the resources available and the extent of manufacturers' support.

Participants at the meeting asked how the COVID-19 pandemic had impacted the workplan for *The International Pharmacopoeia*. Dr Schmidt confirmed that every time the WHO living guideline on COVID-19 had recommended the therapeutic use of a specific COVID-19 medicine, the WHO Secretariat had initiated work to develop a corresponding monograph for *The International Pharmacopoeia*.

The Expert Committee adopted the workplan 2024–2025 as presented.

6.2 General chapters

6.2.1 Microdetermination of water by the Karl Fischer method

The ECSPP was asked to consider a new general chapter in *The International Pharmacopoeia* on the microdetermination of water by the Karl Fischer method. The new chapter would be a reproduction of the existing chapter in the *European Pharmacopoeia*.

The new chapter had been initially drafted, and then discussed at the informal consultation on quality control and pharmacopoeial specifications for medicines, in April 2023. It had then gone for public consultation from August to October 2023.

The ECSPP discussed the new chapter. It suggested renumbering the existing and new chapters on determination of water in *The International Pharmacopoeia* as separate subsections of a single umbrella chapter.

The Expert Committee adopted the new general chapter, subject to the minor amendment discussed.

6.2.2 Melting temperature and range

The ECSPP was asked to consider revisions to the general chapter on melting temperature and range in *The International Pharmacopoeia*. The revisions had been designed to make the chapter relevant to instruments using electronically heated blocks and instruments with heated liquids in vessels.

The revised chapter had been drafted in June 2022 and discussed at the informal consultation on quality control and pharmacopoeial specifications for medicines in April 2023. It had gone for public consultation from July to September 2023.

The ECSPP discussed the revised chapter and feedback received during the public consultation and suggested minor amendments to the text, including use of the term "melting point" instead of "melting temperature".

The Expert Committee adopted the revised general chapter, subject to the minor amendments discussed.

6.2.3 Chromatography

The ECSPP was asked to consider a revision to the general chapter on chromatography in *The International Pharmacopoeia*. The existing chapter, which had been adopted by the fifty-sixth ECSPP, comprised the internationally harmonized text developed by the PDG. The revision had been proposed to reflect recent changes made to the PDG's harmonized text on how to define the signal-to-noise ratio.

The revision had been drafted in December 2022 in line with information received by the PDG and discussed at the informal consultation on quality control and pharmacopoeial specifications for medicines in April 2023.

The ECSPP discussed the revision.

The Expert Committee adopted the revised general chapter.

6.2.4 Test for diethylene glycol and ethylene glycol in liquid preparations for oral use

The ECSPP was asked to consider adopting a new test for diethylene glycol (DEG) and ethylene glycol (EG) in liquid preparations for oral use, within the supplementary information section of *The International Pharmacopoeia*. The new test had been drafted in response to several alerts to substandard cough syrups that had been contaminated with DEG and EG.

The International Pharmacopoeia already had a test for DEG and EG in the monograph on paracetamol oral solutions, based on gas chromatography. But an additional test had been deemed necessary to enable national quality control laboratories without access to a gas chromatograph to quickly identify substandard products that posed a risk to patients. The newly proposed test adopted a two-level approach in which less resourced national quality control laboratories first screened samples for non-compliance using a semiquantitative thin-layer chromatography method and then sent any suspected contaminated products to a collaborating laboratory or regional centre for confirmation by gas chromatography.

The new text had been drafted in February 2023 and discussed at the informal consultation on quality control and pharmacopoeial specifications for medicines in April 2023. It had also been duly revised based on comments received during the public consultation that had been held from July to September 2023.

The Expert Committee discussed the latest draft of the test. It noted that the limited sensitivity of the thin-layer chromatography method meant that there remained a small risk of false negatives for finished products with DEG/EG concentrations between the limit considered to be safe (0.1%) and the detection limit of the method; and that that risk would have to be weighed against the risk of not testing any samples for contamination and not detecting more samples that posed a risk to patients.

Participants discussed the wording of the introduction and scope of the chapter and recommended considering action from regulators based solely on detection made through the screening test by thin-layer chromatography.

After discussing the results of several laboratory investigations on the test (see section 6.2.5), the Expert Committee agreed that the method was fit for its intended use. It clarified that the two-level approach was recommended only for national quality control laboratories without access to a gas chromatograph. All laboratories with a gas chromatograph, and all manufacturers, would still be expected to test for DEG and EG contamination using gas chromatography.

After the ECSPP decided to adopt the new test, it was also asked to consider a revision to the general monograph on liquid preparations for oral use (see section 6.3.1) and a revision to the monograph on paracetamol oral solution (see section 6.4.7). The Expert Committee agreed to all the revisions proposed.

The ECSPP was also asked to suppress the monographs on propylene glycol, glycerol and glycerol 85% from the next edition of *The International Pharmacopoeia* because those excipients were at risk of DEG and EG contamination but their monographs did not include a test for them. The ECSPP was asked to replace the suppressed excipient monographs with the monographs on propylene glycol and glycerol that were being developed by the PDG (once the group had signed off final versions of those texts).

The Expert Committee did not agree to suppress the three excipient monographs from *The International Pharmacopoeia*. Instead, participants suggested including a note in each monograph to refer to the new test for DEG and EG in liquid oral dosage forms in the supplementary information section and make it clear that manufacturers were expected to use the gas chromatography method to test for DEG and EG contamination.

The Expert Committee adopted the new test for inclusion in the supplementary information section of The International Pharmacopoeia*, subject to finalization by a group of experts. The Expert Committee further adopted the revised general monograph on liquid preparations for oral use (see section 6.3.1) and the revised monograph on paracetamol oral solution (see section 6.4.7). The Expert Committee also agreed to include a reference to the new test for DEG and EG in liquid preparations for oral use in the monographs for propylene glycol, glycerol and glycerol 85% (m/m), making it clear that manufacturers must use the gas chromatography method.*

6.2.5 Investigations to evaluate the suitability of proposed procedures

Dr Mingzhe Xu, Co-Chair of the ECSPP, updated the ECSPP on the results of investigations to evaluate the suitability of the procedures proposed for the new DEG and EG test (see section 6.2.4). He described how laboratories in China had performed investigations to optimize the parameters of both the thin-layer chromatography and the gas chromatography methods.

Dr Xu confirmed that the results had shown that both methods were accurate; and that WHO's tiered approach to determine DEG and EG in medicines was science based and feasible, as well as being globally applicable, including in Member States with limited laboratory resources.

The Expert Committee noted the update.

6.3 General monographs for dosage forms

6.3.1 Liquid preparations for oral use

Because the ECSPP had adopted the test for DEG and EG in liquid preparations for oral use (see section 6.2.4), it was also asked to consider a revision to the general monograph on liquid preparations for oral use to add a reference to the new test.

The Expert Committee adopted the revised general monograph.

6.4 Specifications and draft monographs for medicines, including paediatrics and candidate medicines for COVID-19

6.4.1 COVID-19 therapeutics

Molnupiravir

Molnupiravir capsules

Draft monographs on molnupiravir and molnupiravir capsules were proposed for inclusion in The International Pharmacopoeia. As the first public standards on molnupiravir, those monographs would be expected to play an important role in ensuring access to safe, effective, and quality-assured molnupiravir-containing medicines.

Both monographs had been drafted in December 2021 and sent for public consultation in January 2022. They had been discussed at the fifty-sixth ECSPP, where they had been adopted subject to finalization by a group of experts after a public consultation. Laboratory investigations to verify analytical provisions had been completed by August 2022, after which both monographs had gone out for another public consultation and been discussed at the 2023 informal consultation on quality control and pharmacopoeial specifications for medicines, and then sent for a third public consultation from August to September 2023.

The ECSPP reviewed the comments received on both draft monographs and discussed the proposed limits for related substances, which, it was noted, meant that some APIs currently on the market would not comply with the monograph.

The Expert Committee also discussed the proposed dissolution test, specifically the principle of considering a degradation product formed during the testing in the determination of the amount of API released from the dosage form.

The Expert Committee confirmed the adoption of both new monographs.

Nirmatrelvir

Nirmatrelvir tablets

Draft monographs on nirmatrelvir and nirmatrelvir tablets were proposed for inclusion in *The International Pharmacopoeia*. As the first public standards on nirmatrelvir, those monographs would be expected to play an important role in ensuring access to safe, effective, and quality-assured COVID-19 therapeutics.

Both monographs had been drafted in late 2022, based on information received from manufacturers. They had been discussed at the informal consultation on quality control and pharmacopoeial specifications for medicines in April 2023, and then sent for public consultation from July to August 2023.

The Expert Committee discussed both monographs, including comments received through consultation, which had included a proposal to add a test for enantiomeric and diastereomeric purity. The Expert Committee agreed to include the proposed test in the nirmatrelvir monograph. It recommended continuing with laboratory investigations, specifically to verify the test for enantiomeric and diastereomeric purity, check the selectivity of the method used for dissolution and check whether that method would also be suitable for the assay.

The Expert Committee adopted the new monographs, subject to finalization by a group of experts following laboratory investigations and an additional public consultation. If major comments were received during the consultation, or if any major issues arose from the additional laboratory investigations, the monographs would be resubmitted to the next ECSPP.

6.4.2 Medicines for maternal, newborn, child and adolescent health

Estradiol valerate and norethisterone enantate injection

Based on a submission from a manufacturer and on laboratory investigations, the ECSPP was asked to consider including a new monograph on estradiol valerate and norethisterone enantate injection in *The International Pharmacopoeia*.

The proposed draft had been originally received in September 2018 and presented to the 2018 ECSPP meeting. Since then, it had been discussed at nearly every annual informal consultation on quality control and pharmacopoeial specifications for medicines, and at two further ECSPPs (in 2019 and 2020). The draft monograph had been revised several times in response to feedback received after each discussion and sent for public consultation from September to October 2023.

The ECSPP reviewed the latest version of the monograph, including the specifications for related substances, noting that the monograph did not require the determination of the sum of impurities because the signals for estradiol valerate and norethisterone enantate impurities overlapped and responded at different detection wavelengths.

The Expert Committee adopted the new monograph.

6.4.3 Antimalarial medicines

Pyrimethamine tablets

The ECSPP was asked to consider revising the existing monograph on pyrimethamine tablets. In particular, the proposed revision was to use an absorptivity value instead of a reference substance for dissolution testing. The absorptivity value had been determined by the EDQM and the Health Sciences Authority, Singapore.

The proposed revision had been discussed by a group of experts at the 2023 informal consultation on quality control and pharmacopoeial specifications for medicines. The experts had recommended that the revision did not need to go for public consultation because the intent to make a revision was already included in the existing monograph.

The ECSPP reviewed the proposed revision.

The Expert Committee adopted the revised monograph.

6.4.4 Antituberculosis medicines

Rifampicin

Test for MeNP in rifampicin

The ECSPP was asked to consider revising the existing monograph on rifampicin in response to the traces of nitrosamines that had been found in some batches of rifampicin API. The proposed revisions of the monograph would introduce a reference to a test for the suspected carcinogenic nitrosamine 1-methyl-4-nitrosopiperazine (MeNP) in the section on manufacture of the monograph, and would also make some changes to the test for related substances, following the method published in the *European Pharmacopoeia*. A suitable method to test for MeNP in rifampicin API was to be published in the supplementary section of *The International Pharmacopoeia*.

The proposed revisions had first been drafted in November 2020 and discussed at the 2021 information consultation on quality control and pharmacopoeial specifications for medicines. The revised monograph had been through two public consultations, from November 2020 to January 2021 and from July to September 2022. It was submitted to the ECSPP without laboratory verification of the test for related substances.

The method to test for MeNP in rifampicin had been developed and validated by the Health Sciences Authority, Singapore, and sent out for public consultation between June and September 2022. It had been discussed at the consultation on quality control and pharmacopoeial specifications for medicines in April 2023.

The ECSPP discussed the revised monograph and agreed that a suitable method for testing for nitrosamines should be published in the supplementary information section of *The International Pharmacopoeia*.

The Expert Committee agreed that reference should be made to the WHO Prequalification of Medicines Programme website regarding the published limit for MeNP; and that the suitability of the proposed test for MeNP should also be evaluated for all other combination product monographs in *The International Pharmacopoeia*.

The Expert Committee adopted the revised monograph on rifampicin and the new test for MeNP in rifampicin, subject to the amendments discussed.

6.4.5 Antiviral medicines, including antiretrovirals

Efavirenz

The ECSPP was asked to consider revising the existing monograph on efavirenz in *The International Pharmacopoeia*.

The proposed revisions included changes to the test for related substances. They had been drafted from February to May 2023 and discussed at the informal consultation on quality control and pharmacopoeial specifications for medicines in April 2023. The revised draft had been sent for public consultation in June–August 2023.

The ECSPP discussed the proposed revisions and comments received during the public consultation. The Expert Committee recommended a small editorial change to clarify the wording of the identity test.

The Expert Committee adopted the new monograph.

Tenofovir disoproxil fumarate

The ECSPP was asked to consider revising the existing monograph on tenofovir disoproxil fumarate, to add a requirement to the section "Manufacture" to control chloromethyl isopropyl carbonate (CMIC) in the API to a limit of not more than 50 parts per million, in line with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) harmonized guideline M7(R2) *Assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk* (*8*). The European Medicines Agency had recently published concerns over the mutagenicity of CMIC.

CMIC was typically used during the last step of synthesis of tenofovir disoproxil fumarate and residues of the chemical could carry over into the final API. The WHO PQT/MED had been treating the impurity as a likely mutagenic compound and had therefore contacted all prequalification manufacturers that used tenofovir disoproxil fumarate in their products to ask them to lower the limit for the impurity.

A first draft of the revised monograph had been prepared in March 2023 and discussed at the April 2023 informal consultation on quality control and pharmacopoeial specifications for medicines. The draft had then been sent out

for public consultation from August to October 2023 before being submitted to the ECSPP for possible adoption.

The Expert Committee adopted the revised monograph.

Tenofovir disoproxil tablets

The ECSPP was asked to consider revising the existing monograph on tenofovir disoproxil tablets to align it with new requirements for the combination product monograph on dolutegravir, lamivudine and tenofovir tablets that had been approved by the fifty-sixth ECSPP and published in the 11th edition of *The International Pharmacopoeia*.

A first draft of the revised monograph had been prepared in May 2022 and had been followed by laboratory investigations to verify the suitability of the proposed analytical provisions. In August 2022, the draft had been sent out for public consultation. It was discussed at the informal consultation on quality control and pharmacopoeial specifications for medicines in April 2023.

The ECSPP reviewed the impurity limits contained in all monographs containing tenofovir disoproxil that had already been published in *The International Pharmacopoeia*. It noted that the proposed specifications were aligned with the recently adopted monograph for dolutegravir, lamivudine and tenofovir tablets. The Expert Committee questioned whether one of the mutagenic impurities, 9-propenyladenine, was also a degradation product of the API, noting that if it was, it would also need to be controlled in tenofovir disoproxil fumarate finished products. It further noted that after a literature search and consultation with WHO prequalification colleagues, there was no indication that 9-propenyladenine was a degradation product of the API.

The Expert Committee adopted the revised monograph.

Lamivudine and tenofovir tablets

The ECSPP was asked to consider revising the existing monograph on lamivudine and tenofovir tablets to align it with requirements in the monograph on dolutegravir, lamivudine and tenofovir tablets that had been approved by the fifty-sixth ECSPP and published in the 11th edition of *The International Pharmacopoeia*.

A first draft of the revised monograph had been prepared in May 2022 and sent for public consultation from August to September 2022. It had been discussed at the informal consultation on quality control and pharmacopoeial specifications for medicines in April 2023 before being presented to the ECSPP for possible adoption.

The Expert Committee adopted the revised monograph.

6.4.6 Medicines for tropical diseases

Albendazole

Albendazole chewable tablets

Albendazole tablets

The ECSPP was asked to consider revisions to the monograph on albendazole to replace the thin-layer chromatography test for related substances with a high-performance liquid chromatography test. Further revisions were also proposed to inform users that the substance showed polymorphism; introduce a test on "clarity and colour of solution"; update the style of the monograph; and make several other minor edits.

Drafted in February 2018, the revised monograph had already been discussed at four annual informal consultations and two ECSPPs between 2018 and 2023. It had also been through two public consultations (in 2019 and 2023).

The ECSPP was also asked to consider revising the test for related substances in the monograph on albendazole chewable tablets to align it with the method submitted by the originator (gradient high-performance liquid chromatography). That revision had been drafted in July 2023 and sent for public consultation from July to August 2023.

The ECSPP was also asked to consider a proposal for a new monograph on albendazole tablets, which would differ from the monograph on albendazole chewable tablets in its definition section. The new monograph had been drafted in April 2019, discussed at two informal consultations on quality control and pharmacopoeial specifications for medicines and one ECSPP, and sent out for two public consultations (in 2019 and 2023).

The Expert Committee discussed all three monographs.

The Expert Committee adopted the revised monographs on albendazole and albendazole chewable tablets; and adopted the new monograph on albendazole tablets.

6.4.7 Other medicines

Yttrium (^{90}Y) silicate injection

The ECSPP was asked to consider suppressing the monograph on yttrium (^{90}Y) silicate injection from *The International Pharmacopoeia*. That proposal followed a recommendation from the IAEA at the fifty-sixth meeting of the ECSPP, which stated that yttrium (^{90}Y) silicate injections were no longer in clinical use.

The proposed suppression had been sent out for public consultation from January to February 2023 and no comments or objections had been received.

The Expert Committee agreed to suppress the monograph on yttrium (^{90}Y) silicate injection from the next edition of The International Pharmacopoeia.

Paracetamol oral solution

Because the ECSPP had adopted the test for DEG and EG in liquid preparations for oral use (see section 6.2.4), it was also asked to consider revisions to the monograph on paracetamol oral solution. Specifically, the proposed revisions were to delete the section specifying a gas chromatography test for DEG and EG.

The Expert Committee adopted the revised monograph.

6.5 Update on the informal consultations on quality control and pharmacopoeial specifications for medicines

ECSPP members were updated on the April 2023 consultation on quality control and pharmacopoeial specifications for medicines.

At the consultation, 24 experts from across the world had been updated on the progress made on 57 monographs and general texts under development for *The International Pharmacopoeia*. The experts had discussed draft proposals and reports of laboratory investigations; and they had provided guidance and advice on future work.

The Expert Committee thanked all participants of the informal consultations for their work in moving forward the development of monographs and general texts for *The International Pharmacopoeia*.

The Expert Committee noted the update.

7. Quality control: international reference materials

7.1 Update on International Chemical Reference Substances

EDQM representative Dr Remmelt van der Werf and Dr Schmidt presented an update on activities related to International Chemical Reference Substances (ICRS) and infrared reference spectra.

ICRS were used to identify and determine the purity or assay of pharmaceutical substances and preparations; or to verify the performance of test methods. Dr Schmidt noted that the EDQM had been the custodial centre for ICRS since 2010 and as such had been responsible for establishing, storing and distributing ICRS.

Dr van der Werf highlighted some of the EDQM's key achievements in relation to ICRS in 2022, which included completing six ICRS establishment reports for WHO. The EDQM released 12 batches of ICRS for distribution; it also monitored 22 standards for continuous fitness for purpose, with no significant findings on quality to report.

Dr van der Werf informed the ECSPP that since late 2022, the EDQM had been using advanced manufacturing techniques, such as compounding and vial evaporation, in the establishment and manufacturing of ICRS. That marked a significant change in ICRS standards that was expected to help overcome supply problems with candidate materials for impurities. Remdesivir for system suitability, batch 1, had been the first example of an ICRS produced with advanced manufacturing techniques. New approaches were also being explored for other substances (including linezolid impurity E, norethisterone enantate for system suitability and lumefantrine for system suitability).

Dr Schmidt updated the ECSPP on recently established ICRS. Since the previous meeting of the ECSPP in April 2022, the ICRS Board had released the following chemical reference substances, established by the EDQM, for use according to the provisions of *The International Pharmacopoeia*:

- artenimol ICRS, batch 2
- pyrimethamine ICRS, batch 2
- artesunate ICRS, batch 3
- dolutegravir impurity B ICRS, batch 1
- dolutegravir impurity D ICRS, batch 1
- dolutegravir sodium ICRS, batch 1
- remdesivir ICRS, batch 1
- remdesivir for system suitability ICRS, batch 1.

Dr Schmidt noted that when establishing the remdesivir ICRS, the EDQM had determined a second absorptivity value for remdesivir. The ECSPP was asked to consider revising the absorptivity value for remdesivir in the monograph on remdesivir intravenous infusion in the next edition of *The International Pharmacopoeia* to reflect the mean of the two values determined.

The WHO Secretariat expressed its gratitude to:

- the EDQM for its work in establishing, storing and distributing ICRS and for providing guidance and support to primary reference standards;
- the ICRS Board for reviewing the establishment reports and releasing the ICRS;
- the collaborating laboratories for participating in collaborative trials to determine the assigned content.

The Expert Committee discussed the expected advantages for *The International Pharmacopoeia* of using advanced manufacturing techniques to establish ICRS.

The Expert Committee noted the report and confirmed the release of all the ICRS listed above. It further adopted the revised absorptivity value for remdesivir in The International Pharmacopoeia *monograph for remdesivir intravenous infusion*.

8. Quality assurance: good manufacturing practices and inspection

8.1 Good manufacturing practices for excipients used in pharmaceutical products

Dr Estevão Cordeiro and Expert Committee member Dr Adriaan J. Van Zyl updated the Expert Committee on the revised guideline *WHO good manufacturing practices for excipients used in pharmaceutical products*.

The previous version of the guideline – *Good manufacturing practices: supplementary guidelines for the manufacture of pharmaceutical excipients* (*9*) – had been published in 1999. Reports of pharmaceutical products containing contaminated excipients (sometimes leading to patient deaths) suggested a need to review the original guideline. A revised guideline had also been needed to better reflect the latest concepts and principles in good manufacturing practices (GMP), for example ongoing improvement and a life cycle approach.

A first draft of the new document had been developed in late 2022 and sent to a group of experts for comment before being posted for public consultation in March 2023. More than 600 comments on the document had been received. Those had been discussed at a virtual meeting with experts in June 2023 and a revised draft had been prepared for presentation to the fifty-seventh ECSPP.

Compared with the previous guideline, the revised draft had changed in structure, scope and detail to reflect a move from supplementary guidelines towards a full stand-alone GMP guideline. The revised draft provided guidance on, among other things, the production, packaging, labelling, control, release, storage and distribution of excipients used in pharmaceutical products. It had a focus on GMP under an appropriate quality management system that evaluated and controlled risks effectively. The revised draft did not cover protection of the environment, or safety of personnel.

Because excipients were generally used as purchased, the revised guideline emphasized the need for manufacturers to provide quality materials that were homogeneous in chemical and physical characteristics. It stated that manufacturers should have specific analytical procedures to ensure suitability for intended use; and that those should meet pharmacopoeial and regulatory requirements. The revised guideline emphasized the need to implement risk management principles to identify and mitigate risks.

The Expert Committee discussed various aspects of the revised guideline. Following a query from the floor, the applicability of the document was clarified: the revised guideline would apply to all manufacturers of excipients that were intended for use in pharmaceutical products, not only those manufacturers that produced excipients with high risk of impurities. Yet, identifying high-risk

excipients would be important, and the Expert Committee agreed that there was a need to develop a list of excipients with possible impurities and high-risk excipients (such as DEG, EG and nitrosamines) alongside additional guidance on managing risks for those, which could later be appended to the guideline. The Expert Committee agreed that another useful appendix to the guideline would be a document highlighting additional points to consider in manufacturing excipients for pharmaceutical products, such as risk management, separate facilities and track and trace.

The Expert Committee noted that excipient manufacturers were not yet subject to GMP inspections. The revised guideline had been written for regulators and manufacturers and could be applied by both groups of personnel. The Expert Committee noted that it would be up to countries to decide how to take the guideline forward and suggested that a key next step for WHO would be to encourage Member States to take responsibility for implementation to enforce the revised guideline. The Expert Committee agreed that enforcement would not be immediate and there would need to be an appropriate transition time to enable manufacturers of excipients for pharmaceutical products to adjust to the new requirements.

Meeting participants from several WHO departments, including Incidents and Substandard and Falsified Medical Products, PQT/MED, and the WHO Prequalification Team – Inspection Services (PQT/INS), expressed their strong support for the revised guideline. ECSPP members also strongly endorsed the revised guideline. The Expert Committee thanked the drafting group for their work in developing the guideline, noting it was expected to be extremely useful as the world moved to increase control of excipients.

The Expert Committee adopted the WHO good manufacturing practices for excipients used in pharmaceutical products *(Annex 2). The Expert Committee further supported the development of two appendices: a points to consider document, focusing on a risk management-based approach for excipients with possible impurities; and a list of high-risk excipients.*

8.2 Good manufacturing practices for in-house cold kits for radiopharmaceutical preparations

Dr Aruna Korde, Radiopharmaceutical Scientist, IAEA, updated ECSPP members on progress in developing GMP guidelines for radiopharmaceuticals by the IAEA and WHO.

In early 2018, IAEA experts had recommended updating guidance on GMP for radiopharmaceuticals. Since then, the ECSPP had adopted two new guidelines: the *International Atomic Energy Agency and World Health Organization guideline on good manufacturing practices for radiopharmaceutical products* (*10*), which gave a general overview of the minimum GMP requirements

for radiopharmaceutical products; and the *IAEA/WHO guideline on good manufacturing practices for investigational radiopharmaceutical products* (*11*).

The latest proposed guideline focused on GMP for in-house cold kits for radiopharmaceutical preparations. It had been developed to align with previous IAEA/WHO guidelines and covered diverse topics, including quality management system, personnel, documentation, premises, equipment and materials, production, quality control, qualification and validation, stability, and complaints, recalls and returns.

A first working document had been developed by a global expert drafting team from May 2022 to May 2023. That working document had been circulated for comment to global experts and discussed at the June 2023 consultation on good practices for health products manufacture and inspection. A revised version had then been posted for public consultation in July 2023. Comments received had been discussed by the expert drafting team and a revised draft had been prepared before being presented to the ECSPP.

Dr Korde presented some of the key comments received, which had included definitions of key terms, requirements for personnel, and quality control.

Following a query from the Expert Committee, Temporary Adviser Mr Sergio Camillo Todde clarified that the guideline only applied to cold kits that were produced in-house and in small batches; it was not intended to cover the industrial, large-scale production of cold kits.

The Expert Committee adopted the IAEA/WHO good manufacturing practices for in-house cold kits for radiopharmaceutical preparations *(Annex 3)*.

8.3 Good practices for pharmaceutical quality control laboratories

Dr Gwaza and Ms Natércia Guerra Simões, Technical Officer of WHO Laboratory Networks and Services, presented the revised guideline *WHO good practices for pharmaceutical quality control laboratories*. The guideline had previously been updated in 2010 (*12*), but international guidelines related to laboratory quality assurance had changed since then, especially with regard to risk management applicable to laboratories, data integrity and computer validation, and uncertainty of measurement. Experience from inspections of pharmaceutical quality control laboratories had also identified several areas where new or clearer information was required. For example, the COVID-19 pandemic had highlighted the need for clearer guidance on risk management, crisis management and business continuity. A fast-changing regulatory environment had further increased the need for planning and strategic management.

The revised guideline addressed key topics, including performance evaluation, risk management, crisis management, communications management, data integrity and computer validation, and measurement uncertainty. It had

broadened the scope of the previous guideline to include quality control laboratories of manufacturers, which marked a major change compared with the previous guideline.

The revised guideline covered the organization and management system, planning and strategic management, resources, technical activities and safety rules. There were three new appendices. The revised guideline was consistent with ISO/IEC 17025:2017: General requirements for the competence of testing and calibration laboratories.

A first draft working document had been prepared in early 2021 and further developed by an expert working group, in consultation with WHO colleagues. Over the next two years, the document had been discussed and refined through a series of virtual meetings and informal consultations. The resulting second draft had been posted for public consultation from August to October 2023, and the feedback was presented to the ECSPP alongside a third revision of the guideline.

Ms Guerra Simões highlighted some of the challenges expected with implementing the guideline should it be adopted by the ECSPP. Those included reconciliating the needs and requirements for a national quality control laboratory with the requirements for laboratories of manufacturers, which must fully comply with GMP but were not required to comply with internationally accepted good practices for laboratories (such as ISO 17025). Laboratories would also need time to implement the new requirements and a transition period might be needed. Ms Guerra Simões stressed that the newly proposed guideline would never be used in isolation but should rather be used alongside other guidelines.

The Expert Committee reviewed comments received during public consultation and discussed some of the key issues raised, including the validation of methods described under marketing authorizations and the requirements for regular participation in proficiency testing and collaborative studies, which they agreed would be optional for quality control laboratories of a pharmaceutical manufacturer. Other comments discussed by the Expert Committee concerned system suitability tests (which should be required before and throughout any analysis of samples), verification of basic pharmacopoeial methods, traceability and handling of retained samples, uncertainty of measurement, pharmacopoeial decision rules, out-of-specification results, and certificate of analysis.

The Expert Committee adopted the WHO good practices for pharmaceutical quality control laboratories *(Annex 4), subject to all the amendments discussed, and confirmation of the final version in a written procedure. If major comments were received on the final version, the document would be resubmitted to the next ECSPP.*

8.4 Recommendations from the consultations on good practices for health products manufacture and inspection

Dr Gwaza updated ECSPP members on the previous two annual consultations on good practices for health products manufacture and inspection, which took place in November 2022 and June 2023.

During those consultations, a small group of experts had discussed progress on the revision or development of various GMP- and inspection-related guidance texts and had made several recommendations for new guidance texts.

8.4.1 2022 consultation

At the 2022 consultation on good practices for health products manufacture and inspection, the group of experts had recommended developing:

- GMP for pharmaceutical manufacturers of antimicrobials (in collaboration with the United Nations Environment Programme);
- an update on the WHO/UNFPA female condom generic specification (see section 9.1);
- WHO guidance to address nitrosamine contamination from a GMP or inspection perspective;
- training materials and case study examples to support the implementation of the recently adopted guidelines *WHO good practices for research and development facilities of pharmaceutical products* (*13*) and *WHO good manufacturing practices for investigational* products (*14*).

8.4.2 2023 consultation

At the 2023 consultation on good practices for health products manufacture and inspection, the group of experts had discussed the progress of guidance texts on GMP for excipients used in pharmaceutical products (see section 8.1), GMP for in-house cold kits for radiopharmaceutical preparations (see section 8.2), good practices for pharmaceutical quality control laboratories (see section 8.3), and guidance on female condom generic specification (see section 9.1).

The experts had reiterated the need to develop GMP for pharmaceutical manufacturers of antimicrobials and guidance to address nitrosamine contamination. They had further recommended development of:

- a document reflecting WHO expectations for retesting incoming excipients at risk of DEG/EG contamination;
- a points to consider document on continuous manufacturing that could complement *ICH guideline Q13 on continuous manufacturing*

of drug substances and drug products, and facilitate continuous manufacturing in WHO Member States;
- a reflection paper or points to consider document on artificial intelligence in pharmaceutical manufacturing.

The group of experts had also reviewed a gap analysis of the WHO GMP and inspection guidelines and established a list of potential areas where work might be needed to update or develop new guidance. The list had been sent for public consultation and used to inform a proposed workplan (see section 8.5).

The Expert Committee noted the update from the 2022 consultation on good practices for health products manufacture and inspections, and expressed its support for the development of WHO guidance to address nitrosamine contamination from a GMP or inspection perspective and WHO guidance on waste and wastewater management from pharmaceutical manufacturing with a focus on antimicrobials.

The Expert Committee noted the update from the 2023 consultation on good practices for health products manufacture and inspections, and expressed its support for the development of a document reflecting WHO expectations for retesting incoming excipients at risk of DEG/EG contamination; a points to consider document on continuous manufacturing; and a reflection paper or points to consider document on artificial intelligence in pharmaceutical manufacturing.

8.5 Proposals to revise, or develop new, GMP- and inspection-related guidelines

Dr Luther Gwaza presented a 2024–2027 workplan for revising (or developing new) guidance related to GMP and inspection.

The workplan included a shortlist of potential targets for revision or development that had been derived from a gap analysis of the existing WHO GMP compendium of guidelines alongside recommendations from experts (see section 8.4) and public consultation. Stakeholders had been invited to make suggestions for guidelines that needed revising or developing to better meet their existing GMP or inspection needs.

Any GMP- or inspection-related guideline that was more than seven years old, or for which significant changes in the field had been identified, had also been included in the list.

The ECSPP considered the list and prioritized the following documents for development in the workplan:

- WHO guidance on waste and wastewater management from pharmaceutical manufacturing with a focus on antimicrobials;
- guidance to address nitrosamine contamination from a GMP or inspection perspective;

- a points to consider or reflection paper on artificial intelligence in pharmaceutical manufacturing;
- a points to consider or reflection paper on continuous manufacturing from a GMP or inspection perspective;
- guidance on computerized systems.

The Expert Committee also considered 17 guidelines for revision (Table 1).

Table 1
List of GMP- and inspection-related guidelines considered for revision by the ECSPP

Guideline	Year	Annex, TRS
Provisional guidelines on the inspection of pharmaceutical manufacturers	1992	Annex 2, TRS No. 823
Guidelines for inspection of drug distribution channels	1999	Annex 6, TRS No. 885
Guidelines on pre-approval inspections	2002	Annex 7, TRS No. 902
Guidelines on packaging for pharmaceutical products	2002	Annex 9, TRS No. 902
Model certificate of good manufacturing practices	2003	Annex 5, TRS No. 908
WHO guidelines for sampling of pharmaceutical products and related materials	2005	Annex 4, TRS No. 929
WHO good manufacturing practices for active pharmaceutical ingredients	2010	Annex 2, TRS No. 957
WHO good practices for pharmaceutical microbiology laboratories	2011	Annex 2, TRS No. 961
WHO guidelines for preparing a laboratory information file	2011	Annex 13, TRS No. 961
WHO guidelines for drafting a site master file	2011	Annex 14, TRS No. 961
WHO guidelines on quality risk management	2013	Annex 2, TRS No. 981
WHO good manufacturing practices for pharmaceutical products: main principles	2014	Annex 2, TRS No. 986
Assessment tool based on the model quality assurance system for procurement agencies: aide-memoire for inspection	2014	Annex 4, TRS No. 986

Table 1 *continued*

Guideline	Year	Annex, TRS
Guidance on good manufacturing practices: inspection report	2016	Annex 4, TRS No. 996
Guidelines on heating, ventilation and air-conditioning systems for non-sterile pharmaceutical products	2018	Annex 8, TRS No. 1010
Guidance on good practices for desk assessment of compliance with good manufacturing practices, good laboratory practices and good clinical practices for medical products regulatory decisions	2018	Annex 9, TRS No. 1010
Good chromatography practices	2020	Annex 4, TRS No. 1025

TRS: Technical Report Series.

The Expert Committee noted that the prioritization of the list of guidelines for development would depend on available resources and might change.

The Expert Committee adopted the 2024–2027 workplan as presented; and agreed to establish groups of experts to advance work on each of the prioritized guidelines and new topics.

9. Quality assurance: distribution and supply chain

9.1 WHO/UNFPA female condom generic specification

Ms Linda Serwaa, Technical Specialist, UNFPA, and Dr William Potter, Consultant to UNFPA, summarized the WHO/UNFPA collaboration to update the existing prequalification guidance for contraceptive devices and condoms, which had been originally published in 2008 and which no longer reflected the understanding and evidence in the field.

Several updated guidelines for contraceptive devices and condoms had already been adopted by the ECSPP (on prequalification programme guidance, technical specifications for male latex condoms, specifications for plain lubricants, testing male latex condoms, storage and shipping recommendations, post-market surveillance, natural rubber latex male condom stability studies and Tcu380A intrauterine devices).

Draft new guidance for female condom generic specifications was presented to the ECSPP for adoption. The draft document described the general, design, performance and packaging requirements for female condoms and the methods of verification. Compared with the previous guideline, the document's structure had been simplified and changes had been made to the potential design, general requirements, description, clinical investigation, failure modes and generic specification. Ms Serwaa and Dr Potter emphasized that the proposed new guidance aligned with the international standard ISO 25841:2017: Female condoms – requirements and test methods, and reflected practical experience of using the specification for female condom prequalification and for quality assurance and quality control purposes.

The new guidance was intended to help ensure that quality-assured products were purchased and distributed to end users; it should not be considered or used as a standard for regulatory purposes.

The document had been developed until July 2022, and then sent for public consultation. Comments received had been discussed at the November 2022 consultation on good practices for health products manufacture and inspection and, together with the experts' feedback, had been used to prepare a revised draft for a second public consultation in December 2022. Feedback from the second consultation had been discussed at the June 2023 informal consultation on good practices for health products manufacture and inspection and used to draft the latest version of the document, which was presented to the ECSPP.

The ECSPP reviewed the latest version of the document, including revisions made after the second public and informal consultations, which it noted were largely editorial. It noted that definitions for "visible holes" and "non-visible holes" still needed to be added to the document; those would be taken from ISO 25841.

The Expert Committee adopted WHO/UNFPA female condom generic specification *(Annex 5), subject to the minor amendment discussed.*

10. Regulatory guidance and model schemes

10.1 WHO Biowaiver List: proposal to waive in vivo bioequivalence requirements for medicines included in the EML

Dr Estevão Cordeiro and Temporary Advisers Professor Maria del Val Bermejo Sanz and Professor Giovanni M. Pauletti gave an overview of the WHO Biowaiver Project and presented the project's work over the previous year. The project was WHO's solubility classification exercise and provided an important tool for national regulatory authorities and pharmaceutical manufacturing companies by suggesting medical products that were eligible for a waiver from in vivo bioequivalence studies.

The project used sound methods to determine the equilibrium solubility profile of medicines listed in the EML, as detailed in the WHO *Protocol to conduct equilibrium solubility experiments for the purpose of Biopharmaceutics Classification System-based classification of active pharmaceutical ingredients for biowaiver* (*15*). Since 2018, the WHO Biowaiver Project had been organized into annual study cycles. Its results had been incorporated each year in the WHO Biowaiver List – a living document published as an annex to each ECSPP report.

In 2022–2023, as part of cycle V of the WHO Biowaiver Project, a set of APIs had been prioritized and classified. The data from that work were presented to the fifty-seventh ECSPP and had been integrated into an updated version of the WHO Biowaiver List.

Professor del Val Bermejo Sanz noted that preliminary results from cycle V revealed discrepancies in the linezolid solubility experiments. Those discrepancies had been discussed at the 2023 virtual consultation on regulatory guidance for multisource products (see section 10.5), where experts had recommended repeating the linezolid solubility experiments in cycle VI in at least four laboratories (including those involved in linezolid testing for cycle V), with samples from the same batch and manufacturer.

The ECSPP was then presented with a list of 12 APIs as the proposed focus of cycle VI of the WHO Biowaiver Project in 2024 (Table 2). The list included three APIs that were listed as alternatives to the main selection in case of logistical or procedural problems. The draft list of prioritized APIs had been circulated for public consultation in August 2023, followed by discussion at the virtual consultation on regulatory guidance for multisource products in September 2023, before being finalized and presented to the ECSPP.

Table 2
APIs proposed for cycle VI of the WHO Biowaiver Project

API in EML medicine	Therapeutic area	Indication	Highest therapeutic dose
Amitriptyline (hydrochloride)[a]	Medicines for mental and behavioural disorders	Medicines used in depressive disorders	75 mg
Amodiaquine (hydrochloride)[a]	Antiprotozoal medicines	Antimalarial medicines	600 mg
Biperiden (hydrochloride)[a]	Anticholinergic medicines	Parkinson disease	2 mg
Cefalexin (monohydrate)	Antibacterials	Antibiotics (access group)	2000 mg
Diethylcarbamazine (citrate)[a]	Anthelmintic medicines	Antifilarials	6 mg/kg
Hydrochlorothiazide[a]	Cardiovascular medicines	Medicines used in heart failure; antihypertensive medicines; diuretics	100 mg
Linezolid (repetition of cycle V experiments)	Antibacterials	Antituberculosis medicines; antibiotics (reserve group)	600 mg
Loperamide	Antidiarrhoeal medicines	Medicines for other common symptoms in palliative care	4 mg
Miltefosine	Antiprotozoal medicines	Antileishmaniasis medicines	50 mg
Misoprostol	Uterotonic medicines	Postpartum haemorrhage	800 µg
Pyrazinamide[a, b]	Antibacterials	Antituberculosis medicines	2000 mg

Table 2 *continued*

API in EML medicine	Therapeutic area	Indication	Highest therapeutic dose
Zidovudine[a, c]	Anti-infective medicines	Nucleoside/ nucleotide reverse transcriptase inhibitors (HIV)	300 mg

Grey shading: APIs listed as alternatives in case of logistical or procedural problems.

[a] APIs characterized in the WHO 2006 classification.

[b] Pyrazinamide as monocomponent and in fixed-dose combination with isoniazid (listed in the WHO Biowaiver List), ethambutol (listed in the WHO Biowaiver List) and rifampicin (listed in the WHO Biowaiver List).

[c] Zidovudine as monocomponent and in fixed-dose combination with lamivudine (listed in the WHO Biowaiver List).

The ECSPP thanked all those involved in enabling the WHO Biowaiver Project to characterize the solubility profiles of prioritized APIs using experimental laboratory data. It emphasized the value of that work not only for bioequivalence but also for the quality assessment of APIs and finished pharmaceutical products.

Following a query from the floor, Dr Estevão Cordeiro clarified that there were no current plans to classify APIs by permeability, but should the ECSPP recommend that, the WHO Secretariat could investigate the feasibility of developing a project for classifying APIs based on permeability.

The Expert Committee agreed to integrate the results of cycle V into the WHO Biowaiver List (Annex 6). It further suggested promoting the project's results to regulatory authorities and other stakeholders. The Expert Committee also accepted the prioritized APIs proposed for study in cycle VI, including repetition of the linezolid solubility experiments.

10.2 WHO list of international comparator products

Dr Estevão Cordeiro and Temporary Adviser Dr Jan Welink updated ECSPP members on progress to update the WHO list of international comparator pharmaceutical products. The list had originally been published in 2016 as a tool for national regulatory authorities and manufacturers. It provided information on finished pharmaceutical products that could be selected as comparators for pharmaceutical products on the 2013 WHO Model List of Essential Medicines in bioequivalence studies. Dr Estevão Cordeiro summarized the criteria that had been used for selecting international comparators. He emphasized that all information in the list aligned with the *Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability* (*16*) and the WHO *Guidance on the selection of comparator pharmaceutical*

products for equivalence assessment of interchangeable multisource (generic) products (*17*).

Dr Estevão Cordeiro informed the ECSPP that by the start of the 2023 revision there had been four updates to the EML since 2016, which meant that 147 new products and 70 new formulations had been added to the EML since the list of international comparator products was first published.

Dr Welink informed the ECSPP that the newly revised list was being prepared in three phases: new formulations, new additions of products, and already-listed products. The third phase was still ongoing. All revisions had been based on publicly available information from the United States Food and Drug Administration Approved Drug Products with Therapeutic Equivalence Evaluations (commonly known as the Orange Book), European public assessment reports and Martindale: The Complete Drug Reference, with review and input from the WHO PQT/MED.

The revised list would be published as a living database (with the pending update percentage of the already-listed products highlighted) to be regularly revised and updated to reflect users' feedback and changes in the EML and product availability.

The Expert Committee noted the update and supported the proposed approach for publishing and revising the WHO list of international comparator pharmaceutical products.

10.3 WHO guideline on Biopharmaceutics Classification System-based biowaivers

Dr Estevão Cordeiro and Dr John Gordon, Expert Committee member, updated ECSPP members on the development of the *WHO guideline on Biopharmaceutics Classification System-based biowaivers* as recommended by a group of experts at the joint meeting on regulatory guidance for multisource products in November 2022. The new guideline would align with the international requirements in the ICH M9 harmonised guideline *Biopharmaceutics classification system-based biowaivers* (*18*). The ICH had adopted the new M9 guideline in November 2019; since then, many national regulatory authorities around the world had also adopted the new M9 guideline, as had the WHO prequalification team.

The intent of the new ICH M9 guideline was consistent with the existing WHO recommendations and requirements for Biopharmaceutics Classification System (BCS)-based biowaivers set out in the WHO *Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability* (*16*). The new ICH M9 guideline, however, had a more clearly defined scope, which, together with an increased worldwide adoption, had led to a new WHO guideline being recommended.

If adopted by the ECSPP, the new WHO guideline would supersede the BCS-based biowaiver section of the WHO *Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability* (*16*).

The new WHO guideline aimed to support the biopharmaceutics classification of APIs and the BCS-based biowaiver of bioequivalence studies for finished pharmaceutical products. Dr Gordon emphasized that the newly proposed guideline was mostly consistent with the ICH M9 guideline. He highlighted a few key differences in the new guideline, which included a simplified definition of "high solubility" for the purpose of BCS classification of APIs. An additional criterion was introduced on allowable differences in excipient content between proposed and comparator products based on a 20% limit on deviation of the total core weight of the proposed product from that of the comparator product.

A first draft of the new WHO guideline had been undertaken in April and May 2023. In July 2023 it had been sent to a group of experts for comment and posted for public consultation. In total, 106 comments had been received. Feedback received had been discussed at a virtual meeting with an informal drafting group in September 2023, after which a revised document had been prepared for presentation to the ECSPP.

The ECSPP was asked to consider how to reflect the ongoing changes to the WHO guidance on demonstration of interchangeability (*16*).

The ECSPP thanked all those involved in developing the new guideline.

The Expert Committee adopted the WHO guideline on Biopharmaceutics Classification System-based biowaivers *(Annex 7). The Expert Committee decided to republish* Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability *(Annex 8), suppressing sections 10.1 and 10.2 and making reference to the* WHO guideline on Biopharmaceutics Classification System-based biowaivers.

10.4 Guideline on bioanalytical method validation and study sample analysis

Dr Gwaza and Temporary Adviser Dr Alfredo García Arieta updated ECSPP members on progress in developing a new guideline on bioanalytical method validation and study sample analysis, which had been based on *ICH guideline M10 on bioanalytical method validation and study sample analysis* (*19*), which had been adopted by the ICH in 2022 and was in the process of being implemented by ICH members.

The new guideline had been proposed to enable all countries, including those that were not ICH members, to contribute to the development process of a guideline on bioanalytical method validation and study sample analysis; and to

ensure that the resulting guidance would be relevant and applicable to all WHO Member States.

The draft guideline, which applied chromatographic methods and ligand binding assays, was a multidisciplinary guideline that focused on how to validate bioanalytical methods for chemical and biological drug quantification and how to use them in analysing study samples.

A first draft of the new guideline had been undertaken in April–July 2023; and in September 2023 it had been discussed by a working group (12–14 September) and by a group of experts at the informal consultation (22–23 September). Dr Gwaza informed the Expert Committee that a revised version would be circulated for public consultation and submitted to the fifty-eighth ECSPP for possible adoption.

Dr García Arieta presented key elements of the ICH M10, including the scope of the guideline and key points from each section of the document, including chromatography, ligand binding assays, partial validation and cross-validation, and additional considerations.

The Expert Committee reviewed the differences between the proposed WHO guideline and the ICH M10 alongside the latest revisions proposed by the drafting group and informal consultation, which had mostly been made to clarify the text rather than to increase the requirement compared with ICH M10.

The Expert Committee did not agree with the recommendation by experts at the informal consultation that the new WHO guideline should include annotations reflecting the differences with the ICH M10 guideline.

The ECSPP thanked all those involved in developing the new guideline so far.

The Expert Committee noted the update and progress made in developing the guideline. It agreed to the proposed revisions and supported the proposal to circulate the revised draft for public consultation before it was submitted to the next ECSPP for possible adoption.

10.5 Recommendations from the virtual consultation on regulatory guidance for multisource products

Dr Estevão Cordeiro updated ECSPP members on the 2022 and 2023 consultations on regulatory guidance for multisource products organized by the WHO Norms and Standards for Pharmaceuticals Team and PQT/MED, which had been held from 1 to 3 November 2022, and 22 to 23 September 2023.

Like previous meetings, those consultations had provided a platform for the two teams to exchange information on current and future activities in the areas of quality and bioequivalence, supported by experts in the field.

10.5.1 2022 consultation (update by correspondence)

Participants at the 2022 consultation had discussed how best to consider and respond to ongoing developments in quality and bioequivalence guidelines from the ICH.

- **Planning for revised ICH guidelines**. The group of experts considered the recent broadening of membership and scope of ICH and the likely impact on WHO guidelines. It noted the need for a consistent approach to handling the changes and recommended doing robust horizon scanning and developing a systematic comparative evaluation methodology to better plan and implement changes.
- **Impact of ICH Q12 on WHO guidelines**. The group of experts considered the likely impact of the global implementation of ICH Q12 guideline *Technical and regulatory considerations for pharmaceutical product lifecycle management*. It suggested further consideration was needed, specifically from the perspective of low- and middle-income countries, before WHO took any action to revise its own related guidelines.
- **Impact of ICH M9, M10 and M13**. The group of experts suggested that WHO guidance should be harmonized with newly revised ICH guidelines M9 and M10, and ICH guideline M13A *Bioequivalence for immediate-release solid oral dosage forms*, which was under development. To achieve that, the WHO *Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability* (*16*) should be split into separate guidelines and updated independently over time. In particular, the group suggested drafting a new guideline on BCS-based biowaivers (see section 10.3) and bioanalytical method validation and study sample analysis (see section 10.4). It also suggested exploring the feasibility of creating an expert working group to provide input to the ICH guideline development process for ICH M13A.
- **WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce**. The group of experts suggested organizing workshops to support Member States implement the revised WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce. It further suggested developing a frequently asked questions document to clarify some of the revised guideline's provisions.

10.5.2 2023 consultation (update in person)

The group of experts at the 2023 consultation had discussed progress on the revision or development of various regulatory projects and guidelines, including the WHO Biowaiver List (see section 10.1), the WHO list of international comparator products (see section 10.2), a guideline on BCS-based biowaivers (see section 10.3), and bioanalytical method validation and study sample analysis (see section 10.4). The group of experts had also reviewed feedback on outcomes from informal consultations with GMP inspectors on continuous manufacturing and artificial intelligence in pharmaceutical manufacturing.

The group had also reviewed a gap analysis of existing WHO regulatory guidelines and established a list of potential areas where work might be needed to update or develop new guidance. The list had been used to inform a proposed workplan (see section 10.6). In addition to recommending the revision of several existing guidelines, the group had recommended developing:

- some GMP guidance (for example, a points to consider or reflection paper) on continuous manufacturing as recommended by GMP inspectors (see section 8.4);
- a reflection paper or points to consider document on artificial intelligence in pharmaceutical manufacturing, in collaboration with industry;
- a new guideline on good practices for market surveillance and control;
- good practices for national regulatory authorities to implement WHO regulatory guidelines;
- a new guideline on the evaluation of drug–device combinations;
- a new guideline on benefit–risk assessment.

The Expert Committee noted the 2022 and 2023 updates and expressed its support for the proposals and recommendations from the 2023 joint meeting on regulatory guidance for multisource products.

10.6 Proposals for revisions, or new regulatory guidelines

Dr Estevão Cordeiro presented a 2024–2027 workplan for revising and developing new regulatory guidance.

The workplan included a list of targets for revision and development that had been derived from a gap analysis of existing WHO regulatory guidelines alongside expert and public consultation. Stakeholders had been invited to identify guidelines in need of revision or development to better address the constant technical progress in pharmaceutical development, production, regulatory science and quality control. The gap analysis included any WHO

regulatory guideline that was more than seven years old, or for which significant changes in the field had been identified.

The ECSPP considered the list, noting that it had already recommended the development of new guidance on continuous manufacturing and artificial intelligence in pharmaceutical manufacturing (see section 8.5). It agreed to include the following new guidelines as priorities for development in the workplan:

- good practices on market surveillance and control
- good practices for implementing WHO regulatory guidelines
- guidelines for evaluating combination products (drug–device)
- guidelines on benefit–risk assessment to support regulatory decisions
- points to consider on the implementation of e-labelling (e-leaflet or e-PIL)
- points to consider or reflection document on (pre-)registration testing
- guidelines for the safe disposal of pharmaceuticals.

The ECSPP also agreed to withdraw from use the existing guideline *Basic tests for drugs: pharmaceutical substances, medicinal plant materials and dosage forms* (*20*); and to include the revision of five existing guidelines in the workplan (Table 3).

Table 3
List of regulatory guidelines prioritized for revision by the ECSPP

Guideline	Year	TRS No.	Annex
Guidelines on packaging for pharmaceutical products	2002	902	Annex 9
WHO guidelines for sampling of pharmaceutical products and related materials	2005	929	Annex 4
Guidelines for registration of fixed-dose combination medicinal products	2005	929	Annex 5
Development of paediatric medicines: points to consider in formulation	2012	970	Annex 5
WHO general guidance on variations to multisource pharmaceutical products	2016	996	Annex 10

TRS: Technical Report Series.

In each case, work on the new or revised guidelines would follow the established procedure for the development of WHO medicines quality assurance guidelines (*21*). The Expert Committee noted that the development of guidelines would depend on resources and that prioritization might change.

The WHO Secretariat proposed establishing groups of experts to advance work on each prioritized guideline in preparation for future ECSPP meetings.

The Expert Committee adopted the 2024–2027 workplan as presented; and agreed to establish groups of experts to advance work on each of the prioritized guidelines and new topics.

11. Closing remarks

Dr Clive Ondari, Director of WHO Health Products Policy and Standards, thanked the ECSPP for its normative and standard-setting work on behalf of the WHO Director-General, Dr Tedros Ghebreyesus. He emphasized the importance of the standards adopted by the fifty-seventh ECSPP, which he said would have an impact for many people in all WHO Member States by enabling access to quality-assured medical products and by combating substandard and falsified medicines.

Dr Ondari informed the Expert Committee of ongoing discussions for WHO to support global implementation of the Global Substance Identification and Identification of Medicinal Products standards to simplify the exchange of information between stakeholders, for example, adverse event reports in pharmacovigilance.

Dr Ondari thanked the WHO Secretariat for its work in supporting the Expert Committee, and also thanked all ECSPP members, temporary advisers, WHO collaborating institutions and partners, United Nations agencies, other stakeholders and WHO staff from across the world for their contributions and for the high-quality discussions held during the meeting. He thanked the Chair, Co-Chair and rapporteurs for contributing to an efficient meeting. Dr Ondari closed the meeting.

12. Summary and recommendations

The WHO ECSPP advises the Director-General of WHO in the area of medicines quality assurance. It oversees the maintenance of *The International Pharmacopoeia* and provides guidance for use by relevant WHO units and regulatory authorities in WHO Member States, to ensure that medicines meet unified standards of quality, safety and efficacy. The ECSPP's guidance texts are developed through a broad consensus-building process, including iterative public consultation. Representatives from international organizations, State actors, non-State actors, pharmacopoeias and relevant WHO departments are invited to the ECSPP's annual meetings to provide updates and input to the Expert Committee's discussions.

At its fifty-seventh meeting, held in hybrid format from 9 to 13 October 2023, the ECSPP received updates on cross-cutting issues from other WHO bodies, including the ECBS, the Expert Committee on the Selection and Use of Essential Medicines, the PQT/MED, the Member State Mechanism, and ICDRA. Other WHO teams updated the ECSPP on WHO's latest work to support the development of INNs. Updates on collaborative projects were also provided by partner organizations, including the IMWP, the IAEA and UNFPA.

The EDQM updated the ECSPP on its activities as the custodial centre in charge of ICRS for use with monographs of *The International Pharmacopoeia*. Plans for the latest phase of EQAAS, which was organized by WHO with the assistance of the EDQM, were also shared with the ECSPP.

The ECSPP reviewed new and revised specifications and general texts for quality control testing of medicines for inclusion in *The International Pharmacopoeia*. It adopted 21 pharmacopoeial texts (four general chapters, one general monograph and 16 new and revised monographs); and confirmed the release of eight new ICRS established by the custodial centre for use in connection with *The International Pharmacopoeia*.

The ECSPP reviewed proposals for new and updated quality assurance and regulatory guidance, adopting six new guidelines and decisions. The ECSPP updated the WHO Biowaiver List as an annex to its report. It noted the updated WHO list of international comparator pharmaceutical products.

The sections that follow summarize the specific decisions and recommendations made by the ECSPP during its fifty-seventh meeting in 2023.

12.1 Guidelines and decisions adopted and recommended for use

The following guidelines and decisions were adopted and recommended for use:

- *Guidelines and guidance texts adopted by the Expert Committee on Specifications for Pharmaceutical Preparations* (Annex 1);

- *WHO good manufacturing practices for excipients used in pharmaceutical products* (Annex 2);
- *IAEA/WHO good manufacturing practices for in-house cold kits for radiopharmaceutical preparations* (Annex 3);
- *WHO good practices for pharmaceutical quality control laboratories* (Annex 4);
- *WHO/UNFPA female condom generic specification* (Annex 5);
- *WHO Biowaiver List: proposal to waive in vivo bioequivalence requirements for WHO Model List of Essential Medicines immediate-release, solid oral dosage forms* (Annex 6);
- *WHO guideline on Biopharmaceutics Classification System-based biowaivers* (Annex 7);
- *Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability* (republished) (Annex 8).

12.2 Texts adopted for inclusion in *The International Pharmacopoeia*

The ECSPP adopted a series of chapters and monographs, as listed below.

12.2.1 General chapters

- Microdetermination of water by the Karl Fischer method (new)
- Melting point and range (revised)
- Chromatography (revised)
- Test for diethylene glycol and ethylene glycol in liquid preparations for oral use (new)

12.2.2 Monographs

General monographs for dosage forms

- Liquid preparations for oral use (revision)

COVID-19 therapeutics

- Molnupiravir (new)
- Molnupiravir capsules (new)
- Nirmatrelvir (new)
- Nirmatrelvir tablets (new)

Medicines for maternal, infant, child and adolescent health

- Estradiol valerate and norethisterone enantate injection (new)

Antimalarial medicines

- Pyrimethamine tablets (revision)

Antituberculosis medicines

- Rifampicin (revision)
- Test for MeNP in rifampicin (new)

Antiviral medicines, including antiretrovirals

- Efavirenz (revision)
- Tenofovir disoproxil fumarate (revision)
- Tenofovir disoproxil tablets (revision)
- Lamivudine and tenofovir disoproxil tablets (revision)

Medicines for tropical medicines

- Albendazole (revision)
- Albendazole chewable tablets (revision)
- Albendazole tablets (new)

Other medicines

- Paracetamol oral solution (revision)

The ECSPP further agreed to include a reference to the new test for diethylene glycol and ethylene glycol in liquid preparations for oral use in the monographs for propylene glycol, glycerol and glycerol 85% (m/m), making it clear that manufacturers must use the gas chromatography method.

12.2.3 Suppressions

The ECSPP agreed to suppress the following text from *The International Pharmacopoeia*:

- Yttrium (^{90}Y) silicate injection (monograph)

12.2.4 International Chemical Reference Substances (ICRS)

The ECSPP confirmed the release of the following ICRS that have been newly characterized by the custodial centre EDQM:

- artenimol ICRS, batch 2
- pyrimethamine ICRS, batch 2
- artesunate ICRS, batch 3
- dolutegravir impurity B ICRS, batch 1
- dolutegravir impurity D ICRS, batch 1
- dolutegravir sodium ICRS, batch 1
- remdesivir ICRS, batch 1
- remdesivir for system suitability ICRS, batch 1.

12.3 Recommendations

The ECSPP made a series of recommendations related to quality assurance, as listed below. Progress on the suggested actions would be reported to the ECSPP at its fifty-eighth meeting in 2024.

The Expert Committee recommended that the WHO Secretariat, in collaboration with experts as appropriate, should take the actions listed next.

12.3.1 *The International Pharmacopoeia*

- Continue development of monographs, general methods, texts and general supplementary information, in accordance with the 2024–2025 workplan and as decided at the meeting.

12.3.2 Quality control: national laboratories

- Continue EQAAS in support of national and regional pharmaceutical quality control laboratories, including continuing the post-assessment assistance programme.

12.3.3 Good manufacturing practices and related areas

- Develop two appendices for *WHO good manufacturing practices for excipients used in pharmaceutical products*: a points to consider document on issues such as risk management, separate facilities and track and trace; and a list of excipients with possible impurities and high-risk excipients (such as DEG, EG and nitrosamines) alongside additional guidance on managing risks for those.

- Continue to revise existing guidelines, and develop new guidance, in accordance with the 2024–2027 workplan that was agreed at the meeting.

12.3.4 Regulatory mechanisms

- Start the next phase of the WHO Biowaiver Project (cycle VI) to continue the BCS-based classification of nine further APIs (including linezolid as a repetition of cycle V experiments).
- Promote the results of the WHO Biowaiver Project to regulatory authorities and other stakeholders.
- If appropriate, update the WHO list of international comparator pharmaceutical products.
- Submit the revised guideline on bioanalytical method validation and study sample analysis for public consultation.
- Withdraw the guideline *Basic tests for drugs: pharmaceutical substances, medicinal plant materials and dosage forms* from use.
- Continue to revise existing guidelines, and develop new guidance, in accordance with the 2024–2027 workplan that was agreed at the meeting.

12.3.5 Other

- Continue to serve as the Secretariat for the IMWP; and strive to publish articles about the IMWP in open-access peer-reviewed journals.
- Continue updating the Quality Assurance of Medicines Terminology Database on an annual basis.

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Annex 1

Guidelines and guidance texts adopted by the Expert Committee on Specifications for Pharmaceutical Preparations

As recommended by World Health Organization (WHO) partners and donor organizations, a full and updated list of WHO norms and standards for medicines, quality assurance and regulatory guidance texts adopted by the Expert Committee and published in the WHO Technical Report Series (TRS) has been drawn up as follows. The guidelines are published in English as the primary language. In cases where there is a translated version to other WHO official languages, this is indicated in the column "available languages": AR: Arabic, CN: Chinese, EN: English, ES: Spanish, FR: French, JP: Japanese, RU: Russian.

List of guidelines and guidance for pharmaceuticals

Category	Guideline	TRS	Annex	Year	Available languages
All guidelines	Procedure for the development of World Health Organization medicines quality assurance guidelines	1019	Annex 1	2019	
Development	Development of paediatric medicines: points to consider in formulation	970	Annex 5	2012	
Development	Pharmaceutical development of multisource (generic) finished pharmaceutical products: points to consider	970	Annex 3	2012	
Distribution	**Pharmacy services**				
Distribution	Joint FIP/WHO guidelines on good pharmacy practice: standards for quality of pharmacy services	961	Annex 8	2011	
Distribution	**Starting materials**				
Distribution/quality assurance	Good trade and distribution practices for pharmaceutical starting materials	996	Annex 6	2016	
Distribution	**Compounding**				
Distribution	FIP–WHO technical guidelines: Points to consider in the provision by health-care professionals of children-specific preparations that are not available as authorized products	996	Annex 2	2016	
Distribution	**Monitoring**				
Distribution/ quality assurance	Guidelines on the conduct of surveys of the quality of medicines	996	Annex 7	2016	

Category	Guideline	TRS	Annex	Year	Available languages
Distribution	**Finished products**				
Distribution/ regulatory standards	WHO pharmaceutical starting materials certification scheme (SMACS): guidelines on implementation	917	Annex 3	2003	
Distribution/ regulatory standards	Guidelines on import procedures for medical products	1019	Annex 5	2019	
Distribution/ regulatory standards	Guidelines on the implementation of the WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce	1033	Annex 9	2021	
Distribution	**Procurement**				
Distribution/ quality assurance	Model quality assurance system for procurement agencies	986	Annex 3	2014	EN, FR
Distribution/ quality assurance	Interagency finished pharmaceutical product questionnaire based on the model quality assurance system for procurement agencies	986	Appendix 6 to Module VI, Annex 3	2014	
Distribution/ quality assurance/ inspections	Assessment tool based on the model quality assurance system for procurement agencies: aide-memoire for inspection	986	Annex 4	2014	EN, FR
Distribution	**Storage**				
Distribution	Good storage and distribution practices for medical products	1025	Annex 7	2020	

Category	Guideline	TRS	Annex	Year	Available languages
Distribution	**Storage** (*continued*)				
Distribution	Points to consider for setting the remaining shelf-life of medical products upon delivery	1044	Annex 8	2022	
Distribution	Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products	961	Annex 9	2011	
Distribution	Technical supplements to Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products (WHO Technical Report Series, No. 961, 2011), Annex 9	992	Annex 5	2015	
Distribution	*Supplement 1: Selecting sites for storage facilities*	992	Annex 5	2015	
Distribution	*Supplement 2: Design and procurement of storage facilities*	992	Annex 5	2015	
Distribution	*Supplement 3: Estimating the capacity of storage facilities*	992	Annex 5	2015	
Distribution	*Supplement 4: Building security and fire protection*	992	Annex 5	2015	
Distribution	*Supplement 5: Maintenance of storage facilities*	992	Annex 5	2015	
Distribution	*Supplement 6: Temperature and humidity monitoring systems for fixed storage areas*	992	Annex 5	2015	
Distribution	*Supplement 7: Qualification of temperature-controlled storage areas*	992	Annex 5	2015	
Distribution	*Supplement 8: Temperature mapping of storage areas*	992	Annex 5	2015	
Distribution	*Supplement 9: Maintenance of refrigeration equipment*	992	Annex 5	2015	

Category	Guideline	TRS	Annex	Year	Available languages
Distribution	**Storage** (*continued*)				
Distribution	*Supplement 10: Checking the accuracy of temperature control and monitoring devices*	992	Annex 5	2015	
Distribution	*Supplement 11: Qualification of refrigerated road vehicles*	992	Annex 5	2015	
Distribution	*Supplement 12: Temperature-controlled transport operations by road and by air*	992	Annex 5	2015	
Distribution	*Supplement 13: Qualification of shipping containers*	992	Annex 5	2015	
Distribution	*Supplement 14: Transport route profiling qualification*	992	Annex 5	2015	
Distribution	*Supplement 15: Temperature and humidity monitoring systems for transport operations*	992	Annex 5	2015	
Distribution	*Supplement 16: Environmental management of refrigeration equipment*	992	Annex 5	2015	
Inspection					
Inspection/ production	General guidance on hold-time studies	992	Annex 4	2015	
Inspection	WHO guidelines for drafting a site master file	961	Annex 14	2011	
Inspection	Guidance on good manufacturing practices: inspection report. Model inspection report	996	Annex 4, Appendix 1	2016	

Category	Guideline	TRS	Annex	Year	Available languages
Inspection (*continued*)					
Inspection	Guidance on good manufacturing practices: inspection report. Example of a risk category assessment of the site depending on level of compliance and inspection frequency	996	Annex 4, Appendix 2	2016	
Inspection	Quality management system requirements for national inspectorates	1025	Annex 5	2020	
Inspection	Guidelines on pre-approval inspections	902	Annex 7	2002	
Inspection	Provisional guidelines on the inspection of pharmaceutical manufacturers	823	Annex 2	1992	
Inspection	**Desk assessment**				
Inspection/ regulatory standards	Guidance on good practices for desk assessment of compliance with good manufacturing practices, good laboratory practices and good clinical practices for medical products regulatory decisions	1010	Annex 9	2018	
Production	**WHO good manufacturing practices**				
Production	WHO good manufacturing practices for pharmaceutical products: main principles	986	Annex 2	2014	EN, FR
Production	Questions and answers. Medicines: good manufacturing practices	https://www.who.int/medicines/areas/quality_safety/quality_assurance/gmp/en/			

Category	Guideline	TRS	Annex	Year	Available languages
Production	**WHO good manufacturing practices** (*continued*)				
Production	WHO good manufacturing practices for active pharmaceutical ingredients	957	Annex 2	2010	EN, FR
Production	Good manufacturing practices: supplementary guidelines for the manufacture of pharmaceutical excipients	885	Annex 5	1999	
Production	WHO good manufacturing practices for sterile pharmaceutical products	1044	Annex 2	2022	
Production	WHO good manufacturing practices for biological products [jointly with the Expert Committee on Biological Standardization]	996	Annex 3	2016	
Production	WHO good manufacturing practices for blood establishments [jointly with the Expert Committee on Biological Standardization]	961	Annex 4	2011	
Production	WHO good manufacturing practices for pharmaceutical products containing hazardous substances	957	Annex 3	2010	EN, FR
Production	WHO good manufacturing practices for investigational products	1044	Annex 7	2022	
Production	Guidelines on good manufacturing practices for the manufacture of herbal medicines	1010	Annex 2	2018	
Production	International Atomic Energy Agency and World Health Organization guideline on good manufacturing practices for radiopharmaceutical products	1025	Annex 2	2020	

Category	Guideline	TRS	Annex	Year	Available languages
Production	**WHO good manufacturing practices** (*continued*)				
Production	IAEA/WHO guideline on good manufacturing practices for investigational radiopharmaceutical products	1044	Annex 3	2022	
Production	Good manufacturing practices: water for pharmaceutical use	1033	Annex 3	2021	
Production	Production of water for injection by means other than distillation	1025	Annex 3	2020	
Production	Guidelines on heating, ventilation and air-conditioning systems for non-sterile pharmaceutical products [Part 1]	1010	Annex 8	2018	
Production	Guidelines on heating, ventilation and air-conditioning systems for non-sterile pharmaceutical products. Part 2: Interpretation of guidelines	1019	Annex 2	2019	
Production	WHO good manufacturing practices for medicinal gases	1044	Annex 5	2022	
Production/ quality assurance	WHO good manufacturing practices: guidelines on validation	1019	Annex 3	2019	
Production/ quality assurance	Points to consider when including health-based exposure limits (HBELs) in cleaning validation	1033	Annex 2	2021	
Production	**Risk analysis**				
Production/ regulatory standards	WHO guidelines on quality risk management	981	Annex 2	2013	

Category	Guideline	TRS	Annex	Year	Available languages
Production	**Risk analysis** (*continued*)				
Production/ inspection	Points to consider for manufacturers and inspectors: environmental aspects of manufacturing for the prevention of antimicrobial resistance	1025	Annex 6	2020	
Production	**Technology transfer**				
Production	WHO guidelines on technology transfer in pharmaceutical manufacturing	1044	Annex 4	2022	
Production	**Processing practices for herbals**				
Production	WHO guidelines on good herbal processing practices for herbal medicines	1010	Annex 1	2018	
Production	**Data management**				
Production/ quality assurance	Guideline on data integrity	1033	Annex 4	2021	
Quality control	**Screening tests**				
Quality control	Basic tests for drugs: pharmaceutical substances, medicinal plant materials and dosage forms	https://apps.who.int/iris/bitstream/handle/10665/42020/9241545135.pdf?sequence=1			
Quality control	**Pharmacopoeias**				
Quality control	Good pharmacopoeial practices	996	Annex 1	2016	
Quality control	Good pharmacopoeial practices: chapter on monographs for compounded preparations	1010	Annex 6	2018	

Category	Guideline	TRS	Annex	Year	Available languages
Quality control	**Pharmacopoeias** (*continued*)				
Quality control	Good pharmacopoeial practices: chapter on monographs on herbal medicines	1010	Annex 7	2018	
Quality control	***The International Pharmacopoeia* and international reference standards**				
Quality control	Procedure for the elaboration, revision and omission of monographs and other texts for *The International Pharmacopoeia*	1025	Annex 1	2020	
Quality control	*The International Pharmacopoeia*: revised concepts and future perspectives	1003	Annex 2	2017	
Quality control	Updating mechanism for the section on radiopharmaceuticals in *The International Pharmacopoeia*	992	Annex 2	2015	
Quality control	*The International Pharmacopoeia* – related substances tests: dosage form monographs guidance notes	943	Annex 1	2007	
Quality control	WHO International Chemical Reference Substances (ICRS): purposes and use	https://www.edqm.eu/en/WHO-ICRS-Reference-Substances-1393.html			
Quality control	Release procedure for International Chemical Reference Substances	981	Annex 1	2013	
Quality control	General guidelines for the establishment, maintenance and distribution of chemical reference substances	943	Annex 3	2007	
Quality control	Recommendations on risk of transmitting animal spongiform encephalopathy agents via medicinal products	908	Annex 1	2003	

Category	Guideline	TRS	Annex	Year	Available languages
Quality control	**Analysis of samples**				
Quality control	WHO guidelines for sampling of pharmaceutical products and related materials	929	Annex 4	2005	
Quality control	Considerations for requesting analysis of medicines samples	1010	Annex 3	2018	
Quality control	Model certificate of analysis	1010	Annex 4	2018	
Quality control	**Laboratory guidelines**				
Quality control	WHO good practices for pharmaceutical quality control laboratories	957	Annex 1	2010	
Quality control	WHO good practices for pharmaceutical microbiology laboratories	961	Annex 2	2011	
Quality control/ inspection	Good chromatography practices	1025	Annex 4	2020	
Quality control/ inspection	WHO guidelines for preparing a laboratory information file	961	Annex 13	2011	
Quality control	**Plant materials**				
Quality control	Quality control methods for medicinal plant materials	https://apps.who.int/iris/bitstream/handle/10665/41986/9241545100.pdf?sequence=1			
Quality control	WHO guidelines for selecting marker substances of herbal origin for quality control of herbal medicines	1003	Annex 1	2017	

Category	Guideline	TRS	Annex	Year	Available languages
Quality control	**Testing of suspect samples**				
Quality control/ distribution (monitoring)	WHO guidance on testing of "suspect" falsified medicines	1010	Annex 5	2018	
Regulatory standards	**Stability**				
Regulatory standards	Stability testing of active pharmaceutical ingredients and finished pharmaceutical products	1010	Annex 10	2018	
Regulatory standards	Stability testing of active pharmaceutical ingredients and finished pharmaceutical products: Stability conditions for WHO Member States by region (Update March 2021)	953	Annex 2	2021	
Regulatory standards	**Interchangeability**				
Regulatory standards	Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability	1003	Annex 6	2017	
Regulatory standards	WHO "Biowaiver List": proposal to waive in vivo bioequivalence requirements for WHO Model List of Essential Medicines immediate-release, solid oral dosage forms	1044	Annex 11	2022	
Regulatory standards	Protocol to conduct equilibrium solubility experiments for the purpose of Biopharmaceutics Classification System-based classification of active pharmaceutical ingredients for biowaiver	1019	Annex 4	2019	

Category	Guideline	TRS	Annex	Year	Available languages
Regulatory standards	**Interchangeability** (*continued*)				
Regulatory standards	Guidance for organizations performing in vivo bioequivalence studies	996	Annex 9	2016	
Regulatory standards	General background notes on the list of international comparator pharmaceutical products	1003	Annex 5	2017	
Regulatory standards	Guidance on the selection of comparator pharmaceutical products for equivalence assessment of interchangeable multisource (generic) products	992	Annex 8	2015	
Regulatory standards	List of international comparator products (September 2016)	https://cdn.who.int/media/docs/default-source/medicines/norms-and-standards/guidelines/regulatory-standards/list-int-comparator-prods-after-public-consult30-9.xlsx?sfvrsn=3c9ec04b_2			
Regulatory standards	**Medical devices**				
Regulatory standards/ prequalification	World Health Organization/United Nations Population Fund Prequalification Programme guidance for contraceptive devices: male latex condoms, female condoms and intrauterine devices	1025	Annex 9	2020	
Regulatory standards	World Health Organization/United Nations Population Fund guidance on conducting post-market surveillance of condoms	1033	Annex 7	2021	
Regulatory standards/ quality control	World Health Organization/United Nations Population Fund technical specifications for male latex condoms	1025	Annex 10	2020	

Category	Guideline	TRS	Annex	Year	Available languages
Regulatory standards	**Medical devices** (*continued*)				
Regulatory standards/ quality control	World Health Organization/United Nations Population Fund specifications for plain lubricants	1025	Annex 11	2020	
Regulatory standards/ quality control	World Health Organization/United Nations Population Fund guidance on testing of male latex condoms	1033	Annex 6	2021	
Regulatory standards/ quality control	WHO/UNFPA guidance on natural rubber latex male condom stability studies	1044	Annex 9	2022	
Regulatory standards/ quality control	WHO/UNFPA technical specification for TCu380A intrauterine device	1044	Annex 10	2022	
Regulatory standards/ distribution (storage)	World Health Organization/United Nations Population Fund recommendations for condom storage and shipping temperatures	1033	Annex 5	2021	
Regulatory standards	**Quality**				
Regulatory standards	Guidelines on submission of documentation for a multisource (generic) finished product: quality part	986	Annex 6	2014	
Regulatory standards	Recommendations for quality requirements when plantderived artemisinin is used as a starting material in the production of antimalarial active pharmaceutical ingredients	992	Annex 6	2015	

Category	Guideline	TRS	Annex	Year	Available languages
Regulatory standards	**Collaborative procedures and reliance**				
Regulatory standards/ prequalification	Collaborative procedure between the World Health Organization (WHO) Prequalification Team and national regulatory authorities in the assessment and accelerated national registration of WHO-prequalified pharmaceutical products and vaccines	996	Annex 8	2016	
Regulatory standards	Collaborative procedure in the assessment and accelerated national registration of pharmaceutical products and vaccines approved by stringent regulatory authorities	1010	Annex 11	2018	
Regulatory standards	Good practices of national regulatory authorities in implementing the collaborative registration procedures for medical products	1019	Annex 6	2019	
Regulatory standards	Good reliance practices in the regulation of medical products: high level principles and considerations	1033	Annex 10	2021	AR, CN, EN, ES, FR, RU
Regulatory standards	**Others**				
Regulatory standards	Guidelines for registration of fixed-dose combination medicinal products	929	Annex 5	2005	EN, CN
Regulatory standards	Guidelines on active pharmaceutical ingredient master file procedure	948	Annex 4	2008	
Regulatory standards	International nonproprietary names for biological and biotechnological substances: a review	948	Annex 5	2008	

Category	Guideline	TRS	Annex	Year	Available languages
Regulatory standards	**Others** (*continued*)				
Regulatory standards	Good review practices: guidelines for national and regional regulatory authorities	992	Annex 9	2015	
Regulatory standards	WHO general guidance on variations to multisource pharmaceutical products	996	Annex 10	2016	
Regulatory standards	WHO guideline on the implementation of quality management systems for national regulatory authorities	1025	Annex 13	2020	EN, ES, FR, RU
Regulatory standards	Good regulatory practices in the regulation of medical products	1033	Annex 11	2021	AR, CN, EN, ES, FR, RU
Regulatory standards/ inspection	Guidelines for the preparation of a contract research organization master file	957	Annex 7	2010	
Regulatory standards/ inspection	WHO guidelines for drafting a site master file	961	Annex 14	2011	
Regulatory standards/ production	Guidelines on packaging for pharmaceutical products	902	Annex 9	2002	
Regulatory standards/ production	WHO good practices for research and development facilities of pharmaceutical products	1044	Annex 6	2022	
Prequalification	**Prequalification**				
Prequalification	Procedure for prequalification of pharmaceutical products	961	Annex 10	2011	
Prequalification	WHO guidelines on variations to a prequalified product	981	Annex 3	2013	

Category	Guideline	TRS	Annex	Year	Available languages
Prequalification	**Prequalification** (*continued*)				
Prequalification	Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part	970	Annex 4	2012	
Prequalification	Prequalification of quality control laboratories: procedure for assessing the acceptability, in principle, of quality control laboratories for use by United Nations agencies	1003	Annex 3	2017	
Prequalification	Guidelines on the requalification of prequalified dossiers	957	Annex 6	2010	
Prequalification	Procedure for assessing the acceptability, in principle, of active pharmaceutical ingredients for use in pharmaceutical products	953	Annex 4	2009	
Prequalification	Guidelines on submission of documentation for prequalification of finished pharmaceutical products approved by stringent regulatory authorities	986	Annex 5	2014	

Annex 2

WHO good manufacturing practices for excipients used in pharmaceutical products

Background

The WHO guideline *Good manufacturing practices: supplementary guidelines for the manufacture of pharmaceutical excipients* was published in the WHO Technical Report Series No. 885, Annex 5, 1999.

As excipients are sometimes used in large quantities in pharmaceutical dosage forms, and may contain impurities, they can affect the quality of a finished pharmaceutical product.

The manufacturer of the finished pharmaceutical product is normally dependent on the excipient manufacturer to supply excipients meeting the required specification. An appropriately established and implemented quality management system evaluating and controlling risks in the production and quality control of such excipients is therefore required.

Excipient manufacturers should be required to apply the appropriate principles of good manufacturing practices (GMPs) in producing pharmaceutical excipients. Reports of pharmaceutical products that contain contaminated excipients, or excipients with impurities leading to the death of patients, have further highlighted the importance of reviewing the original guideline. Furthermore, the concept of ongoing improvement, the life cycle approach, better quality management systems, risk management, and management review should be described in such a guideline, alongside the necessary good storage, good trade and good distribution practices, to ensure quality throughout the supply chain, as applicable.

The manufacturer of excipients used in pharmaceutical products should be able to identify risks associated with the production (including stages of manufacturing, route of synthesis) and quality control of its products. This includes the premises, equipment, utilities, storage and distribution. The manufacturer of such excipients should assess those risks and identify appropriate measures to mitigate such risks. The effectiveness of the measures should be evaluated to ensure that they are appropriate.

This document provides information on GMP that should be implemented to assist manufacturers to produce and control excipients used in pharmaceutical products that will meet their intended specifications, in a consistent manner. Risk assessment may be useful in determining which excipients should be manufactured in accordance with this guideline.

Contents

1. Introduction and scope

1.1 The purpose of this document is to provide guidance for the production, control, storage and distribution of excipients used in pharmaceutical products, focusing on good manufacturing practices (GMP) under an appropriate system for managing quality. It is also intended to help ensure that such excipients meet the requirements for quality and purity that they purport or are represented to possess.

1.2 The document does not cover aspects of protection of the environment, or safety aspects for the personnel engaged in the manufacture and control of excipients.

1.3 Excipients are often used in large quantities in industrial chemistry, as well as in the food and cosmetic industry. Specifications for excipients used in these applications may vary and may not always be appropriate for use in pharmaceutical products. It is the responsibility of the finished product manufacturer and of the applicant to ensure that the finished product is manufactured using excipients of a suitable grade conforming to its intended use.

1.4 Excipients should be of appropriate quality, as they could affect the safety, quality and efficacy of finished pharmaceutical products.

1.5 The manufacturer of the finished pharmaceutical product is highly dependent on the excipient manufacturer to provide materials that are homogeneous in chemical and physical characteristics, and of the desired quality.

1.6 In general, excipients are used as purchased, with no further refining or purification. Consequently, impurities present in the excipient will be carried over to the finished pharmaceutical product.

1.7 To achieve the objective of ensuring that excipients used in pharmaceutical products are of appropriate quality, an appropriate level of GMP should be established, implemented and maintained during their production, packaging, repackaging, labelling, quality control, release, storage, distribution and other related activities. Additional measures should be taken when manufacturing excipients for which scientific literature, information in the public domain or historical data indicate the presence of higher risk due to potential formation of toxic impurities during manufacturing or contamination during storage and distribution.

1.8 Manufacturers of excipients for pharmaceutical use should have a specific analytical testing procedure to ensure suitability for its intended use. Pharmacopoeial and regulatory requirements should be considered by the manufacturers as a reference for these analytical tests. Information in the public domain should also be considered. Risk management principles should be implemented in order to identify and mitigate risks.

1.9 A thorough knowledge and understanding of the processes and associated risks are required. This includes all unit operations and processing steps, including key steps in the process, critical parameters (such as time, temperature or pressure), the use of recovered solvent or mother liquor, environmental conditions, equipment used, protection from contamination and monitoring points.

2. Glossary

2.1 The definitions given below apply to the terms used in this document. They have been aligned to the extent possible with the terminology in related WHO guidelines and good practices included in the WHO Quality Assurance of Medicines Terminology Database – List of Terms and related guidelines,[5] but may have different meanings in other contexts.

acceptance criteria. Numerical limits, ranges or other suitable measures for acceptance of test results.

adulterated. Pertaining to an intermediate or product (in part or in whole) that is contaminated, unsafe, not shown to be safe, filthy, or produced under unsanitary conditions, or found to have been produced, controlled, stored or distributed not in compliance with good manufacturing practices (such as described in this guideline); or contains any substance that may reduce its quality or purity or render it injurious to health.

auditing. An independent and objective activity designed to add value to and improve an organization's operations by helping it to accomplish its objectives, using a systematic, disciplined approach to evaluate and improve the effectiveness of risk management, control and governance processes.

batch (or lot). A specific quantity of material produced in a single process or series of processes so that it is expected to be homogeneous within specified limits. In the case of continuous production, a batch may correspond to a defined

[5] https://www.who.int/publications/m/item/quality-assurance-of-medicines-terminology-database.

fraction of the production. The batch size can be defined either by a fixed quantity or by the amount produced in a fixed time interval.

batch number (or lot number). A unique combination of numbers, letters or symbols that identifies a batch (or lot) and from which the production and distribution history can be determined.

calibration. The demonstration that a particular instrument or device produces results within specified limits by comparison with those produced by a reference or traceable standard over an appropriate range of measurements.

change control. A formal system by which qualified representatives of appropriate disciplines review proposed or actual changes that might affect a validated status. The intent is to determine the need for action that would ensure that the system is maintained in a validated state.

computer system. A group of hardware components and associated software, designed and assembled to perform a specific function or group of functions.

computerized system. A process or operation integrated with a computer system.

contamination. The undesired introduction of impurities of a chemical or microbiological nature or of foreign matter into or onto a raw material, intermediate or excipient during production, sampling, packaging or repackaging, storage, or transport.

critical. Describes a process step, process condition, test requirement or other relevant parameter or item that must be controlled within predetermined criteria to ensure that the excipient meets its specification.

cross-contamination. Contamination of a material or product with another material or product.

deviation. Departure from an approved instruction or established standard.

excipient for pharmaceutical use. Substance, other than the active ingredient, that has been appropriately evaluated for safety and is included in a drug delivery system to (a) aid in the processing of the drug delivery system during its manufacture; (b) protect, support or enhance stability, bioavailability or patient acceptability; (c) assist in product identification; and (d) enhance any other attribute of the overall safety and effectiveness of the drug during storage or use.

expiry date (or expiration date). The date placed on the container or labels of an excipient designating the time during which the excipient is expected to remain within established shelf-life specifications if stored under defined conditions and after which it should not be used.

finished pharmaceutical product. WHO: A product that has undergone all stages of production, including packaging in its final container and labelling. A finished pharmaceutical product may contain one or more active pharmaceutical ingredients.

impurity. An undesired component in an excipient.

impurity profile. A description of the impurities present in an excipient.

in-process control (or process control). Checks performed during production in order to monitor and, if appropriate, to adjust the process or to ensure that the intermediate or product conforms to its specifications.

intermediate. A material produced during steps of the processing of an excipient for pharmaceutical use that undergoes further molecular change or purification before it becomes an excipient for pharmaceutical use. Intermediates may or may not be isolated.

lot. See "batch".

lot number. See "batch number".

manufacture. All operations of receipt of materials, production, packaging, repackaging, labelling, relabelling, quality control, release, storage and distribution of an excipient and related controls.

material. A general term used to denote raw materials (starting materials, reagents, solvents), process aids, intermediates, active pharmaceutical ingredients, and packaging and labelling materials.

mother liquor. A concentrated solution from which the product is obtained by evaporation, freezing or crystallization. (Or: The residual liquid that remains after the crystallization or isolation processes. A mother liquor may contain unreacted materials, intermediates, levels of the excipient for pharmaceutical use, or impurities. It may be used for further processing).

packaging material. Any material intended to protect an intermediate or excipient for pharmaceutical use during storage and transport.

procedure. A documented description of the operations to be performed, the precautions to be taken and measures to be applied, directly or indirectly related to the manufacture of an intermediate or excipient for pharmaceutical use.

process aids. Materials, excluding solvents, used as an aid in the manufacture of an intermediate or excipient for pharmaceutical use that do not themselves

participate in a chemical or biological reaction (for example, filter aid or activated carbon).

production. All operations involved in the preparation of an excipient for pharmaceutical use, from receipt of materials through processing and packaging of the excipient for pharmaceutical use.

qualification. Action of proving and documenting that equipment or ancillary systems are properly installed, work correctly and actually lead to the expected results. Qualification is part of validation, but the individual qualification steps alone do not constitute process validation.

quality assurance (QA). The sum total of the organized arrangements made with the object of ensuring that all excipients for pharmaceutical use are of the quality required for their intended use and that quality systems are maintained.

quality control (QC). Checking or testing that specifications are met.

quality unit. An organizational unit independent of production that fulfils both QA and QC responsibilities. This can be in the form of separate QA and QC units or a single individual or group, depending upon the size and structure of the organization.

quarantine. The status of materials isolated physically or by other effective means pending a decision on their subsequent approval or rejection.

raw material. A general term used to denote starting materials, reagents and solvents intended for use in the production of intermediates or excipients for pharmaceutical use.

reprocessing. Introducing an intermediate or excipient for pharmaceutical use, including one that does not conform to standards or specifications, back into the process and repeating a crystallization step or other appropriate chemical or physical manipulation steps (for example, distillation, filtration, chromatography or milling) that are part of the established manufacturing process. Continuation of a process step after an in-process control test has shown that the step is incomplete is considered to be part of the normal process and not to be reprocessing.

reworking. Subjecting an intermediate or excipient for pharmaceutical use that does not conform to standards or specifications to one or more processing steps that are different from the established manufacturing process to obtain an intermediate or excipient of acceptable quality for pharmaceutical use (for example, recrystallizing with a different solvent).

shelf-life. The period of time during which an excipient, if stored correctly, is expected to comply with the specification, normally as determined by stability studies. The shelf-life is used to establish the retest or expiry date.

signed (signature). The record of the individual who performed a particular action or review. This record can be in the form of initials, full handwritten signature, personal seal or an authenticated and secure electronic signature.

solvent. An inorganic or organic liquid used as a vehicle for the preparation of solutions or suspensions in the manufacture of an intermediate or excipient for pharmaceutical use.

specification. A list of tests, references to analytical procedures and appropriate acceptance criteria that are numerical limits, ranges or other criteria for the test described. It establishes the set of criteria to which a material should conform to be considered acceptable for its intended use. "Conformance to specification" means that the material, when tested according to the listed analytical procedures, will meet the listed acceptance criteria.

validation. A documented programme that provides a high degree of assurance that a specific process, method or system will consistently produce a result meeting predetermined acceptance criteria.

validation protocol. A written plan stating how validation will be conducted and defining acceptance criteria. For example, the protocol for a manufacturing process identifies processing equipment, critical process parameters and operating ranges, product characteristics, sampling, test data to be collected, number of validation runs and acceptable test results.

verification. The application of methods, procedures, tests and other evaluations, in addition to monitoring, to determine compliance with established requirements and specifications.

3. Quality management

3.1 Manufacturers involved in the production, control, storage and distribution of excipients for pharmaceutical use should establish, document, implement and maintain a comprehensively designed and clearly defined quality management system.

3.2 Senior management should assume responsibility for the quality management system, as well as the quality of the excipients for pharmaceutical use manufactured, controlled, released, stored and distributed.

3.3 The quality management system should encompass the quality policy, organizational structure, procedures, processes and resources. All parts of the quality management system should be adequately resourced and maintained.

3.4 The quality management system should cover all activities necessary to ensure that excipients for pharmaceutical use will meet their intended specifications, including quality and purity.

3.5 The quality management system should incorporate the principles of good practices, which should be applied to the life cycle stages of excipients for pharmaceutical use. This includes steps such as the receipt of raw materials, production, packaging, testing, release, storage and distribution.

3.6 All quality-related activities and procedures should be defined and documented manually or electronically.

3.7 All quality-related activities should be recorded at the time they are performed.

3.8 The quality management system should ensure that:

- sufficient resources are available (for example, equipment, personnel, materials);
- excipients for pharmaceutical use are produced, controlled, stored and distributed in accordance with the recommendations in this document and other associated guidelines, such as good quality control laboratory practices and good storage and distribution practices, where appropriate;
- managerial roles, responsibilities and authorities are clearly specified in job descriptions;
- operations and other activities are clearly described in a written form, such as standard operating procedures and work instructions;
- appropriate arrangements are made for the manufacture, supply and use of the correct containers and labels;
- all necessary controls are in place;
- calibrations, verification or validations are carried out where necessary;
- the excipient for pharmaceutical use is correctly processed and checked according to the defined procedures and specifications;
- deviations, suspected product defects, out-of-specification test results and any other nonconformances or incidents are reported,

investigated and recorded. An appropriate level of root cause analysis is applied during such investigations and the most likely root causes are identified;

- proposed changes are evaluated and approved prior to implementation. After implementation of a change that could impact the quality or the product, an evaluation should be undertaken to confirm that the quality objectives were achieved and that there was no unintended adverse impact on product quality;
- appropriate corrective actions and preventive actions, as well as checks on the effectiveness of those actions (where appropriate), are identified and taken;
- where required, processes are in place to ensure the management of any outsourced activities that may impact product quality, purity and integrity;
- a batch of an excipient for pharmaceutical use is not released and supplied before it has been released by the quality unit with the assurance that the batch has been produced and controlled in accordance with product specifications, and with the recommendations in this document and any other regulations relevant to the production, control and release of these products;
- there is a system for handling complaints, returns and recalls;
- there is a system for self-inspection;
- there is a system for product quality review.

3.9 The quality unit should be independent of production. The responsibilities of the unit should be clearly defined and documented.

3.10 The person or persons authorized to release excipients for pharmaceutical use should have appropriate qualifications, and be specified.

3.1 Quality risk management

3.11 There should be a system for managing risks (*1*). The system for quality risk management should be comprehensive and should cover a systematic process for the assessment, control, communication and review of risks in the production, testing, packaging, storage and distribution of excipients for pharmaceutical use. Controls identified should be appropriate, ensure that risks are eliminated or mitigated, and ultimately protect the patient from receiving a pharmaceutical product containing the wrong, contaminated or unsuitable excipients for pharmaceutical use.

3.12 In order to perform an adequate excipient risk assessment, it would be useful to provide some high-level guidance using an appropriate risk profile or ranking using a question-based risk ranking and filtering system. For example:

- functionality of excipient in formulation
- route of administration
- potential for contamination
- excipient complexity
- prior knowledge or experience with excipient
- packaging size.

3.13 Similarly, a risk score should be calculated for the supply chain (for example, complexity of supply chain, prior knowledge of supply chain, excipient manufacturer performance history, packaging suitability, quality management system standard and certification)

3.14 Note: see *WHO guidelines on quality risk management* (*1*).

3.2 Management review

3.15 There should be a system for regular management review. All elements of the quality management system should be included.

3.16 Management should ensure that the quality management system achieves its intended objectives and measures managing and performance in areas such as:

- self-inspections, inspections, quality audits and supplier's audits
- complaints, returns and recalls
- changes and deviations
- rejected batches
- quality control, out-of-specification results and out-of-trend results
- maintenance
- qualification and validation
- corrective and preventive actions
- risk management.

3.17 Key performance indicators should be identified and monitored with the view of continual improvement.

3.18 Records of meetings, discussions and actions should be maintained.

4. Complaints

4.1 There should be a written procedure describing the recording and investigation of complaints.

4.2 All decisions made and measures taken as a result of a complaint should be recorded.

4.3 Complaint records should include at least the following:

- date of receiving the complaint;
- name, address and other relevant details of complainant;
- details of the complaint, including name of the excipient and batch number;
- details of the investigation and action taken;
- copy of the response provided;
- final decision based on the outcome of the investigation.

4.4 Where necessary, the appropriate corrective action and follow-up action should be taken after the investigation and evaluation of a complaint.

4.5 Where necessary, a recall of the batch or batches should be considered.

4.6 Records of complaints should be retained in order to evaluate trends.

5. Recalls

5.1 There should be a written, authorized procedure describing the managing of a prompt and effective recall of an excipient for pharmaceutical use. Where the recall is as a result of a contaminated or adulterated excipient, or any other reason where the excipient could cause harm to a patient, the manufacturer should report this to the relevant authority without delay.

5.2 The recall procedure should indicate the responsibilities of personnel involved in the recall, how the recall should be initiated, who should be informed about the recall and how the recalled material should be handled.

5.3 The recall of an excipient for pharmaceutical use should be documented. Records should be kept.

6. Returns

6.1 There should be a written procedure describing the handling of returned excipients for pharmaceutical use.

6.2 Returned investigational products should be clearly identified and stored in a dedicated area in a controlled manner.

6.3 Inventory records of returned products should be kept.

Destruction

6.4 The disposition of the returned product should be approved by the quality unit. The conditions under which the excipient for pharmaceutical use had been stored and shipped should be considered when deciding on the fate of the returned product. If the condition of the container itself casts doubt on the safety, quality or purity of the excipient, the product should be destroyed, unless scientific justification can be provided that proves that the product meets the appropriate predefined quality standards.

6.5 A certificate of destruction should be available containing the necessary detail to enable traceability of the product, batch and related information.

6.6 Where returned excipient containers are reused, all previous labelling should be removed. The containers should be appropriately cleaned and there should be no risk of contamination from one material to another.

7. Self-inspection, quality audits, and supplier's audits and approvals

7.1 There should be written standard operating procedures and programmes for periodic self-inspections, quality audits and supplier audits.

7.2 Self-inspections should be performed routinely in accordance with a self-inspection programme.

7.3 The team responsible for self-inspection should consist of personnel with the appropriate knowledge and experience. Team members may be from inside or outside the manufacturer, but members of the team should be free from bias.

7.4 Areas to be covered in self-inspections may include:

- premises
- personnel
- equipment
- maintenance and calibration
- storage conditions of materials and finished products

- production and in-process controls
- quality control
- documentation, data generation and data integrity
- change control and deviations management
- complaints and recalls
- qualification and validation
- cleaning procedures.

7.5 The excipient's end use should be considered during inspection of excipient manufacturers. It is particularly important to know whether the excipient will be used in the preparation of a sterile dosage form. The excipient manufacturer is responsible for ensuring that excipients are pyrogen free if the manufacturer makes such a representation in specifications, labels or a drug master file.

7.6 Self-inspection should also ensure that appropriate measures are in place to prevent contamination of materials during storage and production.

7.7 The outcome of the self-inspection should be documented, including corrective actions and preventive actions.

8. Personnel

8.1 There should be an adequate number of personnel with appropriate qualifications, training or experience to perform their respective activities.

8.2 Responsibilities should be specified in written job descriptions.

8.3 Training should be regularly conducted and should include, for example, GMP and the particular operations of the employee. Assessment of understanding of training topics should be done and documented.

8.4 Records of training should be maintained.

9. Sanitation and hygiene

9.1 Excipients for pharmaceutical use should be protected from contamination. A documented risk assessment should identify controls to be implemented to ensure appropriate sanitation and hygiene actions are taken.

9.2 Written procedures should be followed for cleaning and sanitization, as appropriate, of manufacturing areas, equipment and utilities.

9.3 Personnel should practise good hygiene and health habits.

9.4 Personnel should wear clean clothing suitable for their activities. The wearing of appropriate protective clothing should apply to all persons entering production areas where products or materials are handled. Additional personal protective equipment should be worn when necessary.

9.5 Personnel should avoid direct contact with starting materials and excipients for pharmaceutical use.

9.6 Smoking, eating, drinking, chewing and the storage of food should not be allowed in production and quality control areas.

9.7 Personnel with an infectious disease or who have open lesions on the exposed surface of the body should not engage in activities that could result in compromising the quality of excipients for pharmaceutical use.

9.8 Jewellery and electronic devices such as mobile phones should only be used in authorized areas.

10. Documentation

10.1 Documents such as standard operating procedures, specifications and others related to the production and control of excipients for pharmaceutical use should be prepared, reviewed, updated, approved and distributed according to written procedures.

10.2 The issuance, revision, withdrawal and retention of documents should be appropriately controlled in accordance with good documentation practices.

10.3 Documents should be retained for a defined period of time. The retention time of the documents should be justified to ensure availability of information in case of need. This time should be longer than the product retest or expiry date.

10.4 Where documents require the entry of data, these entries should be clear, legible and indelible. Entries should be in compliance with good documentation practices and data integrity requirements.

10.5 Records should be made or completed when any action is taken and in such a way that all significant activities are traceable to the person making the entry, including signatures and dates. Corrections made to incorrect entries should be dated and signed, with a description of the reason for the change, as appropriate.

10.6 Electronic documents and records should meet the requirements for good documentation practices, and good practices for computerized systems.

10.1 Standard operating procedures and records

10.7 Standard operating procedures and associated records should be available for at least the following:

- equipment
- analytical apparatus and instruments
- out-of-specification results
- maintenance and calibration
- cleaning and sanitization
- personnel matters, such as training, clothing and hygiene
- qualification and validation
- self-inspection and audits
- complaints
- recalls
- returns.

10.8 The standard operating procedures for sampling should specify the person or section authorized to take samples and the sampling instructions.

10.9 The standard operating procedures describing the details of the batch (lot) numbering system should ensure that each batch of excipient for pharmaceutical use is identified with a specific batch number.

10.10 Records of analysis should be maintained.

10.11 Written release and rejection procedures should be available.

10.12 Records should be maintained of the distribution of each batch of excipient for pharmaceutical use.

10.13 Records should be kept for major and critical equipment, as appropriate, of any qualifications, calibrations, maintenance, cleaning or repair operations, including the dates and the identities of the people who carried out these operations.

10.2 Specifications

10.14 Specifications should be established and maintained for starting materials, packaging materials, excipients for pharmaceutical use, and other related materials where necessary.

10.15 Quality attributes, acceptance limits and test procedures should be defined. Relevant pharmacopoeial monographs, when available, should be considered for use or to be used as a basis for the development of internal manufacturer's specifications.

10.16 A positive identification test uniquely applicable to the excipients should be established through analytical technology, such as infrared spectrophotometry and chromatography.

10.17 Appropriate limits for impurities should be specified. These limits should be based upon appropriate toxicological data, or limits described in national compendial requirements. Manufacturing processes should be adequately controlled so that the impurities do not exceed such established specifications.

10.18 Where excipients are extracted from or purified by the use of organic solvents, specifications should include tests and limits for residues of solvents and other reactants.

10.19 Container specifications should be established for all excipients to ensure consistency in protecting the product during storage and transport, to maintain the stability of the product, and to protect against contamination and infestation.

10.3 Batch documentation

10.20 Procedures such as a master batch manufacturing document with instructions for each excipient for pharmaceutical use should be prepared and authorized (dated and signed).

10.21 A master batch manufacturing document should include the following:

- the name of the excipient for pharmaceutical use being manufactured;
- a complete list of materials (formula) and quantities;
- the production location;
- equipment to be used;
- detailed production instructions, in process controls and flow chart, if needed;
- where appropriate, precautions to be followed;
- labelling and packaging materials and instructions.

10.22 A record should be available for the excipient for pharmaceutical use produced. It should contain detailed information relating to the production and control thereof.

10.23 The manufacturing record should provide traceable information, including the following:

- the batch number
- dates and, when appropriate, times
- identification number of equipment used
- actual results from testing
- information regarding any sampling performed
- signatures of operators and supervisors
- records of packaging, packaging materials and labels
- records of any deviations that occurred
- results of release testing.

10.24 The manufacturer should demonstrate that:

- the batch is homogeneous and compliant with its specification;
- a capable process is used to ensure batch-to-batch consistency;
- a batch has not been commingled with material from other batches for the purpose of either hiding or diluting an adulterated substance;
- samples have been taken, where required, in accordance with a sampling plan that ensures a representative sample was taken;
- the batch has been analysed using scientifically established tests and procedures;
- the shelf-life of the excipient for pharmaceutical use is supported by scientific justification, including data and literature citations, taking account of the stability of the excipient in its packaging.

10.25 Where computerized systems are used in the production of a batch, the electronic data and records should comply with the guidelines on good practices for computerized systems. The system should be suitable for the intended use.

10.26 When computerized systems are in use, aspects such as access and privileges, data integrity, audit trail, and back-up systems should be considered during risk assessment, with appropriate controls identified and implemented.

10.4 Labels

10.27 Excipients for pharmaceutical use should be labelled. Labels should be clear, unambiguous and in compliance with national or regional legislation, as appropriate. Procedures for handling incorrect labelling

should be established, covering the investigation, evaluation and treatment of nonconforming products.

10.28 Information on labels should include as a minimum the following:

- the name of the excipient and grade;
- the batch number assigned by the manufacturer;
- the expiry or retest date, if applicable;
- any special storage conditions or handling precautions that may be necessary;
- warnings and any other appropriate precautions;
- the name and address of the manufacturer.

10.29 For further information, see WHO *Guideline on data integrity and WHO Good manufacturing practices: guidelines on validation. Appendix 5: Validation of computerized systems* (*2*, *3*).

11. Premises

11.1 The premises where excipients for pharmaceutical use are manufactured should provide sufficient space for the production, quality control testing and storage operations.

11.2 The premises should be located, constructed, cleaned and maintained to suit the operations to be carried out.

11.3 The layout and design of the premises should aim to minimize the risk of errors, mix-ups, contamination and cross-contamination. In addition, it should allow effective cleaning and maintenance without any adverse effect on the quality of the products.

11.4 Only authorized persons should have access to relevant areas.

11.5 Adequate lighting should be provided.

11.6 The decision to use a separate or dedicated facility for the manufacturing of high-risk excipients used in pharmaceutical manufacturing should be based on the outcome of a holistic risk assessment performed by the excipient manufacturer. The risk assessment should take into account the requirement of health-based exposure limits, as described in the literature (*4*, *5*).

11.7 Note: The method used to achieve this separation will depend on the nature, extent and risk of the overall operation.

12. Equipment and utilities

12.1 Equipment and utilities should be selected, located, designed, constructed and maintained to suit the operations to be carried out.

12.2 The installation and use of equipment and utilities should aim to minimize the risk of errors and contamination, cross-contamination, build-up of dust or dirt and, in general, any adverse effect on the quality of products.

12.3 Written procedures should be established and followed for repairs, maintenance and cleaning. These operations should not have any adverse effect on the quality of the excipient for pharmaceutical use. Records of these activities should be maintained.

12.4 Equipment and instruments identified as being part of the quality management system should be appropriately controlled. These include those used in production and quality control. The control programme should include standardization, verification, and calibration of reagents, instruments, apparatus, gauges, and recording devices at defined, suitable intervals. Written procedures should contain specific instructions, schedules, acceptance limits and handling of the excursions. Records should be maintained.

12.5 Reagents, lubricants, instruments, apparatus, gauges and recording devices that can affect the quality of the product should not be used.

12.6 Computerized systems that may impact the quality of the excipient for pharmaceutical use should be suitable for their intended use. These should be appropriately validated. Quality data should comply with the requirements for data integrity, including data management, audit trails, access and privileges for users.

12.7 An appropriate level of validation should be performed for computerized systems.

12.8 Equipment, utilities and computer systems should be commissioned and qualified, as appropriate.

12.9 Utilities such as heating, ventilation and air-conditioning (HVAC), water, nitrogen and compressed air systems should be appropriate for their intended use, should not have any negative impact on either operations or the quality of the excipient for pharmaceutical use, and should not be a source of contamination.

12.10 Where HVAC systems are used, air should be filtered to an appropriate level. The design should ensure that the risk of contamination or cross-

contamination is minimized and that specified environmental conditions, where required, are achieved and maintained, at the required grade or class, temperature and relative humidity.

12.11 Water purification systems, where used, should be suitably designed, installed, maintained and operated. Water should be sampled and tested, and should meet its relevant specification.

12.12 Compressed air and nitrogen generation systems should be designed and controlled in accordance with the outcomes of risk assessment.

12.13 Measuring and control devices requiring calibration should be calibrated at defined intervals.

13. Materials

13.1 Materials, including raw materials and packaging materials, should be sourced from approved suppliers.

13.2 A procedure for supplier approval and supplier monitoring should be followed. Records should be maintained.

13.3 Written procedures should be followed for the receiving, sampling, storage, testing and release of materials for use.

13.4 Materials should meet their agreed specifications. Materials that may have a negative impact on the quality of the excipient for pharmaceutical use should not be used.

13.5 Materials should be stored in accordance with their status and labelling requirements.

13.6 Specific tests, based on risk assessment of the material and pharmacopoeial requirements, should be done where applicable. Impurities should be identified and appropriately controlled.

13.7 A procedure for handling nonconforming products should be established covering the investigation, evaluation and treatment of nonconforming products. The disposition of nonconforming materials, intermediates and finished products should be approved by the quality unit and recorded.

13.8 Recovered materials, such as solvents, should only be used if scientifically justifiable, and if they meet their relevant specification. The process of recovery should follow written procedures, and records should be maintained.

13.9 Materials used in batches of excipients for pharmaceutical use should be traceable.

13.10 Materials from waste should be appropriately treated and discarded in a manner that will not have any negative effect on the environment.

13.11 A procedure for waste management should be followed. Records of waste treatment and disposal should be maintained.

14. Production

14.1 Raw materials for manufacturing of excipients for pharmaceutical use should be weighed or measured in appropriate areas, under appropriate conditions, using suitable devices.

14.2 The material to be used in production should be kept in suitable containers bearing labels with required details, such as the name of the material and a traceable control number.

14.3 Equipment in production areas should be labelled, for example, with an asset or other unique identification number and, if applicable, calibration status.

14.4 Where appropriate, materials should not be kept for periods longer than the validated hold time.

14.5 The extent, stringency and type of testing (for example, in-process), as well as acceptance criteria, should be defined. All tests and results should be fully documented as part of the batch record.

14.6 The sampling process should not increase the risk of contamination of the material. Samples should be handled with care and their integrity maintained.

14.7 Manufacturers should have written procedures and related documents for the production and control of excipients for pharmaceutical use.

14.8 Batches should be produced following written procedures or instructions.

14.9 The manufacturing process should be described in detail, and risks associated with the production and control of the excipient for pharmaceutical use should be appropriately controlled. This includes requirements specified in the recognized pharmacopoeia, transmissible spongiform encephalopathy (TSE) or bovine spongiform encephalopathy (BSE), and impurities.

14.10 Batches should be produced using suitable equipment in an appropriate environment, and should be protected from possible contamination and cross-contamination.

14.11 In-process sampling and testing should be done in accordance with written instructions. Records should be maintained.

14.12 Checks and maintenance operations should not affect the quality of the excipient for pharmaceutical use.

14.13 Changes and deviations in production should be managed through the relevant procedures.

14.14 Blending operations should be controlled to ensure homogeneity of the final batch. A blended batch should be assigned a unique batch number, and batches used in the blend should be traceable.

14.15 A sampling procedure should be followed to ensure that a sample collected from the blend is representative of the batch.

14.16 Each batch of product to be mixed should be produced in accordance with the batch manufacturing document, be tested separately, and meet the corresponding specifications. The mixed batch should be tested and should be in compliance with its specification.

14.17 Blending or mixing of batches should be controlled and validated. Procedures and records should be maintained. Blending of batches to salvage out-of-specification batches or adulterated material is not an acceptable practice.

14.18 Manufacturers should regularly review the capability of the process and ensure batch-to-batch consistency of the excipient for pharmaceutical use, meeting its specification.

14.19 Written procedures should be followed for the receipt, identification, quarantine, sampling, examination or testing, and release/rejection, and handling of packaging and labelling materials. Records should be kept.

14.20 Packaging materials such as containers should provide adequate protection against deterioration or contamination of the excipient for pharmaceutical use. They should be clean and dry, and should not be reactive, additive or absorptive.

14.21 Printed packaging materials such as labels should be in the prescribed format.

14.22 Access to printed packaging material storage areas should be controlled.

14.23 Stock should be reconciled at periodic intervals, including received, issued, and returned quantities. Discrepancies found should be investigated.

14.24 Batch coded labels not used for the specified batch, and obsolete and outdated labels, should be destroyed. Reconciliation should be done. Records should be maintained.

14.25 Written procedures should be followed for packaging operations. Controls should be in place to prevent any mix-ups during packaging. These should include line opening and line closing checks, segregation between packaging lines, and verification of materials on the packaging line prior to the start of packaging.

14.1 Rework

14.26 Reworking should only be undertaken when the outcome of a risk assessment indicates that this is acceptable and approved by the quality unit.

14.27 Batches that have been reworked should be subjected to appropriate quality control testing and stability testing, if required. A reworked batch should be released by the quality unit when it has been determined, by applying the relevant analytical testing procedures, that the specification has been met.

14.28 Records should be maintained.

14.2 Reprocessing

14.29 Reprocessing should only be undertaken if this activity and process have been evaluated internally and found to be acceptable.

14.30 Records should be maintained.

15. Qualification and validation

15.1 The scope and extent of qualification and validation should be determined based on risk management principles.

15.2 Manufacturers should be able to provide documented evidence to show that premises, equipment, utilities, procedures and processes are appropriate and are consistently rendering the specified outcome.

15.3 Authorized procedures, protocols and records should be maintained for qualification and validation performed.

15.4 The extent of qualification and validation may be further justified when considering the data from development and scale-up, process capability studies, and product quality reviews.

16. Quality control

16.1 The layout of the quality control section should be appropriate.

16.2 Personnel should be suitably qualified and trained.

16.3 Materials, including raw materials, packaging materials (as applicable) and excipients for pharmaceutical use, should be tested for compliance with their current specifications by following authorized procedures. as described in pharmacopoeias, if available, or by validated in-house procedures.

16.4 Laboratory equipment and instruments should be appropriate for their intended use. These should be suitably designed, installed, labelled, used, maintained, qualified and calibrated (where so determined), according to written procedures. Records should be kept.

16.5 Equipment and instruments that are out of order or out of calibration should be clearly identified to indicate that they are not to be used.

16.6 Authorized procedures should be used for activities including sampling, operation of equipment and instruments, and analysis.

16.7 Analytical test procedures should be developed and validated to control potential and actual impurities that have been identified following a risk assessment and used routinely to ensure that each batch meets the specification.

16.8 To facilitate traceability of each analysis, a record of analysis should be maintained. This includes a certificate of analysis.

16.9 Records of analysis should normally include at least the following:

- name of the excipient for pharmaceutical use;
- batch number;
- test results and reference to any specifications (limits) and test procedures;

- date and reference number of testing;
- date and initials of the persons who performed the testing and the person who verified the testing and the calculations, where appropriate;
- a clear statement of release or rejection (or other status decision) and the date and signature of the designated responsible person.

16.10 Test results should be incorporated into a certificate of analysis.

16.11 Out-of-specification results should be thoroughly investigated and documented as per defined procedures. Appropriate actions should be taken.

16.12 Reference and retention samples should be kept in a secure, suitable location under appropriate conditions. An appropriate quantity should be kept to allow investigation and testing, when these are required.

16.13 Where stability testing is indicated, a procedure and programme should be followed. The procedure and programme should include:

- a written schedule that is reviewed at least annually;
- reference to the number of batches and frequency of a batch to be placed on stability;
- type of containers to be used;
- conditions of storage, including stress conditions (such as elevated temperature, light, humidity or freezing), where appropriate;
- use of stability-indicating test procedures, as applicable.

16.14 The results from stability testing should be reviewed and trended. An expiry or retest date should be allocated based on scientific data.

16.15 Storage conditions should be specified on the label if these are identified (for example, protection from light, temperature).

17. Life cycle and continuous improvement principles

17.1 Manufacturers of excipients for pharmaceutical use should implement the life cycle approach and continuous improvement philosophy. These principles should be applied, in the relevant areas of the premises, to equipment, instruments, utilities, products and processes.

17.2 Manufacturers should implement measures to continuously improve the quality management system, manufacturing and testing procedures, and

the quality of their products. These measures may include the review of root causes of nonconformances, quality complaint investigations and outcomes, and results from self-inspections, audits and other trends.

18. Storage and distribution

18.1 Storage

18.1 Storage areas should be appropriately designed, constructed and maintained. They should be kept clean and dry. There should be sufficient space and suitable ventilation.

18.2 Storage areas should normally be under cover with sufficient space. Where excipients for pharmaceutical use are stored outside buildings, risk assessment should be done to determine the necessary controls to protect the products from contamination and deterioration.

18.3 Excipients for pharmaceutical use should be stored in suitable containers, under appropriate storage conditions. Where special storage conditions are required, these should be provided, controlled, monitored and recorded.

18.4 There should be a written programme for pest control in storage and other relevant areas.

18.2 Distribution

18.5 Excipients for pharmaceutical use should be distributed through traceable routes. Product, batch, container identity and integrity should be maintained at all times. All labels should remain legible.

18.6 Excipients for pharmaceutical use should be transported in accordance with the conditions stated on the labels.

18.7 Distribution records should be sufficiently detailed to allow traceability in case of a recall.

18.8 Note: for further information, see WHO *Good trade and distribution practices for pharmaceutical starting materials* (6).

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Appendices

Note: The following appendices to the *WHO good manufacturing practices for excipients used in pharmaceutical products* will be developed and included:

Appendix 1. Points to consider document focusing on a risk management-based approach for excipients with possible impurities.

Appendix 2. List of high-risk excipients (for example, considering contamination with diethylene glycol, ethylene glycol, nitrosamines).

Annex 3

IAEA/WHO good manufacturing practices for in house cold kits for radiopharmaceutical preparations

Background

Radiopharmaceuticals are used routinely in clinical diagnosis and therapy with increasing importance. A cold kit is an efficient and simple means of preparation of many radiopharmaceuticals at hospital radiopharmacies worldwide. While in some regions of the world radiopharmaceutical cold kits may be available from commercial manufacturers that hold marketing authorizations for specific products, in other regions commercial cold kits may not be available. In those instances, the radiopharmaceutical cold kits are produced in house on a smaller scale to ensure that individual patients have access to these drugs, including cold kits to be used for the preparation of radiopharmaceuticals for clinical trials.

Due to the above considerations, it is essential to harmonize the minimum requirements for good manufacturing practice that should be followed when producing cold kits for subsequent radiolabelling under the practice of nuclear medicine. Considering the absence of dedicated guidance specific to the manufacturing of cold kits for radiopharmaceutical preparation at the health care institutions providing nuclear medicine services, the World Health Organization (WHO), in partnership with the International Atomic Energy Agency (IAEA), has raised the urgency for drafting a new IAEA/WHO guideline on good manufacturing practices for in-house cold kits for radiopharmaceutical preparations.

This text has been developed in alignment with the *International Atomic Energy Agency and World Health Organization guideline on good manufacturing practices for radiopharmaceutical products* (*1*) and *IAEA/WHO guideline on good manufacturing practices for investigational radiopharmaceutical products* (*2*).

Contents

Abbreviations

API	active pharmaceutical ingredient
GMP	good manufacturing practices
HPLC	high-performance liquid chromatography
IAEA	International Atomic Energy Agency
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
iTLC	instant thin layer chromatography
NMR	nuclear magnetic resonance
WHO	World Health Organization

1. Introduction

1.1 Radiopharmaceuticals offer a unique methodology to help elucidate the presence and extent of a disease, and its characterization. They can assist in the selection of specific patients for a particular therapy or the evaluation of a treatment response. Among various types of radiopharmaceuticals, an important class is represented by products that are obtained by the reconstitution of cold kits.

1.2 Cold kits for radiopharmaceuticals are, by definition, any sterile and apyrogenic non-radioactive preparation or set of reagents that, once reconstituted or combined with a radionuclide solution without any further chemical purification, yield the final radiopharmaceutical product.

1.3 As the scope of usage of cold kits is expanding and the cost and demand are increasing, several Member States have set up local facilities for the internal production of cold kits to meet local demand. In some Member States, cold kits may also be directly produced by health care providers, subject to regulatory approval. The in-house cold kit manufacturing pattern is accompanied by a set of challenges due to both the technical complexity of the preparation process and the absence of dedicated regulatory guidance on the requirements that must be followed with respect to assuring the quality of the prepared product. In fact, in some Member States, the in-house production of radiopharmaceutical cold kits is not covered by any legal or regulatory requirements.

1.4 Having inadequate quality standards may have a deleterious effect on patient usage or jeopardize the clinical outcome. On the other hand, strict

compliance with good manufacturing practice (GMP) rules, particularly in the initial stage of development, incurs the risk of slowing down the pace of the development process. In light of these challenges, adopting a balanced risk-based approach with respect to manufacturing process controls is essential.

1.5 To minimize the risks and to ensure product safety, quality and efficacy, cold kits should be manufactured, stored, transported and managed in accordance with an effective quality management system and the recommendations contained in this guideline.

2. Scope

2.1 The recommendations in this guideline are applicable to cold kit production for subsequent radiolabelling under the practice of nuclear medicine. Depending on the region of the world, this practice may be referred to as magistral compounding, in house preparation, extemporaneous compounding or pharmacy compounding.

2.2 This document provides the minimum GMP requirements specific to the in-house preparation of radiopharmaceutical cold kits and is aligned with other World Health Organization (WHO) GMP guidelines and International Atomic Energy Agency (IAEA) radiation protection documents related to radiopharmaceuticals (*3*–*5*).

2.3 The recommendations of this guideline do not apply to industrial production of cold kits, which, depending on the regulatory framework of the intended Member States, may require a marketing authorization.

2.4 In situations where a locally or regionally adopted compendial monograph for a specific cold kit product exists, the relevant aspects of cold kit preparation described in the product-specific monograph should be followed in lieu of the corresponding aspects described in this guidance.

3. Glossary

3.1 The definitions given below apply to the terms used in this document. They have been aligned to the extent possible with the terminology in related WHO guidelines and good practices included in the WHO Quality Assurance of Medicines Terminology Database – List of Terms and related guidelines,[6] but may have different meanings in other contexts.

[6] https://www.who.int/publications/m/item/quality-assurance-of-medicines-terminology-database.

active pharmaceutical ingredient. With respect to a cold kit, the active pharmaceutical ingredient (or active substance or drug substance) is considered to be that part of the formulation that is intended to bind the radionuclide (*6*).

cold kit for radiopharmaceutical preparation. Any sterile and apyrogenic non-radioactive preparation or set of reagents that, once reconstituted or combined with a radionuclide solution without any further chemical purification, yields the final radiopharmaceutical product.

container closure system. The cold kit drug product primary packaging, usually in the form of a stoppered and crimped glass vial.

good manufacturing practices. A set of practices using a traceable process that ensures that products, in this case cold kits, are consistently produced and controlled to the quality standards appropriate for their intended use. Good manufacturing practices fall under the umbrella of the overall quality management system.

in-use stability. The experimental evaluation of the stability over time of the radiopharmaceutical product obtained after reconstitution of the cold kit with the intended radionuclide.

lyophilization. Lyophilization or freeze drying is a process in which water is removed from a product after it is frozen and placed under vacuum, allowing the ice to change directly from solid to vapour without passing through a liquid phase.

manufacturing. Within the scope of this guidance, manufacturing refers to all the operations performed leading up to the finished cold kit product, including the purchase of starting materials, production, quality control release and storage of cold kits.

quality control. A set of analytical tests designed to demonstrate compliance of the quality of starting materials, intermediates and cold kit final products with predetermined quality acceptance specifications.

quality management system. An appropriate system encompassing the organizational structure, procedures, processes, resources and systematic actions necessary to ensure adequate confidence that the cold kit product will satisfy the given requirements for quality.

quality risk management. A systematic process for the assessment, control communication, and review of risks to the quality of the pharmaceutical product across the product life cycle.

radiopharmaceutical compounding. The preparation of radiopharmaceuticals with no marketing authorization but pursuant to the order for a specific patient or patients from a physician certified or qualified for nuclear medicine practice. In various regions of the world, this practice may also be referred to as "in-house preparation", "in-house manufacturing", "magistral preparation", "galenic preparation" or "hospital preparation".

radiopharmaceutical preparation or cold kit reconstitution. Within the scope of this guidance, preparation or cold kit reconstitution refers to the process of addition of a radionuclide solution and other reagents, as needed, to the cold kit, yielding the final radiopharmaceutical product.

radiopharmaceutical product. Any pharmaceutical product containing one or more radionuclides (radioactive isotopes) included for medicinal purposes.

4. Quality management system

4.1 The preparation of in-house cold kits for radiopharmaceutical preparations falls into the general category of manufacturing pharmaceuticals intended for use in patients. The manufacturing of cold kits should be conducted in compliance with an overarching quality management system designed to consistently yield finished products of adequate quality. The basic principles of a quality management system, described in referenced WHO guidelines for manufacture of non-radioactive pharmaceuticals, should also apply to the in-house cold kits for radiopharmaceutical preparation (*7*–*9*).

4.2 In general, the scope and extent of implementation of the quality management system will depend on the scale and complexity of the intended process, but it is expected that the system should address at least the following:

- qualification and training requirements for all personnel and the individuals responsible for the entire manufacturing process;
- adequate resources, including a sufficient number of personnel;
- ensuring compliance with relevant legislation and good practice guidelines;
- process control requirements, including controls applied to the selection and acceptance of starting materials, production of intermediates (if applicable), manufacture of bulk products, conduct of in-process controls and quality control;
- appropriate storage and distribution;

- compliance with relevant standard operating procedures;
- managing deviations and out-of-specification results;
- implementation of an adequate corrective or preventive action system;
- implementation and management of an adequate change control system to manage all changes that may affect the quality of the product, including changes in preparation methods, quality control, equipment, software and suppliers. The quality management system should include a change control system that is flexible enough to allow for controlled changes, whenever necessary and justified;
- conducting periodic audits and self-inspections.

5. Quality risk management

5.1 Quality risk management is an element of the quality management system. There should be a system for managing risks based on a properly implemented plan. Quality risk management for radiopharmaceutical cold kit production should cover a systematic process for the assessment, control, communication and review of risks related to the quality of the product and, ultimately, to the protection of the patient.

5.2 Assessing the risk should be carried out by a team assigned for the particular job. Usually, activities or processes are broken down into a variety of separate tasks. For each task, the potential harm or negative outcomes and the conditions behind those negative outcomes should be considered, especially in cases where the cold kits may be distributed to entities outside the manufacturing institution.

5.3 When assessing the risks associated with a task, the following minimum primary risk factors should be considered (*10*):

- storage conditions
- microbiological controls, including sterility and endotoxin content
- method of sterilization
- in vitro stability of the product and expiry date
- mass of the ligand, excipients and other ingredients
- transport conditions
- methods of lyophilization
- container closure system.

5.4 Quality risk management should also ensure that:

- the evaluation of the risk is based on scientific knowledge and experience with the process and product;
- procedures and records for quality risk management are retained;
- the level of effort, formality and documentation of the quality risk management process is commensurate with the level of risk.

6. Personnel

6.1 There should be at least two persons with the necessary qualifications and practical experience to carry out all the cold kit manufacturing tasks, including batch release.

6.2 For the in-house manufacture of cold kits, the same person may be qualified to perform the duties of either production operator or quality controller, or both. Training and professional qualification should be documented. Periodic retraining should be carried out and documented. Normally, the production and quality control testing of the same batch of cold kits must be conducted by two separate operators.

6.3 For the in-house manufacture of cold kits, it should be possible for a person responsible for batch release to also participate in either the batch production or quality control of a particular batch of cold kits and then conduct a batch release on the produced batch of the finished product.

6.4 Individual responsibilities should be clearly defined and understood by the persons concerned and recorded as written descriptions.

6.5 Personnel should be aware of the principles of GMP and receive initial and continuing training, including hygiene instructions, relevant to their job description.

6.6 The key personnel responsible for each stage of cold kit manufacture should be established. The key personnel should include the following.

6.1 Person responsible for production

6.7 A person responsible for production should:

- ensure that cold kits are produced and stored in compliance with the requirements of GMP and according to the appropriate documentation to obtain the required quality;

- approve the standard operating procedures related to cold kit production and ensure their strict implementation;
- evaluate production records;
- ensure the qualification and maintenance of the premises and production equipment;
- ensure that process validation has been performed;
- ensure that the required initial and continuing training of production personnel is carried out and adapted according to the need.

6.2 Person responsible for quality control

6.8 The person responsible for quality control must be independent from the person responsible for production, and should:

- organize the quality control laboratory in accordance with the requirements of GMP;
- approve or reject starting materials, packaging materials, intermediates used for production of cold kits, and bulk and finished products;
- ensure that all necessary testing is carried out and the associated records are evaluated;
- approve specifications, sampling instructions, test methods and other quality control procedures;
- ensure the stability monitoring of products;
- approve and monitor any outsourced quality control activities;
- ensure the qualification and maintenance status of the quality control equipment;
- ensure that analytical methods are validated;
- ensure that the required initial and continuing training of the quality control personnel is carried out and adapted according to the need.

6.3 Person responsible for the release of manufactured cold kit batches (authorized person)

6.9 The authorized person should possess adequate qualifications, scientific education and practical experience in the relevant field. The qualification requirements might differ according to national and local rules and legislation.

6.10 The authorized person ensures that every batch of cold kits is produced and tested in accordance with the quality standards and specifications. The verification process conducted by the authorized person prior to batch release should ensure that:

- all the necessary tests and controls were performed, including monitoring the production conditions;
- any planned and unplanned changes or deviations in manufacturing or quality control were managed in accordance with a well defined reporting system before any product is released;
- any additional sampling, inspection, tests and checks were carried out or initiated, as appropriate, to cover planned changes and deviations;
- all necessary production and quality control documentation were completed and endorsed by supervisors trained in appropriate disciplines;
- appropriate audits, self-inspections and spot-checks were carried out by experienced and trained staff.

7. Documentation

7.1 Good documentation is an essential part of a quality management system. The documents should be appropriately designed, prepared, reviewed, controlled and distributed.

7.2 The documents should be approved, signed and dated by the appropriate responsible person or persons. No authorized document should be changed without the prior authorization and approval of the responsible person or persons.

7.3 The documentation requirements applied during the in-house manufacture of cold kits may be less rigorous than the documentation requirements applied during large-scale commercial cold kit manufacture, but they would still need to be adequate to allow traceability of the manufacturing process. The processing records of regular production batches must provide a clear and complete account of the manufacturing history of each batch of cold kit, showing that production, testing, storage and distribution have been carried out in accordance with the applicable standard operating procedures (*7*).

7.4 A comprehensive system of standard operating procedures should be created and implemented. These should cover activities including

production, quality control, storage and product release. Specifications for starting materials, primary packaging materials, intermediates, and bulk and finished products, including batch formulae, should be as precisely detailed as possible.

7.5 Batch records should be retained for the duration required by local regulatory authorities or at least two years after the expiry date if no such information is available from the local regulatory authorities.

7.6 The documents should be periodically reviewed and updated, ensuring appropriate traceability to any previous versions.

8. Premises

8.1 Facilities should be located, designed, constructed, adapted and maintained to suit the operations to be carried out, and to minimize contamination of materials and products.

8.2 A facility should be properly designed to ensure the minimization of risk of microbial contamination of finished product during production. The process of producing the cold kits must be carried out in areas with proper air quality conditions. Normally, the process of preparation involves the preparation of bulk mixtures containing the precursor to be radiolabelled and other reagents and excipients, if applicable, followed by sterile filtration, aseptic product aliquoting into vials, lyophilizer loading, lyophilization, stoppering and crimping. While the bulk mixture preparation may be conducted in a class C cleanroom environment, the aseptic operations, including sterile filtration and the subsequent handling of sterilized product, must be conducted in a segregated class A environment, using sterile components and aseptic techniques. Alternatively, in the absence of a class C cleanroom, the entire preparation process may be conducted inside an aseptic barrier isolator specifically designed for sterile cold kit preparation. Additional details on the isolator design requirements are provided in the "Equipment and utilities" section below.

8.3 Heating, ventilation and air-conditioning systems should be designed to maintain the appropriate temperature and relative humidity where required in order to ensure appropriate equipment performance, correct material storage and the safety and comfort of personnel.

8.4 The premises should be maintained regularly. Special precautions should be exercised to ensure that facility repairs and maintenance operations do not compromise product quality. There should be adequate space for

operations to be carried out, enabling efficient workflow. The facilities should be designed in a manner that minimizes the risk of entry of insects, pests and vermin.

8.5 Interior surfaces (walls, floors and ceilings) should be smooth, impervious and free from cracks. They should not shed particles and should permit easy cleaning and decontamination.

8.6 To reduce the accumulation of dust and facilitate cleaning, there should be no uncleanable recesses, while equipment should be kept to a minimum extent. Doors should be carefully designed to avoid uncleanable recesses; sliding doors may be undesirable for this reason.

8.7 The placement of sinks and drains directly in the production areas should be avoided.

8.8 Changing rooms should be designed to minimize the contamination of clothing and to protect clean preparation areas from carry-through of contaminants. The final stage of the changing room should be, in the at-rest state, of the same grade as the clean preparation area (*11*, *12*). Clear instructions for personnel, preferably integrated with visual media such as illustrations and pictograms, on how to dress up before entering a cleanroom should be available in the changing rooms.

8.9 Pipes and valves should be appropriately labelled, designed and located to facilitate identification, cleaning and decontamination. Vent filters should be appropriately controlled.

8.10 The heating, ventilation and air-conditioning system and pressure cascade for the different areas should be appropriately designed and maintained to minimize the risk of product contamination. The pressure differentials should be controlled, monitored and recorded.

8.11 Storage areas should be of sufficient capacity to allow the orderly storage of the intended materials and products. Where special storage conditions are required (for example, temperature, humidity), these should be provided, checked, monitored and reported.

8.12 Segregated areas should be provided for the storage of rejected, recalled or returned materials or products.

8.13 The storage of materials in quarantine status should be ensured in separate areas that should be clearly marked, and their access should be restricted to authorized personnel.

8.14 Quality control laboratories should be separated from production areas. Sufficient space and procedures should be in place to avoid mix-ups and cross-contamination. There should be adequate suitable storage space for samples and records.

9. Equipment and utilities

9.1 Equipment should be designed, installed and appropriately qualified for its intended use. This includes user requirement specifications, design qualification, if applicable, and installation, operational and performance qualification. Equipment and devices, as appropriate, should be calibrated and maintained. Consideration should be given to reducing the risk of product contamination and optimizing ergonomics in order to facilitate equipment operation, maintenance and cleaning. Records should be retained.

9.2 Manufacturing equipment should be thoroughly cleaned, with particular emphasis on the equipment involved in the critical steps of vial filling and lyophilization. Equipment should be cleaned according to written, detailed procedures.

9.3 Manufacturing equipment should not present any hazard to products. Parts of production equipment that come into contact with the product should not be reactive, additive or absorptive to such an extent that it will affect the quality of the product and, thus, present any risk.

9.4 An appropriate level of qualification of computerized systems, such as those controlling the production and quality control equipment, should be performed.

9.5 Where steam systems are used (for example, for lyophilizer chambers), they should be appropriately designed, qualified and monitored for temperature, pressure and time at appropriate locations during routine use, to ensure that all areas are effectively and reproducibly sterilized (*12*).

9.6 Isolators used for cold kit manufacturing should have an adequate space, ideally with one compartment with at least a grade C environment dedicated to the preparation of the bulk solution, a second one with a grade A environment dedicated to vial dispensing, and a third one with another grade A environment where the door of the freeze-dryer and the space for putting freeze-drying vials are located. The isolator design should allow material transport into the grade A areas of the isolator without the risk of air reflux from the class C areas into the class A areas.

Material flow should be represented as a single direction line that does not cross the other flow lines.

9.7 Isolators should be used for manufacturing purposes only after appropriate qualification, which should take into account all critical factors of isolator technology (for example, the quality of the air into the various compartments, sanitization of the isolator, the transfer process and isolator integrity). Monitoring should be routinely carried out and should include leak testing of the isolator, including the glove and sleeve system, if present (*11*, *12*).

9.8 The sterilization of lyophilizers and associated equipment (such as trays, vial support rings) should be validated and holding times between sterilization cycles appropriately challenged during aseptic process simulations.

9.9 The lyophilization equipment should be designed to ensure that kit component sterility is maintained during lyophilization by preventing microbial and particulate contamination.

9.10 Lyophilizers that are manually loaded and unloaded should normally be sterilized before each load. For lyophilizers loaded by automated closed systems, or in cases where operator interventions are excluded, the frequency of sterilization can be different, but that should be justified and documented.

9.11 The transfer of partially closed containers to a lyophilizer should be undertaken under a grade A environment at all times and handled in a manner designed to minimize direct operator intervention.

9.12 Automation of the processes may contribute to reducing contamination and minimizing critical interventions in grade A environment areas.

9.13 Utilities and ancillary equipment, such as gas and a sterile water supply system, should be qualified and regularly maintained and records should be archived.

9.14 Quality control equipment should be qualified, validated, calibrated and regularly maintained, and records should be archived.

9.15 Cleaning and depyrogenation of reusable glassware, if applicable, should be performed in accordance with established standard operating procedures.

9.16 Suitable desicattors should be available to store moisture-sensitive chemicals.

9.17 Refrigerators and freezers used for storage should be connected to an uninterruptible power supply and monitored with temperature recording systems or devices. Recording devices should be calibrated at least once in a year.

10. Materials

10.1 Starting materials should be of adequate quality and suitable for intended purpose. The following are recommendations relevant to the selection of materials and components for a radiopharmaceutical cold kit product.

10.2 The active pharmaceutical ingredient (API) should be either obtained from a qualified supplier or produced in-house using a controlled process. In either case, the quality of this material should be well established, with the minimum applied acceptance specifications being the confirmation of chemical identity and chemical purity. Acceptance of pharmaceutical or compendial grade material may be based on the review of the certificate of analysis from the qualified API material supplier. Internally produced API materials may be accepted based on the review of the relevant quality control documentation that has been generated for that specific batch of material.

10.3 Kit excipients, such as bulking agents, radioprotectants, buffers and water, should be selected based on both the availability of pharmaceutical grade quality material and a demonstrated absence of negative impact on the subsequent radiolabelling process.

10.4 Pharmaceutical or compendial grade excipients may be accepted based on a review of the certificate of analysis provided by a qualified supplier. In cases where an excipient of pharmaceutical or compendial quality is not available, the material's identity, chemical purity and assay should be confirmed by performing additional confirmatory analytical testing on samples of material.

10.5 The container closure system (the vial and the stopper) must be appropriately selected for the intended kit design. In cases where the container closure components are "ready to use", no additional processing by the cold kit producer is required. In other cases, additional processing steps, such as component washing and sterilization, may need to be developed and applied by the cold kit manufacturer. In all cases, the materials may be accepted based on a review of the certificate of compliance provided by the material manufacturer.

10.6 Possible leaching of metals from the container closure system, either during radiolabelling or during long-term storage, is of particular concern when producing cold kits intended for use with radiometals. In those situations, the use of low trace metal leaching components made of materials such as cyclic olefin polymer or glass and rubber that have been precoated with materials that prevent leaching of metallic contaminants is recommended.

11. Production

11.1 Manufacturing operations

11.1 The manufacturing of cold kits is a multistep process that should be conducted in accordance with relevant and approved standard operating procedures. The following minimum requirements should be followed.

- A list of all materials used in each batch should be documented. Manufacturing formulae are to be specified for the batch size according to the number of vials to be produced in the desired batch.
- Formulation is an important step in the process of manufacturing. Each step should be strictly followed in accordance with the established standard operating procedures and should be documented.
- The weight readings of individual chemicals should be printed or photographed and attached to the batch record as supporting documentation.
- The lyophilizer used should be fit for the intended purpose of producing a sterile lyophilized cold kit. The applied lyophilization cycle conditions must be designed so that they result in the adequate removal of moisture and do not adversely affect the contents of the vial.

11.2 The cleaning, sterilization and operation of freeze-drying equipment should be conducted in accordance with the approved standard operating procedures.

11.3 Environmental monitoring should be performed in accordance with approved standard operating procedures, ensuring appropriate functioning of the classified areas for all desired operations during cold kit production (*9*).

11.4 Tests that may be used to monitor air quality include non-viable particle counts and microbiological monitoring via the use of active air samplers, growth media settling plates and media contact plates.

11.5 Instructions for line clearance, based on cleaning validation, should be implemented and followed to eliminate the risk of cross-contamination when preparing a batch of the cold kit.

11.2 Packaging and labelling

11.6 The labelling on the primary packaging (that is, the vials) of the prepared cold kit drug product should include at least the following information:

- name of the product, batch number and expiry date
- name of the manufacturer
- date of manufacturing
- mass, if appropriate.

11.7 The following minimum information should be listed on the secondary packaging container label, in addition to any information listed on the primary packaging:

- qualitative composition
- excipient information
- storage instructions
- address of the manufacturer.

11.8 Both primary and secondary packaging must be designed to ensure that the quality and integrity of cold kits remain uncompromised during transport and storage.

12. Quality control

12.1 Quality control testing must be conducted to establish the cold kit batch conformance with the predetermined acceptance specifications.

12.2 The quality of the final radiopharmaceutical obtained after reconstitution of the kit with the intended radionuclide should also be tested.

12.3 The following minimum tests should apply to every batch of prepared cold kit drug product.

- **Drug substance identity and content.** The identity of the API should be confirmed using the appropriate identity confirmation method – for example, high-performance liquid chromatography (HPLC). The reference standard used during identity confirmation testing should be a separate well characterized – for example, by

means of mass spectrometry or nuclear magnetic resonance (NMR) – lot of the chemically identical material.

The API should be quantified using the appropriate quantification method (for example, HPLC) in order to make sure the API characteristics are within an acceptable range for adequate radioincorporation, yielding a reconstituted product of intended molar activity range, if applicable.

In cases where an API is a large macromolecule or its aggregate, or for any reason its inherent nature does not allow identification and quantification using, for example, HPLC, other confirmation methods, such as electrophoresis, size exclusion chromatography or other suitable method, have to be selected and implemented.

- **Excipient identity and content.** The identity of excipients should be confirmed using an appropriate identity confirmation method. The reference standard used during identity confirmation testing should be a separate well characterized lot of the chemically identical material. The content of excipients should be quantified using an appropriate quantification method to confirm that the amounts of the excipients are within the intended range, yielding a radiopharmaceutical with adequate quality.
- **Endotoxin content (bacterial endotoxins test).** The amounts of endotoxins present in the cold kit product should be determined to ensure that it conforms to the acceptance specification limit. When developing the acceptance specification for the cold kit, the possible contribution of endotoxins from materials used during the reconstitution process (such as the radionuclide solution) to the overall endotoxin in the reconstituted radiopharmaceutical drug product should be taken into account.
- **Sterility tests.** The sterility of the prepared batch of the finished product should be confirmed by applying compendial sterility testing methods (for example, direct inoculation of media or membrane filtration) to a selected number of batch samples. The exact number of samples used during testing is batch size dependent and should agree with the relevant sterility testing guidance documents used or issued by the regulatory authorities in the applicable country or region (*12*, *13*).
- **Chemical impurities.** Proper chemical impurity limits should be established. These limits may be based on scientific knowledge, pharmaceutical development data and the preparation process validation data.

- **Container closure integrity.** Container integrity testing should be applied to confirm that the container closure is adequately sealed, minimizing the risk of drug product contamination and moisture ingress. For closures intended to be pierced several times (for example, in the case of multidose radiopharmaceutical preparation), a self-sealing test should also be performed.

12.4 The following minimum tests should be applied to every batch of reconstituted radiopharmaceutical.

- **Appearance.** The reconstituted radiopharmaceutical should be visually assessed to ensure that the obtained appearance corresponds to the expected appearance.
- **pH.** The pH of the reconstituted solution should be checked to ensure it conforms to the acceptance specification range that is reflective of the physiological pH range. The pH can be checked either with a pH meter or using pH paper strips that have been validated against pH meter readings.
- **Radionuclide incorporation (radiolabelling efficiency).** The degree of radionuclide incorporation in the reconstituted radiopharmaceutical and the corresponding amount of the unbound radionuclide or radiochemical impurities should be determined using an appropriate validated chromatographic technique – for example, radio-instant thin layer chromatography (radio-iTLC) or HPLC – to ensure conformance with the acceptance specification.
- **Radiochemical identity.** Whenever possible, the identity of radioactive API in the reconstituted radiopharmaceutical should be confirmed using the appropriate identity confirmation method (for example, HPLC or iTLC). The reference standard used during identity confirmation testing should be a separate well characterized lot of the chemically identical material (that is, the reference standard should be in the form of the ligand molecule coupled to a non-radioactive isotope of the radionuclide). However, it is recognized that in some circumstances the chemically identical standard may not be available (for example, in cases where a naturally occurring non-radioactive isotope of the intended radionuclide does not exist); in this event, it is permissible to use material with almost identical chemical structure and chromatographic behaviour (for example, the precursor material) after carrying out a radio-HPLC analysis to establish its predominant single entity (level to be defined in the acceptance criterion, for example > 98%).

- **Radiochemical purity.** The radiochemical purity of the reconstituted drug product should be evaluated using analytical chromatographic techniques (for example, HPLC or iTLC) that are capable of identifying and quantifying the potential radioactive impurities that may appear either during the radiolabelling process itself or over time as the drug product is subjected to autoradiolysis.

12.5 Once the compliance of a batch of the finished product with the acceptance criteria has been demonstrated via the successful completion of the quality control release testing described above, the following minimum quality control release test should be routinely performed by the cold kit end user after reconstitution of every vial:

- appearance by visual inspection;
- pH determination by pH strips;
- radiolabelling efficiency using a suitable chromatographic technique.

13. Qualification and validation

13.1 With respect to validation and qualification requirements, general considerations applicable to the manufacture of non-radioactive pharmaceuticals also apply to the manufacture of radiopharmaceutical cold kits (*14*). However, the extent of validation or qualification procedures and requirements should also be determined considering the risk assessment for a particular intended process. In the absence of local regulatory requirements, the following minimum aspects of qualification and validation should be considered.

13.2 The qualification of instruments or equipment and validation of methods or procedures are essential to prove that the critical aspects of their operation are controlled.

13.3 Qualification and validation activities, including clearly defined responsibilities and experimental data, should be documented and archived.

13.4 The planning of qualification and validation activities should consider the complexity and critical aspects of the intended cold kit production and subsequent radiolabelling.

13.5 The facilities and equipment need to be properly maintained and calibrated. A schedule of planned preventive maintenance should be established for instruments or equipment, as well as regular verification or calibration, as appropriate.

13.6 The requalification of equipment may be warranted under certain circumstances (for example, in cases of significant changes, deviations or out-of-specification results that may affect the quality of the product).

13.7 The qualification of production and quality control equipment should demonstrate that they have been installed, operated and performed in accordance with the requirement of GMP and are fit for the intended purpose.

13.8 Cleaning validation should be especially focused on critical areas for cold kit production, such as working surfaces and, in general, surfaces that come into direct contact with the operators and with starting materials, intermediates or products.

13.9 Processes and procedures should ultimately be established based upon validation and qualification results.

13.10 The critical aseptic processes performed during the sterile cold kit batch preparation must be validated via suitable validation studies (that is, media fills). All new operators involved in conducting critical aseptic operations must be qualified through the successful completion of at least three media fill simulation studies and periodically re-evaluated. The frequency of periodic qualification, or the need for any additional aseptic process revalidation studies, should be determined by and be at the discretion of the authorized person.

13.11 Manufacturing process validation should be carried out after all of the critical requirements (for example, media fill testing, relevant standard operating procedure for operator training and equipment qualification) have been completed. The validation campaign should include an adequate number of batches of the intended cold kit. The number of batches and the batch size range should be predetermined as part of a risk assessment performed prior to process validation.

13.12 Similar to other non-radioactive pharmaceutical manufacturing process validation requirements, the new cold kit's preparation process should be validated through the successful completion of at least three prospective production runs and stability studies. However, the number of batches may need to be increased in certain situations. For example, additional validation and stability runs may be required when the manufacturer is trying to qualify multiple suppliers of a particular critical component.

13.13 Should the manufacturing process encounter significant changes that may impact the quality of the final drug product (for example, new supplier of precursor drug substance, new container closure system or

new production equipment), manufacturing process revalidation studies may need to be conducted. The decision regarding whether or not the additional revalidation studies are warranted should be made by the authorized person.

13.14 The manufacture of cold kits for phase I clinical trials may not necessarily require an analytical method validation. Instead, the application of a specific analytical method to a given investigational product could be justified through available scientific knowledge and verified during the conduction of a product's pharmaceutical development and process qualification studies (*2*).

13.15 If an analytical method validation is needed, protocols should agree with the guidelines issued by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) standards (*14*, *15*).

13.16 Compendial analytical methods that are described in relevant pharmacopoeia do not require validation but may require verification prior to the initiation of manufacture. For example, the compendial endotoxin testing method may be implemented after the verification of drug product-specific inhibition or enhancement tests.

14. Stability

14.1 For a stability assessment of the prepared cold kits, the same batches manufactured for process validation studies may be used. The experimental data can then be used to assign an appropriate shelf-life to the future batches of the drug product and to define the appropriate storage conditions with respect to temperature and protection from light. The stability study design should be at the discretion of the authorized person. In general, the relevant WHO guidance could be used when designing the stability studies protocol (*16*).

14.2 The in-use stability of the reconstituted radiopharmaceutical should be determined to assign an appropriate expiry time for the future batches of the reconstituted radiopharmaceuticals. The exact parameters or specifications that should be assessed during an in-use stability evaluation should be at the discretion of the authorized person. At a minimum, the in-use stability testing should include monitoring for changes in radiochemical purity, appearance and pH.

15. Complaints

15.1 In situations where the prepared cold kits may be distributed to entities outside the institution (that is, distributed for extra-institutional clinical use), there should be written standard operating procedures for handling the investigation of product complaints.

15.2 The standard operating procedures should provide a clear and concise description of responsibilities and actions that may need to be undertaken, such as communication pathways and structure, traceability, and reporting requirements, in the event that a complaint is received.

15.3 Any complaint concerning a product defect should be recorded with all the original details and thoroughly investigated in order to determine the cause and to take any necessary corrective and preventive action.

15.4 All decisions made and measures taken as a result of a complaint should be recorded and referenced to the corresponding batch records of the cold kit.

15.5 Whenever necessary, the appropriate follow-up action, possibly including product recall, should be taken after the investigation and evaluation of the complaint.

15.6 If the kits are prepared and used within the same institution, and if there are clear communication pathways between the nuclear medicine department and the kit manufacturer (if different), then the implementation of a complaint standard operating procedure is not required.

16. Recalls and returns

16.1 In situations where the prepared cold kits may be distributed to entities outside the institution (that is, distributed for extra-institutional clinical use), there should be written standard operating procedures for product recall and return concerning the cold kit, defined by the responsible person and approved by authorized staff members.

16.2 The standard operating procedures should provide a clear and concise description of the managing of responsibilities for actions that may need to be undertaken, communication pathways and structure, traceability, and reporting requirements in the event of initiation of a product recall and return.

16.3 The recall and return of a product should be documented and inventory records should be kept.

16.4 Multiple project-specific recall and return procedures may need to be implemented in order to reflect the requirements for a specific product. For example, the product recall requirements in the case of a cold kit supplied within the same institution or hospital where the kits are manufactured may differ significantly from the case of kits delivered to other external hospitals. In all cases, the exact requirements need to be clearly defined and the staff need to be consistently trained.

16.5 Recalled and returned cold kits should be segregated and should not be reused.

16.6 If the kits are prepared and used within the same institution, and there are clearly established communication pathways between the clinic and the kit producer, then the implementation of standard operating procedures for recall and a return is not required.

17. Distribution and shipping

17.1 In situations where the prepared cold kits may be distributed to entities outside the institution (that is, distributed for extra-institutional clinical use), the following points should be considered for the distribution and shipping of cold kits.

17.2 The distribution of in-house prepared cold kits to other institutions should only be done if the benefit of using the kits extra-institutionally outweighs the associated potential quality risks (for example, in a scenario where patients at another institution are able to gain access to in-house prepared kit-derived radiopharmaceuticals that do not have a commercially manufactured alternative available in a given country or region).

17.3 The shipping of cold kits should be carried out in accordance with written procedures laid down in the protocol or shipping order given by the responsible person.

17.4 The shipping processes of cold kits should also be in accordance with international and local rules for medicinal products (*17*).

17.5 Clearly defined transportation conditions are essential. Supportive temperature monitoring data (that is, temperature-logged data that shows absence of temperature excursions during shipment) should be kept together with the distribution records.

18. Destruction

18.1 Radiopharmaceutical cold kit destruction should be carried out in compliance with local or regional requirements for compounded drug destruction.

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Further reading

- International Ethical Guidelines for Health-related Research Involving Humans prepared by the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO), Geneva, 2016. Geneva: CIOMS; 2016 (https://cioms.ch/wp-content/uploads/2017/01/WEB-CIOMS-EthicalGuidelines.pdf, accessed 13 January 2024).
- The International Pharmacopoeia, 11th edition. Geneva: World Health Organization; 2023 (https://www.who.int/teams/health-product-policy-and-standards/standards-and-specifications/norms-and-standards-for-pharmaceuticals/international-pharmacopoeia, accessed 13 January 2024).
- Guide for the elaboration of monographs on radio-pharmaceutical preparations. European Directorate for the Quality of Medicines and HealthCare; 2018 (https://www.edqm.eu/documents/52006/66555/07-elaboration-monographs-radio-pharmaceutical-preparations-october-2018.pdf/50c9d3d8-ec14-10b9-40b7-ceedd94e3afb?t=1623146155879, accessed 13 January 2024).
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- Gillings N, Hjelstuen O, Ballinger J, Behe M, Decristoforo C, Elsinga P et al. Guideline on current good radiopharmacy practice (cGRPP) for the small-scale preparations of radiopharmaceuticals. EJNMMI Radiopharmacy and Radiochemistry. 2021;6:8.

Annex 4

WHO good practices for pharmaceutical quality control laboratories

Contents

Abbreviations

API	active pharmaceutical ingredient
DQ	design qualification
ECSPP	Expert Committee on Specifications for Pharmaceutical Preparations
EQ	equipment qualification
IQ	installation qualification
IT	information technology
LCL	lower content limit
LIMS	laboratory information management system
NAP	normal analytical practice
NMRA	national medicines regulatory authority
NQCL	national quality control laboratory
OQ	operational qualification
PQ	performance qualification
QCL	quality control laboratory
QMS	quality management system
RSD	relative standard deviation
SMART	specific, measurable, achievable, relevant, and time bound
UCL	upper content limit
WHO	World Health Organization

1. General considerations

1.1 In 1999, the World Health Organization (WHO) Expert Committee on Specifications for Pharmaceutical Products (ECSPP) adopted the WHO *Good practices for national pharmaceutical control laboratories*, which were published as Annex 3 of the WHO Technical Report Series No. 902, 2002. These guidelines were subsequently revised as *WHO good practices for pharmaceutical quality control laboratories*, published as Annex 1 of the WHO Technical Report Series No. 957, 2010.

1.2 Since the last revision of the guidelines, the experience from inspections of pharmaceutical quality control laboratories (QCLs) has enabled WHO to identify sections requiring clarification and the need to add new sections. Also, the COVID-19 pandemic made it clear that risk management, crisis management and business continuity are subjects that should be addressed to ensure that laboratories are prepared to face similar situations.

1.3 The present document provides advice on the quality management system (QMS) within which the analysis of pharmaceutical products by QCLs should be performed to ensure that accurate and reliable results are obtained. Compliance with the recommendations provided in these guidelines will help promote international harmonization of good practices for pharmaceutical QCLs and facilitate mutual recognition of test results.

1.4 This guideline is consistent with the requirements of the *WHO good manufacturing practices for pharmaceutical products* (*1*) and international standard ISO/IEC 17025:2017 (*2*), providing detailed guidance for laboratories performing quality control testing of medicines.

1.5 The good practice outlined below is to be considered as a general guide, which may be adapted to meet individual needs, provided that an equivalent level of assurance is achieved. For the items in the following subsections (mainly in the new section 4 on "Planning and strategic management"), a period of adaptation will be given to allow laboratories to implement these new requirements properly:

- 4.3: Performance management
- 4.4: Quality risk management
- 4.5: Crisis management
- 4.6: Communication management
- 6.7: Measurement uncertainty.

1.6 This guideline is applicable to any pharmaceutical QCL, be it a national QCL (NQCL), a commercial QCL, a third-party contract QCL or a QCL of a pharmaceutical manufacturer. However, it does not include guidance for those laboratories involved in the testing of biological products (for example, vaccines and blood products), or for microbiology laboratories. Separate guidance for such laboratories is available, for example, *WHO good practices for pharmaceutical microbiology laboratories* (*3*), which is based on and supplements the requirements described in this document.

1.7 It should be noted that specifications and quality assurance objectives may be different for NQCLs and the QCL of a pharmaceutical manufacturer.

1.1 Pharmaceutical quality control testing

1.8 In a QCL of a pharmaceutical manufacturer, testing usually comprises repetitive testing and analysis of pharmaceutical products. However, an NQCL has to be able to test and evaluate a much wider range of products, requiring the application of a wider range of analytical test procedures and techniques. The same is applicable to commercial and third-party contracted laboratories.

1.9 For the quality of a pharmaceutical product to be correctly assessed, the following should be considered:

- the submission of a sample to the laboratory should be accompanied by a statement indicating the reason why the analysis has been requested;
- the analysis should be correctly planned and executed.

1.10 The test results should be evaluated to determine whether the sample complies with the specifications or other relevant requirements.

1.2 National quality control laboratories (NQCLs)

1.11 A government, normally through the national medicines regulatory authority (NMRA), may establish and maintain an NQCL. Large countries may require several NQCLs to conform with national legislation. The role of NQCLs should be defined in the pharmaceutical legislation of Member States. Appropriate arrangements should, therefore, be in place to monitor compliance with a QMS. Throughout the process of marketing authorization and post-marketing surveillance, the laboratory or laboratories may work closely with the NMRA.

1.12 An NQCL should provide effective support to and collaborate with the NMRA. The analytical results obtained should accurately describe the properties of the samples assessed, permitting correct conclusions as to their quality. Where results from testing of samples show non-compliance with specifications, further investigations should be carried out by the NMRA and, where necessary, the appropriate legal action should be instituted.

1.13 NQCLs usually encompass two types of activity:

- compliance testing of pharmaceutical products employing official methods, which include pharmacopoeial methods, validated analytical procedures provided by the manufacturer and approved by the relevant national or regional authority for marketing

authorization and, whenever necessary, analytical procedures developed and validated by the NQCL;

- investigative testing of suspicious, illegal, or falsified substances or products submitted for analysis, for example by the respective health authorities, customs authorities or police.

1.14 Compliance testing is expected to be performed by NQCLs in accordance with a post-market surveillance testing plan, prepared with the inputs of inspection, assessment and pharmacovigilance and taking into account the criticality of the products, supported by a risk analysis.

1.15 The implementation of these guidelines in NQCLs allows harmonization of laboratory procedures, methodologies and technical competence, enabling mutual trust and recognition among peers.

2. Glossary

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

acceptance criteria for an analytical result. Predefined and documented criteria by which a result is considered to be within the limits (conforms) or to exceed the limits (does not conform) indicated in the specification.

accuracy. The closeness of agreement between the value that is accepted either as a conventional true value or as an accepted reference value and the value found.

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

analytical acceptance criteria. Performance criteria applied to results obtained from the analysis performed. These criteria are predefined and are dependent on the nature of the product, the analytical procedure, and its original validation, as well as the specification limits given in the compendial monograph or in the marketing authorization, such as precision and accuracy.

analytical test report. An analytical test report usually includes a brief description of the test procedures employed, results of the analysis, discussion (if applicable) and conclusions or recommendations for one or more samples submitted for testing.

analytical worksheet. A printed form, an analytical workbook, or electronic means (e records) for recording information about the sample, as well as reagents and solvents used, instruments and equipment used, test procedure applied, calculations made, results and any other relevant information or comments.

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

batch number (or lot number). A distinctive combination of numbers or letters that uniquely identifies a batch on the labels, its batch records and corresponding certificates of analysis.

calibration. The set of operations that establish, under specified conditions, the relationship between values indicated by an instrument or system for measuring (especially weighing), recording and controlling, or the values represented by a material measure, and the corresponding known values of a reference standard. Limits for acceptance of the results of measuring should be established.

certificate of analysis. The list of test procedures applied to a particular sample with the results obtained and the acceptance criteria applied. It indicates whether or not the sample complies with the specification.

certified reference material. Reference material, characterized by a metrologically valid procedure for one or more specified properties, accompanied by documentation (a certificate) that provides the value of the specified property, its associated uncertainty, and a statement of metrological traceability.

collaborative study. A study performed with a set of laboratories with different purposes, for example to establish a new batch of a reference standard or to validate a new test method to be published with regard to its robustness, which can be used to compare the results between different laboratories.

compliance testing. Active pharmaceutical ingredients, pharmaceutical excipients, packaging material or pharmaceutical products according to the requirements of a pharmacopoeial monograph or a specification in an approved marketing authorization.

confirmed out-of-specification result. A result that has been subjected to a thorough investigation and has been confirmed to be out of specification.

control sample. A sample used for testing the continued accuracy and precision of the procedure. It should have a matrix similar to that of the samples to be analysed. It has an assigned value with its associated uncertainty.

conventional true value. Value attributed to a particular quantity and accepted value.

crisis management. A set of planned strategies defined in advance to assist an organization in managing an unexpected event with a relevant negative impact. These strategies should ensure that business processes, assets and personnel are protected and are able to adapt to function in the event of such a disruption, such as a natural disaster (fire, flood, weather-related events), a cyberattack or a pandemic.

data integrity. The degree to which data are complete, consistent, accurate, trustworthy and reliable, and to which these characteristics of the data are maintained throughout the data life cycle. The data should be collected and maintained in a secure manner, such that they are attributable, legible, contemporaneously recorded, original or a true copy, accurate, complete, consistent, enduring and available (commonly referred to as "ALCOA+"). Assuring data integrity requires appropriate quality and risk management systems, including adherence to sound scientific principles and good documentation practices.

design qualification. A documented collection of activities that define the functional and operational specifications of the instrument and criteria for selection of the vendor, based on the intended purpose of the instrument.

equipment qualification. Action of proving and documenting that any analytical equipment complies with the required specifications and performs suitably for its intended purpose.

expanded uncertainty (*U*). Quantity defining an interval about the result of a measurement that may be expected to encompass a large fraction of the distribution of values that could reasonably be attributed to the measurand. Typically, it is calculated from a combined standard uncertainty and a coverage factor *k*. Estimation of uncertainty from a certain source of variation can already be indicated as an expanded uncertainty (for example, the maximum permissible deviation from the nominal volume of a volumetric apparatus).

good manufacturing practices. That part of quality assurance that ensures that pharmaceutical products are consistently produced and controlled to the quality

standards appropriate to their intended use and as required by the marketing authorization.

installation qualification. The performance of tests to ensure that the analytical equipment or system used in a laboratory is correctly installed in accordance with established specifications, enabling it to operate in the expected range.

interlaboratory comparison or testing. The organization, performance and evaluation of measurements or tests on the same or similar items by two or more laboratories in accordance with predetermined conditions.

level of confidence. A number expressing the degree of confidence in a quoted result, for example, 95%. It represents the probability that the conventional true value of the measurand lies within the quoted range of uncertainty.

management review. A formal, documented review of the key performance indicators of a quality management system performed by senior management on a regular basis.

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

marketing authorization (product licence, registration certificate). A legal document issued by the competent medicines regulatory authority that authorizes the marketing or free distribution of a pharmaceutical product in the respective country after an evaluation for safety, efficacy and quality. In terms of quality, it establishes inter alia the detailed composition and formulation of the pharmaceutical product and the quality requirements for the product and its ingredients. It also includes details of packaging, labelling, storage conditions, shelf-life and approved conditions of use.

measurement uncertainty. A parameter associated with the result of a measurement that characterizes the dispersion of the values that could be reasonably attributed to the measurand.

metrological traceability. The property of a measurement result whereby the result can be related to a reference through a documented, unbroken chain of calibrations, each contributing to the measurement uncertainty.

operational qualification. Documented verification that the analytical equipment performs as intended over all anticipated operating ranges.

out-of-specification result. A test result that has been investigated and confirmed to fall outside the specifications or acceptance criteria established in product dossiers, drug master files, or pharmacopoeias, or by the manufacturer.

out-of-trend result. A result, from a series of analytical results obtained during a certain period of time, that complies with the acceptance criteria (be it specification, internal limits or analytical acceptance criteria) but falls outside the expected and predicted interval or the statistical process control criteria. It requires performance of trend analysis for test results during stability testing, environmental controls and yields, where applicable.

performance qualification. Documented verification that the analytical equipment operates consistently and gives reproducibility within the defined specifications and parameters for prolonged periods.

pharmaceutical excipient. A substance, other than the active pharmaceutical ingredient, that has been appropriately evaluated for safety and is included in a medicines delivery system to:

- aid in the processing of the medicines delivery system during its manufacture;
- protect, support, or enhance stability, bioavailability, or patient acceptability;
- assist in pharmaceutical product identification; or
- enhance any other attribute of the overall safety and effectiveness of the medicine during its storage or use.

pharmaceutical product. Any material 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, which is subject to control by pharmaceutical legislation in the exporting State or the importing State.

precision. The closeness of agreement among individual results when the procedure is applied repeatedly to multiple samplings of a homogeneous sample. Precision, usually expressed as relative standard deviation, may be considered at three levels: repeatability (precision under the same operating conditions over a short period of time), intermediate precision (within laboratory variations) and reproducibility (precision between laboratories).

primary reference substance (or standard). A substance that is widely acknowledged to possess the appropriate qualities within a specified context, and whose assigned content is accepted without requiring comparison with another chemical substance.

proficiency testing. The evaluation of participant performance against pre-established criteria by means of interlaboratory comparisons. It is common that laboratories are provided with aliquots or portions of a large homogeneous

bulk material to make the necessary tests and measurements within a defined time period, and are provided with a report describing the global performance of the proficiency testing and the individual performance of the laboratory, supported by statistical calculation leading to a Z-score or an equivalent measure, converted into satisfactory, questionable or unsatisfactory results.

quality control. All measures taken, including the setting of specifications, sampling, testing and analytical clearance, to ensure that raw materials, intermediates, packaging materials and finished pharmaceutical products conform with established specifications for identity, strength, purity and other characteristics.

quality management system. An appropriate system, encompassing the organizational structure, procedures, processes and resources, and systematic actions necessary to ensure adequate confidence that a product or service will satisfy given requirements for quality.

quality manager. A member of staff who has a defined responsibility and authority for ensuring that the management system related to quality is implemented and followed at all times.

quality manual. A handbook that describes the various elements of the quality management system for assuring the quality of the test results generated by a laboratory.

quality risk management. A systematic process for the assessment, control, communication and review of risks to the quality of the product during its life cycle.

quality unit. An organizational unit, independent of production, that fulfils both quality assurance and quality control responsibilities. This can be in the form of separate quality assurance and quality control or a single individual or group, depending on the size and structure of the organization.

reference material. Material sufficiently homogeneous and stable with respect to one or more specified properties that it has been established to be fit for its intended use in a measurement process.

reference substance (or standard). An authenticated, uniform material that is intended for use in specified chemical and physical tests, in which its properties are compared with those of the product under examination, and which possesses a degree of purity adequate for its intended use.

risk. Combination of the probability of occurrence of harm and severity of the harm.

secondary reference substance (or standard). A substance whose characteristics are assigned or calibrated by comparison with a primary reference substance. The extent of characterization and testing of a secondary reference substance may be less than for a primary reference substance.

signed (signature). Record of the individual who performed a particular action or review. The record can be initials, a full handwritten signature, a personal seal or an authenticated and secure electronic signature.

specification. A list of detailed requirements (acceptance criteria for the prescribed test procedures) with which the substance or pharmaceutical product has to conform to ensure suitable quality. "Conformance to specification" means that the drug substance and drug product, when tested according to the listed analytical procedures, will meet the acceptance criteria (numerical limits, ranges, or other) and is considered acceptable for its intended use. Specifications are critical quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities as conditions of approval.

standard operating procedure. An authorized written procedure giving instructions for performing operations, both general and specific.

standard uncertainty (u). Uncertainty of the result of a measurement expressed as a standard deviation.

starting material. Any substance of a defined quality used in the production of a pharmaceutical product, including packaging material.

suspected out-of-specification result. The first out-of-specification result obtained for a testing parameter, which has not been investigated and confirmed as out of specification.

system suitability test. A test that is performed to ensure that the analytical procedure fulfils the acceptance criteria that had been established during the validation of the procedure. This test is performed before starting the analytical procedure and is to be repeated regularly, as appropriate, throughout the analytical run to ensure that the system's performance is acceptable at the time of the test.

target uncertainty (U^{tg}). Measurement uncertainty is specified as an upper limit and decided on the basis of the intended use of measurement results. Unless otherwise indicated, U^{tg} is expressed as an expanded uncertainty.

trend analysis. An analysis of sets of data intended to detect patterns or trends, with the purpose of understanding the current behaviour and predicting future behaviours of that same type of data. This analysis enables the implementation of actions to control the trends that are observed.

uncertainty evaluation procedure. The procedure used for estimating the overall uncertainty.

validation of an analytical procedure. The documented process by which an analytical procedure (or method) is demonstrated to be consistently suitable for its intended use.

verification of an analytical procedure. The process whereby a pharmacopoeial method or official method approved by regulatory authorities is demonstrated to be suitable for the samples intended to be tested, and the process whereby a laboratory demonstrates it can adequately operate the pharmacopoeial method or official method approved by regulatory authorities.

verification of performance. A test procedure that is regularly applied to a system (for example, liquid chromatographic system) to demonstrate consistency of response.

3. Organization and management system

3.1 Structural and general requirements

3.1 The laboratory, or the organization of which it is part, should be legally authorized to function and be held responsible for the test results, certificates of analysis and other types of work that it performs.

3.2 Senior management is responsible for the establishment, implementation and control of an effective quality system and data governance system by ensuring that policies, training and technical systems are in place.

3.3 The laboratory should:

- have managerial and technical personnel with the authority and resources (financial, human and infrastructure) needed to carry out their duties;
- have arrangements to ensure that its management and personnel are not subject to commercial, political, financial and other pressures or conflicts of interest that may adversely affect their work or compromise impartiality;
- have procedures in place to declare conflicts of interest, as well as possible measures that should be taken to mitigate risks arising from declared interests, and to evaluate, review and document continuously the declarations of interest with respect to the ongoing work;

- have a policy and procedures to ensure confidentiality of all information (oral, paper and electronic) shared with or generated by the laboratory during the performance of laboratory activities, including information contained in marketing authorizations, analytical methods, and the transfer of results or reports;
- be responsible, through legally enforceable commitments, for the management of all information obtained or created during the performance of laboratory activities;
- ensure that all personnel, including contractors, personnel of external bodies or individuals acting on the laboratory's behalf, keep confidential all the information obtained or created during the activities (except as required by law), act impartially and competently, and work in accordance with the laboratory's QMS;
- define, with the aid of organizational charts, the organization and management structure of the laboratory, its place in any parent organization (such as the ministry of health or the NMRA in the case of an NQCL), and the relationships between management, technical operations, support services and the QMS;
- specify the responsibility, authority and interrelationships of all personnel who manage, perform, verify, review or approve work that affects the results of laboratory activities, for instance, in the job description;
- ensure the precise allocation of responsibilities, particularly in the designation of specific units for particular types of medicines, if deemed necessary;
- nominate trained substitutes or deputies for key management and specialized scientific personnel;
- ensure adequate supervision of staff, including trainees, by senior staff familiar with the testing or calibration, validation and verification of methods and procedures, as well as their purpose and the assessment of the results;
- have management that has the overall responsibility for the technical operations and the provision of resources needed in order to ensure the required quality of laboratory operations;
- designate a member of staff as quality manager, who, irrespective of other duties the staff member may have, will ensure compliance with the QMS. The nominated quality manager should have direct access to the highest level of management;

- ensure adequate information flow and communication between staff at all levels; staff are to be made aware of the relevance and importance of their activities, as well as having a good understanding of the mission, the strategic direction and operational priorities;
- ensure the traceability of the sample from receipt, throughout the stages of testing, to the completion of the analytical test report; a registry should be in place for receiving, distributing and supervising the consignment of the samples to the specific units. The records on all incoming samples and all accompanying documents should be maintained;
- maintain an up-to-date collection of all specifications and related documents (paper or electronic) used in the laboratory;
- have appropriate safety procedures (section 7).

3.2 Quality management system

3.4 The quality manager should ensure the establishment, implementation and maintenance of a QMS appropriate to the scope of activities in the laboratory.

3.5 The QMS should be communicated and understood by the appropriate personnel prior to its implementation. The elements of this system should be documented (for example, electronically or on paper).

3.6 The quality manual, or equivalent document, should contain, as a minimum:

- a quality policy statement, including at least the following:
  - a statement of the laboratory management's intentions with respect to the standard of service it will provide, including policies and objectives that address the competence, impartiality and consistent operation of the laboratory;
  - a commitment to developing, implementing, and maintaining an effective QMS and continuously improving its effectiveness;
  - the laboratory management's commitment to compliance with the content of these guidelines;
  - a requirement that all personnel concerned have access to the management system documentation and related information applicable to their responsibilities and are aware of the requirements for implementation of the policies and procedures in their work;
- the structure of the laboratory (organizational chart or equivalent document);

- the operational and functional activities pertaining to quality so that the extent and the limits of the responsibilities are clearly defined;
- an outline of the structure of documentation used in the laboratory QMS;
- the general internal quality management procedures and standard operating procedures;
- the requirements of qualification, experience and competencies of personnel and the policy for initial and in-service training of staff;
- policies for:
  - internal and external audits;
  - implementing and verifying corrective and preventive actions;
  - dealing with complaints;
  - performing management reviews of the QMS;
  - selecting, establishing and approving analytical procedures;
  - handling atypical and out-of-specification results;
  - data governance;
  - the employment, handling and storage conditions of appropriate reference substances and reference materials;
  - participation in proficiency testing schemes and collaborative studies, as appropriate, for the assessment of performance (this requirement is optional for the QCL of a pharmaceutical manufacturer);
  - addressing risks and opportunities;
  - evaluation, selection, monitoring of performance and re-evaluation of select service providers and suppliers.

3.7 The quality manager should ensure the establishment, implementation and maintenance of standard operating procedures for all administrative and technical operations, including the following (numbers in parentheses refer to relevant subsections):

- personnel matters, including qualifications and training (5.1);
- control of documents, records and data integrity (3.3, 3.5 and 3.6);
- change control (3.4);
- corrective and preventive actions (3.7);
- internal audits (3.8);
- complaints (3.9);

- purchase and receipt of consignments of supplies (for example, reagents and materials) (4.1 and 5.4);
- procurement, preparation and control of reference substances and reference materials (5.5);
- qualification of equipment, including calibration (5.3);
- preventive maintenance and verification of instruments and equipment (5.3);
- internal labelling and storage of materials and solutions (5.4);
- sampling, if performed by the laboratory (6.1);
- testing of samples with descriptions of the methods and equipment used (6.5);
- validation and verification of analytical procedures (6.3);
- validity of test results (6.8);
- atypical and out-of-specification results (6.9);
- nonconforming work (6.11);
- risks and opportunities (4.4);
- cleaning of laboratory facilities, including bench tops, equipment, workstations, clean rooms (aseptic suites) and glassware (5.2);
- monitoring of environmental conditions (for example, temperature and humidity) (5.2);
- monitoring of storage conditions (5.2);
- disposal of reagents, standards and samples (5.2, 5.4, 6.2, 6.12 and 7).

3.8 The key elements of a qualification and validation programme of the laboratory should be clearly defined and documented in a validation master plan.

3.9 The activities of the laboratory should be systematically and periodically audited to verify compliance with the requirements of the QMS through internal (see subsection 3.8) and external audits.

3.3 Control of documentation

3.10 A master list identifying the current version and the distribution of documents should be established and be readily available, either electronically or on paper.

3.11 The procedures to control and review all documents (both internally generated and from external sources) should ensure that:

- each document, whether a technical or a quality document, has a unique identifier, version number and date of implementation;
- authorized standard operating procedures are readily accessible at the relevant locations, either electronically or physically;
- the documents are reviewed regularly and updated if required;
- any invalid document is removed and replaced with the authorized, revised document with immediate effect (either electronic or paper-based);
- a revised document includes references to the previous document;
- previous versions and invalid documents are retained in the archives (either electronic or paper-based) to ensure traceability of the content and the evolution of the procedures; any other existing copies are destroyed;
- all involved staff are trained on the new and revised standard operating procedures;
- all documentation, including records (either electronic or paper-based), is retained according to national legislation but for not less than five years.

3.12 Staff should be informed when new and revised procedures enter into force. The quality management system in place (see subsection 3.2) should ensure that:

- revised documents are prepared by the initiator (or a person who performs the same function), reviewed, and approved at the same level as the original document and subsequently released by the quality manager (or their team);
- staff acknowledge that they are aware of applicable changes and their implementation date by a signature (electronic or manual) or by an alternative mechanism.

3.13 Detailed recommendations are provided in the WHO guideline on data integrity (*4*) and should be implemented.

3.4 Change control

3.14 The laboratory should have a standard operating procedure to manage changes. Steps in the procedure should include the assessment of impact, gaps, risks and opportunities. Requests for changes should be reviewed and implemented only after approval by management. Records should be kept.

3.15 When changes are required, necessitated by, for example, improvement to current procedures or introduction of a new method or relevant procedure, or increase or decrease in workload, range of laboratory activities, or staffing levels, these should be approved and monitored by senior management.

3.16 If relevant, change processes should also be addressed as part of management review (see subsection 3.10), enabling monitoring by senior management.

3.17 The quality manager should ensure that changes are documented, assessed for impact, approved, planned, implemented and reviewed.

3.18 Staff should acknowledge by signature that they are aware of applicable changes and their date of implementation.

3.5 Control of records

3.19 Identification, collection, indexing, retrieval, storage, backup, access, maintenance and disposal of all quality and technical or scientific records (paper, electronic or hybrid) should be described in the applicable standard operating procedure.

3.20 All original observations, including calculations and derived data, calibration, validation, verification records and final results, should be retained according to national legislation or contractual agreements, but for not less than five years.

3.21 The records should include the data recorded in the analytical worksheet by the technician or analyst on consecutively numbered pages with references to the appendices containing the relevant recordings either on paper (for example, balance weighing records) or electronically (for example, chromatograms and spectra).

3.22 For the data recorded in forms or templates, a procedure should be in place to control the issuance of blank paper templates (or forms) for data recording with reconciliation and authenticity controls where required (*4*).

3.23 The records for each test should contain sufficient information to permit the tests to be repeated or the results to be recalculated, if necessary. The records should include the identity of the personnel involved in the sampling, preparation and testing of the samples.

3.24 The records of samples to be used in legal proceedings should be kept according to the applicable legal requirements.

3.25 A data and information management system ensuring traceability of operations, which is either paper based or software based – for example, a laboratory information management system (LIMS) – should be applied. Access to stored electronic data should be restricted to authorized personnel.

3.26 Samples tested in the laboratory should be retained for a shelf-life plus one year for a pharmaceutical product on the market and 15 years for an investigational product, unless national regulations are more stringent or contractual arrangements require otherwise.

3.27 All quality and technical or scientific records (including analytical test reports, certificates of analysis and analytical worksheets) should be legible, readily retrievable, stored and retained within a secure and suitable environment preventing damage, deterioration or loss.

3.28 The conditions under which all original records are stored should be such so as to ensure their security and confidentiality, and access to them should be restricted to authorized personnel. Electronic storage and signatures are employed but with restricted access and in conformance with requirements for electronic records (*4–12*).

3.29 Quality management records should include reports from internal and external audits, inspections and management reviews, risk assessment, and records of all complaints and their investigations and corrective and preventive actions.

3.6 Control of data

3.30 A master plan should be prepared for the validation of any information system used for the collection, processing, recording, reporting, storage or retrieval of data. Any validation report to demonstrate suitability for use should be prepared and verified by the quality manager or designated person for the task and available to the staff concerned after approval of the laboratory director or designated person. A standard operating procedure should be available that describes the use of a LIMS or a paper or electronic recording system, access rules, and the periodicity and type of backup, either cloud-based or on another server, including the restoration of data.

3.31 Commercial off-the-shelf software in general use within its designed application range can be considered to be sufficiently validated. When applicable, validation documentation should be available and readily retrievable, as for any analytical system.

3.32 The laboratory should authorize, document and validate any changes before implementation, which includes laboratory software configuration or modifications to commercial off-the-shelf software. Where applicable, a validation report should be available.

3.33 The information systems should be:

- protected from unauthorized access to ensure data integrity (that is, using individual access login and password);
- safeguarded against tampering and loss;
- operated in an environment that complies with provider or laboratory specifications;
- capable of recording system failures and the appropriate immediate and corrective actions.

3.34 The quality manager should ensure that for test data in computerized systems:

- electronic data are protected from unauthorized access, and an audit trail is enabled, maintained and periodically checked;
- computer software developed by the user is documented in sufficient detail and appropriately validated or verified as being suitable for use;
- computers and automated equipment are maintained so as to function properly and are provided with the environmental and operating conditions necessary to ensure the integrity of test data;
- electronic data are backed up at appropriate regular intervals, are retrievable and are stored suitably to prevent data loss.

3.35 Electronic forms, prepared from modifications to commercial off-the-shelf software (such as Microsoft Excel), should be duly validated and their validation should be described in a validation report (*12*).

3.36 When a LIMS is managed and maintained off site or through an external host, it should be ascertained that the host of the system complies with all applicable requirements of this document.

3.37 Further information (*4*) can be consulted. Further guidance on the validation of data-processing equipment can be found in other sources (*7*, *9*–*12*).

3.7 Corrective and preventive actions

3.38 Any deviation or nonconformity reported by any member of the staff or otherwise found should be investigated by conducting a root cause analysis with the analyst to identify the problem found and take appropriate action to rectify the nonconformity.

3.39 The laboratory should:

- identify the responsible persons for any action deemed necessary and establish timelines for implementation;
- review the effectiveness of any corrective action taken to eliminate the problem;
- evaluate any risks and opportunities that were identified;
- prepare a report to include evidence of the nature of the deviations, determined causes, any subsequent actions taken, and the results of any corrective action implemented, which should be recorded and retained.

3.40 A critical analysis of the deviations and nonconformities detected by the laboratory and their impact on the management system and the risks and opportunities identified by the laboratory should be performed on a regular basis (see subsection 3.10).

3.41 Any situation that may lead to a potential deviation or nonconformity should be adequately addressed, leading to preventive action. Preventive actions can be treated as a risk or as an opportunity, depending on the type of potential impact of the action (see subsection 4.4).

3.8 Internal audits

3.42 The quality manager is responsible for organizing internal audits addressing all relevant elements of the QMS, comprising the following actions: plan, establish, implement and maintain an audit programme including the frequency, methods and responsibilities, which also takes into consideration the importance of the laboratory activities concerned, changes affecting the laboratory and the results of previous audits.

3.43 A standard operating procedure should be established, incorporating a detailed procedure for the planning and performance of the audits, which will:

- ensure that internal audits are planned and scheduled periodically by the quality manager (at least once a year) to enable systematic assessments;

- define the scope of each audit and use risk-based criteria to determine the most critical activities to be audited, including the implementation of corrective and preventive actions after the last audit, if relevant;
- ensure that audits are carried out by trained personnel who are independent of the activity to be audited;
- ensure that the results of the audits (audit conclusion) are reported to relevant management, discussed during management review (see subsection 3.10), and communicated to staff;
- implement appropriate corrections and corrective actions without delay should any nonconformity be identified;
- monitor the effectiveness of the implemented corrective actions;
- retain records as evidence of the implementation of the audit programme and the audit results.

3.44 Laboratories may also be subject to audits by external auditors to assess their procedures and systems (for example, medicine inspectorate for manufacturers, peer review or ISO accreditation for NQCLs and other types of QCLs).

3.9 Complaints

3.45 The laboratory director should be aware of complaints received and ensure that the process for handling complaints is coordinated and comprises, as a minimum, the following:

- a description of the process for receiving, verifying, investigating and tracking a submitted complaint, and deciding what actions are to be taken in response;
- assurance that the appropriate action is taken within previously defined timelines to resolve the complaint, if needed;
- verification that the whole process is documented and fully traceable;
- informing the complainant of the outcome of the investigation performed, where possible and if requested.

3.46 Where possible, the process should include a member of the staff not directly related to the matter of the complaint. The quality manager should ensure that all the necessary information is collected, verified and recorded and inform the complainant of the outcome of the process, if the complainant's identity is available.

3.10 Management review

3.47 Laboratory management reviews should be convened at planned intervals (at least annually) to monitor the effectiveness of the management system.

3.48 Senior management consisting of, as a minimum, the responsible management board director, the laboratory director (or equivalent job title) and the quality manager should ensure that the decisions taken previously have had the expected impact on the laboratory's activities and resources. Additionally, planning for the following period should be undertaken to enable the continued suitability, adequacy and effectiveness of the laboratory QMS.

3.49 The outcomes of management reviews should be recorded, documenting all decisions and actions related to the effectiveness of the QMS, improvement of the laboratory activities, required resources and necessary improvements.

3.50 The records of the management review should also include information related to the following specific activities or items:

- suitability of policies and procedures;
- performance management (see subsection 4.3);
- status of actions from previous management reviews;
- changes in internal and external factors that have an impact on the laboratory;
- outcome of internal and external audits or inspections and any follow-up required to correct any deficiencies;
- changes in the laboratory activities (type, volume, range);
- adequacy of resources (human, financial, material);
- training programme;
- feedback from customers and staff;
- the outcome of complaints received;
- corrective and preventive actions;
- effectiveness of any implemented improvements;
- follow-up and monitoring of identified risks and opportunities;
- the results of external quality control (collaborative studies or proficiency tests) and any investigations carried out when doubtful or unsatisfactory results are obtained;
- results of trend analysis;
- atypical and out-of-specification results.

3.11 Improvement

3.51 The laboratory should identify and select opportunities for improvement and implement any necessary actions. These opportunities can be identified through a review of policies, procedures and objectives, audit and inspection results, corrective and preventive actions, risk assessment, management review, staff suggestions, and analysis of data, trends, and proficiency testing results.

3.52 The laboratory should request feedback from its customers, for instance, using customer satisfaction surveys, communication records and review of reports. This information should be used as an improvement tool.

4. Planning and strategic management

4.1 Externally provided services and supplies

4.1 The process for the selection and purchase of products (supplies) and services that the laboratory requires should be described, for example, measurement materials (including reference materials and certified reference materials), chemical and biological reference substances, equipment, reagents and services (for example, calibration, qualification, sampling, testing, maintenance, proficiency testing schemes, and assessment and auditing).

4.2 The laboratory should record:

- the review and approval of the laboratory's requirements for externally provided products and services;
- the definition of the criteria for evaluation, selection, and monitoring of performance and re-evaluation of the external providers;
- the evaluation of suppliers of critical products and services that affect the quality of testing, and listing of approved suppliers that have been demonstrated to be of suitable quality with respect to the requirements of the laboratory;
- any actions taken arising from evaluation, monitoring of performance and re evaluation of the external providers.

4.3 The laboratory should communicate its requirements to external providers for:

- the products and services to be provided and their acceptance criteria;

- competence (if applicable), including any required qualification of personnel;
- activities that the laboratory or its customer intends to perform at the external provider's premises.

4.4 The laboratory should prepare a master list of suitable external suppliers for the products and services considered to be essential.

4.2 Review of tenders and contracts

4.5 The procedure established by the laboratory (customer) for the review of requests, tenders and contracts should ensure that:

- the requirements are adequately defined and documented;
- the contract laboratory or a contracted organization has the capability and resources to meet the requirements;
- appropriate methods or procedures are selected, which are capable of meeting the requirements of the laboratory and suitable for the samples to be tested;
- the contracted laboratory informs the laboratory when the method requested is considered to be inappropriate or out of date and provides any clarification to the customer's request.

4.6 There should be a written contract that clearly establishes the duties and responsibilities of each party and defines the contracted work and any technical arrangements made in connection with it, which may include monitoring the contract laboratory's performance in relation to the work performed.

4.7 Any differences between the request or tender and the contract should be resolved before laboratory activities commence, and each contract should be acceptable to both the contracted laboratory and the customer. Deviations requested by the customer should not compromise the integrity of the contract laboratory or the validity of the results.

4.8 The customer should be informed of and agree to any deviation from the contract.

4.9 If there is a need for an amendment to the contract after the commencement of the work, the contract should be reviewed, and the affected personnel of the contract laboratory should be informed. Records of reviews should be retained.

4.10 Records of relevant discussions with a customer relating to the customer's requirements or the results of the contract laboratory activities should be retained.

4.11 When subcontracting is required:

- only organizations approved for the type of activity required should be addressed;
- the contract should allow the laboratory to audit the facilities and competencies of the contracted organization and ensure access by the laboratory to records and retained samples;
- the contracted laboratory should inform and gain approval from the customer about the specific activities to be performed;
- the contracted organization should not pass any work entrusted to it under contract to a third party without the laboratory's prior evaluation and approval of the arrangements.

4.12 The laboratory is responsible for periodically assessing the competence of any contracted organization.

4.13 The laboratory should maintain a register of all subcontractors used, with records of the assessment of their competences.

4.14 The laboratory takes responsibility for all results reported, including those supplied by the subcontracting organization.

4.3 Performance management

4.15 The laboratory management review should set objectives, performance indicators and measurable targets for its activities for a specific time frame, which should be monitored regularly and, if necessary, appropriate actions taken. The objectives should be SMART: specific, measurable, achievable, relevant, and time bound. Some examples of performance indicators are the number of products tested versus the number of products planned to be tested, the percentage of complaints resolved within the given time frame, or the percentage of analytical test reports issued within a specific time frame.

4.16 If the laboratory is part of an organization, such as an NMRA, the objectives and targets should be fully aligned with the mission, vision and strategic goals of the organization and should be translated into operational plans and individual staff objectives, which should be monitored.

4.17 The laboratory should monitor the technical performance regularly with regard to the following:

- the competence of personnel (see subsection 5.1);
- the validity of test results (see subsection 6.8), in particular, the regular assessment of performance related to participation in a proficiency test scheme;
- nonconforming work (see subsection 6.11) and its impact in terms of risk management.

4.4 Quality risk management

4.18 The laboratory should have a formal, well established approach to risk management involving the identification, assessment, treatment, prioritization, continuous monitoring and review of risks. It should consider the potential impact of all types of risks associated with processes, activities, stakeholders, products and services, and should define procedures and methodologies to minimize, monitor and control the probability or impact of unfortunate and undesired events and potential failures (*13*).

4.19 Two primary principles of quality risk management are:

- the evaluation of the risk to quality should be based on scientific knowledge and, ultimately, link to the protection of the patient;
- the level of effort, formality and documentation of the quality risk management process should be commensurate with the level of risk.

4.20 The laboratory should establish, whenever possible and if applicable, an interdisciplinary team led by the quality manager, including experts from different areas, to coordinate, facilitate and improve science-based decision-making with respect to risks – whether they be general risks for the laboratory or risks related to analytical testing. Possible steps to initiate and plan a quality risk management process may include:

- defining the risk (or opportunity), including the potential cause of the event identified;
- assembling background information on the potential impact (positive or negative, or opportunity);
- specifying a timeline, deliverables and an appropriate level of decision-making for the risk management process.

4.21 The laboratory should plan:

- actions to address the risks and opportunities identified, which should be appropriate to the potential impact on the validity of laboratory results or any laboratory activities (this can include

identifying and avoiding threats, eliminating the risk source, changing the likelihood of losses or consequences, adopting new practices, or using new technologies);

- how to integrate and implement these actions into its management system;
- how to evaluate the effectiveness of these actions.

4.22 The process of identification and treatment of risks and opportunities should be recorded, monitored and duly reviewed on a regular basis by senior management during management review (see subsection 3.10).

4.23 The risks and opportunities identified and monitored should be sufficiently communicated to staff.

4.5 Crisis management

4.24 Specific concerns relate to ensuring the correct and efficient functioning of the laboratory at all times, which depends on suitable planning and budgeting to obtain the necessary resources (maintenance of infrastructure and energy supply, as well as securing the continuity of laboratory activities). Business continuity planning allows the laboratory to take effective measures when issues or incidents arise, enabling management of those issues and providing continuity of business. Thus, key functions of the business, in particular key public health functions, can be fully recovered in the shortest possible time at acceptable costs.

4.25 The laboratory should establish and document a system of prevention and recovery in the event of an unplanned disruption to service, which guarantees employees' security and allows the continuation of work.

4.26 The established system or plan should be preventive and defined in advance, so that business processes, assets, and personnel are protected and able to regain functional competency quickly in the event of a significant disruption, such as a natural disaster (fire, flood or weather-related events), a cyberattack or a pandemic. The documented recovery plan should include the following:

- inputs from key stakeholders and personnel;
- the definition of critical activities, which will determine key resources, such as information technology (IT), infrastructure and key personnel;
- the performance of a risk analysis to establish any risk that can affect the laboratory's activities and the impact of those risks;

- implementation of measures to mitigate risks and recover activities that are identified as critical to the organization, which should be tested for efficacy and reviewed periodically to ensure that the risk analysis is up to date;
- where possible, the definition of a continuity team of adequately trained members, responsible for establishing and implementing appropriate planning and recovery strategies, and, when necessary, adapting these strategies to changing circumstances.

4.27 Recovery strategies for IT should be developed, such as implementing manual workflows so that the activities will continue while computer systems are being restored. An IT disaster recovery plan should be defined.

4.28 The laboratory should test the business continuity plan established, for example by simulation, to confirm its suitability for the intended purpose. Evidence of the testing of the business continuity plan should be maintained.

4.29 Other departments within the organization (if applicable) and stakeholders should be informed whenever a situation capable of presenting a risk to public health occurs, and should be apprised of the remedial actions taken.

4.6 Communication management

4.30 The laboratory should ensure that staff and stakeholders are informed and aware of the results of performance monitoring, either from management review (see subsection 3.10) or from other monitoring tools (see subsection 4.3).

4.31 A laboratory that is part of an organization, such as an NMRA or manufacturing company, should have communication channels with other parts of the organization that are defined and established to facilitate decision-making processes and other relevant processes.

5. Resources

5.1 Personnel

5.1 Personnel with the necessary education, training, technical knowledge and experience for their assigned functions should be employed either permanently or under contract. The competence requirements for personnel for each function should be documented. The laboratory should have procedures and criteria for selecting and assessing the competence of the personnel in accordance with the QMS.

5.2 Job descriptions should be in place for all personnel involved in tests and other laboratory activities, for example, calibration, validation, verification, qualification and maintenance. The laboratory should maintain records of the competencies of the personnel, including their education, qualification, training and experience.

5.3 The laboratory should have the following managerial and technical personnel:

- A laboratory director (or manager or head of the laboratory, or an appropriate job title) with appropriate qualifications (university degree in an appropriate discipline) for the position, with experience in a supervisory role in pharmaceutical analysis in a quality control laboratory, in the regulatory sector or in industry, who assumes full responsibility for all operations, including analytical, organizational, administrative and educational. This person is also responsible for ensuring that:
  - members of the laboratory staff have the competencies and qualifications appropriate to their required functions and their grades reflect their responsibilities;
  - the adequacy of existing training procedures for staff is reviewed periodically;
  - the technical management is adequately supervised;
  - the certificates of analysis, analytical test reports and other important reports and protocols are approved.

  The laboratory director should preferably be supported and complemented by one or more technical managers (or senior analysts) with extensive experience in pharmaceutical analysis in a quality control laboratory, who have been designated responsibility for the analytical operations and for direct management and supervision of the team of analysts and technicians.
- A quality manager who shall have the responsibility and authority to implement and ensure compliance with the QMS and quality control activities. The quality manager should remain independent of routine laboratory analytical activities, depending on the size of the laboratory. The quality manager organizes internal audits of various laboratory activities, with the participation, preferably, of another member of staff from another section, according to a schedule approved during the management review. The quality manager, with the support of technical managers whenever necessary, ensures that:

  - personnel operating specific equipment, instruments or other devices are competent for the tasks they are performing;
  - personnel involved in tests or calibrations, validations or verifications are competent for the tasks they are performing;
  - regular in-service training programmes are arranged to update and extend the skills of both analysts and technicians;
  - the laboratory participates regularly in suitable proficiency testing schemes and, whenever possible, collaborative studies (as applicable);
  - due arrangements are made for the safekeeping and control of substances that are subject to poison regulation or to the controls applied to narcotic, psychotropic and radioactive substances, and which should be stored under lock and key, and handled and used in designated places under the supervision of an authorized person.
- Qualified analysts, who normally should be graduates in pharmacy, analytical chemistry or other relevant subject, with the requisite knowledge, skills and ability to adequately perform the tasks assigned to them by managers or supervisors. Appropriately qualified and experienced analysts with a thorough understanding of the management system, including the review, interpretation and reporting of test results, the maintenance of an internal chain of custody, and proper implementation of corrective and preventive actions in response to analytical problems, should also be available to serve as laboratory supervisors.
- Technicians should hold diplomas in their subjects awarded by technical or vocational schools or have the requisite hands-on experience to perform the assigned activities.

5.4 Staff undergoing training should be appropriately supervised and assessed upon completion of the training. This assessment should be fully documented.

5.5 The laboratory director or designated person should authorize personnel to perform specific laboratory activities. Only sufficiently qualified and trained personnel should be allowed to perform specific laboratory activities.

5.6 The laboratory should have procedures and criteria for the continuous assessment of personnel competence, which should be documented.

5.7 The laboratory should provide training or requalification of personnel, as appropriate.

5.8 The laboratory should maintain a list or matrix of the competencies of each staff member, documented procedures, and criteria for the continuous assessment of personnel competencies, which may include:

- performance of specific tests (such as pH, density and dissolution);
- verification and review of results;
- performance of analytical equipment qualification;
- preparation and management of laboratory solutions;
- preparation of standard operating procedures (at the request of the quality manager).

5.9 The laboratory director, or designated person, is responsible for:

- the consignment of samples to specific units;
- approval of analytical test reports and certificates of analysis.

5.10 Any designated qualified personnel are responsible for:

- review of all analytical data to ensure the validity of the test results by checking the work performed and results obtained by the technician or analyst;
- general technical activities that, by definition, are performed by the technical management, such as the review of technical documents (for example, analytical test reports and certificates of analysis), as long as this activity is delegated;
- the implementation and execution of specific tests or analytical techniques requiring advanced technical training and knowledge, including verifying and reviewing raw data and analytical worksheets.

5.11 The laboratory should have an appropriate training schedule for staff, particularly for those staff who respond to the technical and managerial needs of the laboratory. Inputs to the training plan can be gathered from internal audits, management reviews, risk and opportunity assessments, or other available options. On successful completion of training, the results of evaluation should be recorded and made available, and the information should be added to the competency matrix or master list.

5.2 Premises

5.12 The requirements for facilities intended for laboratory activities should be documented and should be of a suitable size, construction and location.

5.13 Premises should adequately accommodate the features required of a pharmaceutical testing laboratory and should minimize the risk to the health of staff and the quality of the analytical results. Emergency exits should be available.

5.14 Appropriate entrance and sample reception areas must be provided for staff, visitors and samples.

5.15 Rest and refreshment rooms and toilets should be separate from laboratory areas.

5.16 Changing areas should be easily accessible and appropriate for the number of users.

5.17 The laboratory storage facilities should be organized for the correct storage of samples, reagents and equipment. Separate storage facilities should be maintained for the secure storage of samples, retained samples, reagents, laboratory accessories, and reference substances or materials. In general, storage facilities should ensure the following criteria are met.

- Storage facilities should be appropriate to store samples and reagents at the appropriate temperature and humidity conditions to maintain stability, if necessary, under refrigeration (2–8 °C) and frozen (–20 °C) conditions, or other necessary storage conditions, and be securely locked.
- Reagents, reference substances and samples subject to poison regulations or to the controls applied to narcotic and psychotropic substances should be clearly marked and be kept separately in locked cabinets in accordance with national legislation. A designated responsible member of staff should have responsibility for their safekeeping, maintaining a register of these substances, and controlling their use.
- The head of each unit should accept personal responsibility for the safekeeping of any of these controlled reagents or other controlled substances kept in the workplace. All specified storage conditions should be controlled and monitored, and records maintained. Access should be restricted to designated personnel.
- The appropriate safety procedures should be rigorously implemented wherever toxic or flammable reagents are stored or used.

- The laboratory should provide appropriate separate storage rooms for storing flammable substances, fuming and concentrated acids and bases, volatile amines, peroxide-forming reagents, and self-igniting materials, such as metallic sodium and potassium.
- Small stocks of acids, bases and solvents may be kept in the laboratory.
- Gases can come from installed generators or external gas tanks stored outdoors in a well ventilated area, preferably isolated from the main building. Wherever possible, gas bottles are to be avoided in the laboratory. If gas bottles are present in the laboratory, they should be firmly and safely secured. However, it is recommended that gas generators be installed.

5.18 The laboratory should be equipped with adequate instruments and equipment, including workbenches, workstations and fume hoods. Separate instrument rooms for different measurement techniques should be available as required for method performance or to avoid contamination. There should be adequate safety equipment appropriately located, and measures should be in place to ensure good housekeeping and cleaning routines.

5.19 Weighing areas should be located where adequate environmental conditions of temperature and humidity are controlled.

5.20 Where necessary, the preparation and analysis of cytotoxic and genotoxic substances should be performed in a room equipped with, for example, an isolator and laminar flow workbench to handle, weigh, and manipulate cytotoxic and genotoxic (and highly toxic) substances. Appropriate procedures should be in place to avoid exposure and contamination of the staff, such as the use of gowns, suitable particle masks, goggles and protective gloves.

5.21 Archive facilities should be provided to ensure the secure storage and retrieval of all documents. The design and condition of the archives should be such as to protect the contents from deterioration.

- Records should be kept in a secure room with access restricted to authorized personnel.
- Electronic records should be retained, and duplicate copies should be retained in an external facility, for example, saved to an external server or cloud.

5.22 The environmental conditions, including lighting, energy sources, temperature, humidity and air pressure, should be appropriate to the

functions and operations to be performed in the various locations. The specific conditions requiring control and monitoring should be based on the needs of the activity. The laboratory should ensure that the relevant environmental conditions are monitored, controlled and documented.

5.23 Procedures should be in place for the safe removal of types of waste, conforming to the local environmental standards, including toxic waste (chemical and biological), reagents, samples, solvents and air filters.

5.3 Equipment, instruments and other devices

5.24 The laboratory should have the required apparatus, equipment, instruments or instrument system used in pharmacopoeial analyses (analytical equipment) for the correct performance of the tests and related activities.

5.25 A list of equipment considered by the Expert Committee to be adequate, for either a first-stage or medium-sized pharmaceutical quality control laboratory, is provided in Appendix 1.

5.26 All equipment and their modules and accessories must be uniquely identified, including:

- the manufacturer's name, instrument name, model and serial number;
- any identifying number allocated by the laboratory;
- the location, where appropriate;
- the equipment manufacturer's instructions, if available, or an indication of their location;
- the version and due date for requalification of any computer hardware, firmware and software.

5.27 All analytical equipment should be fit for its intended purpose, which is demonstrated by equipment qualification (EQ), which encompasses design qualification (DQ), installation qualification (IQ), operational qualification (OQ), and performance qualification (PQ).

5.28 All four stages will apply to the purchase of new equipment. Aspects of DQ and IQ may need to be repeated following major changes (see subsection 3.4). PQ aspects of OQ should be carried out throughout the entire life cycle of the equipment.

5.29 EQ must comply primarily with pharmacopoeial requirements and should address the intended purpose, and should follow the manufacturer's recommendations.

5.30 The laboratory is ultimately responsible for EQ. For complex equipment, the laboratory may use a specialized service.

5.31 The laboratory should ensure that the EQ process meets compliance requirements and that qualification processes are being followed and supported by complete, valid and documented data.

5.32 In the equipment purchasing phase, the laboratory should compile a user requirement specification document for each piece of equipment and specify in it that the supplier of the equipment provides documents, tools and services to support EQ – in particular, to provide clear instructions and details of tests required to demonstrate satisfactory performance, either performed by the laboratory or by the supplier or other external service provider. The laboratory should maintain oversight of such testing, ensuring that the qualification protocols are followed and supported by data, fully complete and documented. The laboratory should also ensure that the supplier or an external service provider delivers the necessary training, maintenance, repair and installation support.

5.33 The laboratory should establish a policy for when equipment should be serviced (that is, subject to maintenance, calibration and qualification). The following must be clearly described for each type of analytical equipment in use:

- the regularity of any service
- the events after which service is necessary.

5.34 An EQ plan or matrix should be available to allow a clear overview of which equipment undergoes any intervention, when the intervention will take place, and whether or not it is performed by staff or by an external service provider. The laboratory should keep track of the interventions that were performed and when they were performed in case there is a significant deviation from the established schedule (see subsection 3.7).

5.35 A preventive maintenance schedule should be established in an equipment qualification and maintenance plan. Activities under the plan can be performed by the laboratory or entrusted to a competent organization and should be followed by appropriate EQ tests.

5.36 All analytical equipment requiring qualification, calibration or maintenance should be labelled, coded or otherwise identified to indicate the status and the date when the applicable action is scheduled.

5.37 All calibrations or equipment qualifications should be (where relevant and possible) traceable to an appropriate reference, for example, certified reference materials, or to the relevant national or international standards, such as the International System of Units (SI).

5.38 The laboratory should ensure a change control process to guide the assessment, execution, documentation and approval of any changes to the analytical equipment. Designated qualified personnel should assess the effects of any changes to determine if any requalification activities are required.

5.39 Typical changes, after which analytical equipment should undergo the appropriate requalification, are:

- movement or relocation of the equipment;
- interruption to services or utilities;
- repair or maintenance (including preventive);
- modifications;
- change of purpose or use;
- suspect analytical results that, after a suitable investigation, indicate that an analytical instrument employed does not meet EQ requirements.

5.40 Analytical equipment shown to be defective or out of the specified limits should be taken out of service and clearly labelled or marked. It should not be used until it has been repaired and requalified.

5.41 Each stage of the qualification process involves:

- the preparation of a qualification plan defining the scope of qualification (for example, the tests to be performed with their acceptance criteria, which can be combined with the qualification protocol);
- the implementation of the plan to ensure that the results of the tests are recorded as the tests are performed;
- the issuance of a report (and, if required, a certificate) in which the results of EQ are documented.

5.42 Specific standard operating procedures for the maintenance and qualification of analytical equipment performed regularly should be established. The personnel responsible for each operation with analytical equipment (authorized) must be clearly defined.

5.43 Documentation covering EQ should satisfy at least the following requirements:

- define clearly the responsible persons to perform the required tests for maintenance, calibration and EQ;
- provide details of each check and test to be performed, the specification and acceptance criteria;
- provide sufficient information on the procedures and materials required to perform each check and test;
- state the date on which the EQ test was performed and the result of qualification for each check or test;
- state the reason for performing qualification (for example, following the installation of new equipment, following routine service, or following equipment malfunction);
- provide clear information about the action to be taken in the event of test or qualification failure;
- state the circumstances that may or will necessitate requalification of the equipment (for example, following repair, service or recalibration);
- provide the name and signature of the person (or persons) who actually performed the tests, and the name and signature of the quality manager or designated qualified personnel authorizing the completion of a qualification.

5.44 Equipment logbooks should be maintained to:

- identify the individual modules and accessories that constitute the equipment;
- record the overall history of the equipment (including the initial qualification and entry into service);
- include dates of when subsequent maintenance, calibration and qualification have been performed and when these are next scheduled.

5.45 The software used by the laboratory must be appropriately validated, preferably at the time of development; otherwise, if the laboratory is unable to control the development of the software, a software validation certificate from the manufacturer, ensuring compliance with the requirements of the pharmaceutical sector, should be acceptable.

5.46 The level of software validation is determined by its function. It is customary to distinguish between firmware levels (lack of user access) and software used for equipment control, data acquisition and processing.

- Further guidance on qualification of equipment is available in the literature (*6*, *14–17*).

5.4 Reagents and materials

5.47 Reagents and chemicals, including solvents and materials used in tests and assays, should be of appropriate quality and suitable for the intended use.

5.48 Commercial reagents should be obtained from verified and approved qualified providers.

5.49 Reagents from external providers should be accompanied by the certificate of analysis and the safety data sheet, if required.

5.50 Management of the reagents must cover the entire life cycle of the reagents from purchasing and preparation (in the case of preparations) to use and disposal, and should be covered by a standard operating procedure.

5.51 The following major points should be considered in the life cycle of reagents:

- type of reagents and the quality, depending on their use;
- selection of the supplier;
- verification of reagents upon receipt;
- labelling of the reagent (avoiding misuse or misidentification);
- storage conditions;
- ensuring that the reagent is not compromised in any way before being used;
- checking the expiry dates of reagents before use (it is not necessary to document this verification);
- documenting the use of reagents used in analyses, ensuring traceability at least to batch number and expiry date;
- disposal of the reagent.

5.52 The verification should comprise an administrative part (a documented check of the invoice, delivery note, and the integrity of the container, including storage temperature) and a scientific part (a documented check of the actual quality of the reagent given on the label or certificate against the requested quality). Specific in house testing may be required for some reagents.

5.53 For reagents purchased in their original container and purchased reagents that have been transferred into another container, the verification on receipt should be made.

5.54 The level of detail of the verification should be determined by the laboratory, unless otherwise stated.

5.55 The labelling information for all types of reagents should be stated on the container or in a leaflet, register or LIMS (or equivalent), which should include the following:

- name of the substance or reagent;
- date of receipt and date of opening of the container (or preparation date);
- expiry date (or retest date, as justified);
- storage conditions and, if applicable, any specific protection measures (such as protection from heat, light or atmosphere);
- concentration or purity of the reagent, if applicable;
- hazard and precaution codes.

5.56 For purchased reagents in their original container, the following additional information is expected on the label:

- manufacturer, supplier, brand and reference of the substance;
- batch number;
- identification: where the same batch is supplied in several containers, appropriate identification (for example, vial 1, 2, 3) can be indicated in the labels;
- name or initials of the person who opened it.

5.57 For purchased reagents that have been transferred into another container, the following additional information is expected on the label:

- name or initials of the person who transferred the reagent;
- batch number;
- transfer date;
- identification – in cases of transfer to several vials (aliquoted), appropriate identification (for example, vial 1, 2, 3) should be indicated in the labels.

5.58 In-house reagents (preparation of reagent solutions in the laboratory) should have the following labelling:

- name or initials of the person who prepared the reagent;
- date of preparation and validity period;
- name, reference, batch number and quantity of the reagents in the preparation (can be replaced by a reference, for example a project number);
- titre (or concentration or standardization factor);
- date of the determination of the titre and validity period, based on risk management and sound scientific principles;
- name or initials of the person who determined the titre.

5.59 For water manufactured by the laboratory, the following labelling is expected:

- name or initials of the person who dispensed the water and date of dispensing;
- if more than one production apparatus is available, the identity of the apparatus used must be documented.

5.60 For volumetric solutions, the following labelling is expected:

- name or initials of the person who prepared the reagent;
- date of preparation and validity period;
- name of the reagents in the preparation;
- titre (or concentration or standardization factor);
- date of the determination of the titre and validity period, based on risk management and sound scientific principles;
- name or initials of the person who determined the titre.

5.61 For the preparation of reagent solutions in the laboratory:

- responsibility for this task should be clearly stated in the qualification matrix or in the job description of the assigned staff member;
- standard operating procedures should be used that cover the entire life cycle of the use of reagents in the laboratory and are in accordance with published pharmacopoeial or other appropriate standards (*18*);
- records should be kept of the preparation of reagent solutions and standardization of volumetric solutions.

5.62 For the transportation and subdivision of reagents:

- whenever possible, they should be transported in the original containers;
- when subdivision is necessary, suitable clean containers should be used and appropriately labelled.

5.63 All reagent containers should be visually inspected to ensure that the seals are intact, both when they are delivered to the store and when they are distributed to the units. Containers that appear to have been tampered with should be rejected.

5.64 The appropriate grade of water for a specific test should be used as described by the pharmacopoeias or in an approved test.

5.65 The quality of the water should be verified regularly to ensure that the required grade of water complies with the appropriate specification.

5.66 Reagents should be stored under the appropriate storage conditions (temperature, ventilation, fire hazard) and appropriately maintained (organized, tidy, segregated).

5.67 A designated staff member trained in safe handling of chemicals should be responsible for the storage facilities and their inventory, and for noting the expiry date of chemicals and reagents (*18*).

5.68 The expiry period policy must be documented by the laboratory (as part of standard operating procedures).

5.69 The expiry date (before opening) given by the manufacturer must be considered valid. In the following cases, the laboratory shall determine a suitable expiry date, and a justification for assigning a new expiry date shall be documented:

- no expiry data is provided by the supplier;
- when, after opening or transfer, environmental conditions (such as air or humidity) or further operations (such as dissolving a lyophilized material) affect the quality of the reagent.

5.70 The expiry date can be prolonged by providing scientifically sound and documented justifications, for example in cases where expired reagents can be used for a special purpose. In this case, the container must be relabelled appropriately.

5.71 Reagents should be disposed of appropriately when the expiry date is exceeded or when they are no longer required.

5.72 Disposal may be done at defined intervals or when the expiry date is checked prior to potential use, as applicable.

5.73 Reagents must be disposed of appropriately, safely and in compliance with legal requirements.

5.5 Reference substances and reference materials

5.74 Reference substances are necessary to ensure adequate quality control of pharmaceutical products.

5.75 Pharmacopoeial reference substances should be employed when available and appropriate for the analysis. Otherwise:

- An NQCL should use reference substances from a reputable commercial source or supplied by the manufacturer of the pharmaceutical product approved by the national medicines licensing authority (19) and used for the testing of a sample. The use of secondary reference substances by an NQCL is discouraged when primary reference substances are available and suitable for the intended use.
- The manufacturer's laboratory should establish primary reference substances. It can establish secondary (working) reference substances traceable to primary reference substances for use in routine analyses, provided that metrological traceability is ensured for the property value concerned. Pharmacopoeial reference substances are considered primary reference substances against which secondary (working) reference substances can be calibrated.

5.76 A nominated staff member should be responsible for the control of reference substances and reference materials.

5.77 An identification number should be assigned to all reference substances and reference materials. The laboratory may exclude pharmacopoeial reference substances from this identification system, as they are fully traceable by their pharmacopoeial reference number and batch or lot number.

- A new identification number should be assigned to each new batch.
- This number should be marked on each vial of the reference substance.
- The identification number, along with the validity statement, should be quoted in the analytical worksheet each time the reference substance is used.

5.78 A register for all reference substances and reference materials should be maintained and contain the following information:

- the identification number of the substance or material;
- a precise description of the substance or material;
- the source;
- the date of receipt;
- the batch designation or other identification code;
- the intended use of the reference substance or reference material;
- the location of storage in the laboratory and any special storage conditions;
- any further necessary information (such as the results of visual inspections);
- expiry date or retest date (if applicable), and valid use-by date;
- a certificate or leaflet of a pharmacopoeial reference substance and a certified reference material that indicates the use, the assigned content, if applicable, and its status (validity);
- in the case of secondary reference substances or certified reference material, the certificate of calibration or analysis;
- a file (paper-based or electronic) should be kept in which all information on the properties of each reference substance is entered, including the safety data sheets.

5.79 The intended use, expiry date or retest date of reference substances and reference materials used in the laboratory should be confirmed before use, and the corresponding information should be included in the test report. The use of the pharmacopoeial reference substance for purposes other than those specified in the pharmacopoeia is discouraged and is at the user's discretion, based on a risk assessment.

5.80 Reference substances prepared and stored in the laboratory should be retested at regular intervals to ensure that deterioration has not occurred. The interval for retesting depends on a number of factors, including the stability of the substance, storage conditions, type of container (for single or multiple uses) and the frequency of opening the container. If a non-compliant result is obtained on retesting a reference substance, a retrospective check of the tests performed using that reference substance should be carried out. For the evaluation of outcomes of retrospective checks and consideration of possible corrective actions, a risk analysis should be applied.

5.81 More detailed information on the handling, storage and retesting of reference substances established by the laboratory is given in the WHO *General guidelines for the establishment, maintenance and distribution of chemical reference substances* (*19*).

6. Technical activities

6.1 Sampling

6.1 If the laboratory is responsible for the sampling of pharmaceutical products for subsequent testing, a standard operating procedure should be established to include both a recognized sampling plan to ensure that a representative sample is obtained and measures to ensure that the chain of custody is effective.

6.2 The laboratory should have a sampling plan when it carries out sampling of substances, materials or products for subsequent testing or calibration. The sampling method should address the factors to be controlled to ensure the validity of subsequent testing or calibration results. The sampling plan and method shall be available at the site where sampling is undertaken. Sampling plans should, whenever reasonable, be based on appropriate statistical methods.

6.3 The laboratory shall retain records of sampling data that form part of the testing that is undertaken. These records shall include, where relevant:

- reference to the sampling method used;
- date and time of sampling;
- data to identify and describe the sample (for example, amount, name, number, and correspondence to container from which it was taken, when applicable);
- identification of the personnel performing sampling;
- identification of the tools used for sampling;
- environmental or transport conditions;
- diagrams or other equivalent means to identify the sampling location, when appropriate;
- deviations from, additions to or exclusions from the sampling method and sampling plan.

6.4 Further information is provided in *WHO guidelines for sampling of pharmaceutical products and related materials* (*20*) and *WHO guidance on testing of "suspect" falsified medicines* (*21*).

6.2 Incoming samples

6.5 Paragraphs 6.6 and 6.7 are applicable to NQCLs. The principle of the four W's (who, what, when and where) should be applied. The chain of custody of each sample should be recorded.

6.6 Samples received by a laboratory may be for compliance testing or investigative testing.

- Samples for compliance testing include routine samples for control or samples submitted in connection with a marketing authorization process. Close collaboration with the providers of the samples is important. In particular, the quantity or amount of a sample should be sufficient to enable, if required, a number of replicate tests to be carried out and for part of the sample to be retained.
- Samples for investigative testing comprise suspicious, illegal, falsified or suspected substandard pharmaceutical products (*21*). Well documented screening procedures should be in place, as well as confirmatory analytical procedures to verify the identity of the substance or the ingredients. If an estimation of the content of an identified ingredient is required, then an appropriate quantitative analytical procedure should be applied. The value obtained may be reported with an indication of the uncertainty of measurement, if required, especially in the case of borderline test results.

6.7 It is common for a sample to be divided into three approximately equal portions for submission to the laboratory: one for immediate testing, the second for confirmation of testing, and the third for retention in case of dispute. It is important to ensure that the sample is large enough to enable, if required, a number of replicate tests to be carried out, and to ensure that, if there is a need for microbiological testing, a separate container for testing is provided.

6.8 A standard test request form should be completed for each sample submitted to the laboratory. In the case of a pharmaceutical manufacturer's laboratory, the requirements may be given in the master production instructions.

6.9 The test request form should contain the following information:

- the name of the person or institution that provided the sample and the date of receipt;
- the source of the material;
- a full description of the sample, including stated composition, international nonproprietary name and brand names (if available and whenever relevant);

- the package and container;
- dosage form and concentration or strength, the manufacturer's name, and the batch or lot number (if available);
- the size of the sample;
- the reason for requesting the analysis;
- the date of sampling;
- the size of the consignment from which it was taken (if appropriate);
- the expiry date or retest date, if known;
- reference documents and the specifications to be used for testing;
- a record of any further comments (for example, discrepancies found or associated hazard);
- the required storage conditions.

6.10 The laboratory should review the test request to ensure that:

- the sample amount is sufficient for the tests requested;
- the laboratory has the required capability and resources to perform the appropriate analytical tests, as previously defined;
- the appropriate tests or methods available are capable of meeting customers' requirements.

6.11 Any issue should be resolved with the originator of the request for analysis before testing starts, and a record of the review should be retained. If the laboratory is responsible for deciding which samples are to be tested, the test request form should be adapted accordingly.

6.12 Each sample and accompanying documentation (for example, the test request) should be assigned a unique registration number. Separate numbers should be assigned to requests referring to two or more medicines, different dosage forms, different batches of the same medicine, or different sources of the same batch.

6.13 A label bearing the unique registration number should be affixed to each container of the sample. Care should be taken to avoid masking any other markings or inscriptions.

6.14 A register should be kept in which the following information is recorded:

- the registration number of the sample;
- the date of receipt;
- the specific unit or units to which the sample is to be forwarded for analysis.

6.15 The sample received should be visually inspected by laboratory staff to ensure that the labelling conforms with the information contained in the test request. The findings should be recorded, dated and signed. If discrepancies are found, or if the sample is obviously damaged, this should be recorded without delay on the test request form. Any queries should be immediately referred back to the provider of the sample.

6.16 The sample prior to testing, the retained sample and any portions of the sample remaining after the performance of all the required tests should be retained and stored appropriately.

6.17 The specific unit to which the sample is sent for testing is determined by the laboratory director (or designated person).

6.18 A request for analysis may be accepted verbally only in emergencies. All details should immediately be placed on record pending the receipt of written confirmation.

6.19 Unless a computerized system is used, copies or duplicates of all documentation should accompany each numbered sample when sent to the specific unit in order to verify the identification, origin and purpose of the sample for receipt and testing activities, as well as any relevant additional information.

6.20 Testing should be performed as described in subsection 6.5.

6.3 Selection, validation and verification of analytical procedures

6.21 The analytical procedures to be used for testing – either compliance testing or investigative testing – should be selected by the laboratory prior to the start of the analysis.

6.22 All analytical procedures employed for testing should be suitable for the intended use. When a non-pharmacopeial substance or product is to be analysed, it is preferable to apply the approved methods of the manufacturer; otherwise, validation of the method to be employed should be undertaken (*6*), which also serves to establish acceptance criteria for the system suitability tests that are subsequently employed for the verification of the analytical procedure before analysis.

6.23 For investigative testing, well documented screening procedures should be in place, as well as confirmatory analytical procedures to verify the identity of the substance or the ingredients. If an estimation of the content of an identified ingredient is required, then an appropriate quantitative analytical procedure should be applied. The value obtained should be reported with

an indication of the uncertainty of measurement, if required, especially in the case of borderline test results.

6.24 Validation should be performed according to an approved validation protocol, which includes analytical performance characteristics to be verified for various types of analytical procedures. Typical characteristics that should be considered are listed in Table A4.1 (in the development phase of an analytical procedure, robustness, such as the ability of the procedure to provide results of acceptable accuracy and precision under a variety of conditions, should also be considered). The results are to be documented in the validation report. Some large-scale pharmaceutical manufacturers control the production of products by applying real-time release testing on the production site, using process analytical technology. Such technology must be validated to ensure that the product meets the specification throughout the production cycle and has been approved by the relevant licensing authority.

Table A4.1
Characteristics to be considered during validation of analytical procedures

Type of analytical procedure	Identification	Testing for impurities		Assay
Characteristics		Quantitative tests	Limit tests	dissolution (measurement only) content/potency
Accuracy	–	+	–	+
Precision				+
Repeatability	–	+	–	+
Intermediate	–	+[a]	–	+
Precision				+
Specificity	+	+	+	+
Detection limit	–	–[b]	+	–
Quantitation limit	–	+	–	–
Linearity	–	+	–	+
Range	–	+	–	+

– Characteristic is normally not evaluated; + characteristic should normally be evaluated.

[a] In cases where a reproducibility study has been performed, intermediate precision is not needed.

[b] May be needed in some cases.

6.25 Pharmacopoeial procedures and those approved by the licensing authority can be considered as validated for the use described in the monograph. If validation is not required, method verification should be performed according to an approved protocol or procedure to demonstrate that the laboratory can successfully execute the method and that the pharmacopoeial procedure used is suitable for the sample being tested. The laboratory should, in particular, confirm that:

- for a finished pharmaceutical product, no interferences arise from the excipients present;
- for an active pharmaceutical ingredient (API), impurities coming from the route of synthesis are adequately differentiated;
- the system suitability requirements are fulfilled;
- the reporting threshold for related substances is met;
- the accuracy and the precision of the procedure are within predefined limits.

6.26 If the pharmacopoeial method is adapted for a new purpose other than the purpose described in the pharmacopoeia, it should be validated for such a use. Similarly, the sample preparation process must be critically assessed for the need for validation.

6.27 System suitability tests should be performed prior to and throughout the analysis of samples to ensure that the complete analytical system (including instrument, reagents, columns and analysts) is continuously suitable for the intended application.

6.28 Verification is not required for basic pharmacopoeial methods, such as colour of solution, pH determination and wet chemical methods. However, requirements given in the respective general chapters must be fulfilled at all times to ensure suitability for the intended use.

6.29 If method verification is required, but the results obtained do not comply with the analytical acceptance criteria, then they should be considered as nonconforming work (see subsection 6.11).

6.30 A major change to the analytical procedure, or in the composition of the product tested or in the synthesis of the API, should require revalidation (or reverification) of the compendial procedure or the analytical procedure approved by the licensing authority.

6.31 The performance of analytical procedures should be monitored throughout their life cycle.

6.32 Further guidance on the validation of analytical procedures is available in *WHO good manufacturing practices: guidelines on validation* (*6*).

6.4 Technical records

6.33 The analytical worksheet, or any suitable alternative document, is an internal document to be used by the analyst for recording information about the sample, the test procedure, reagents, standards, materials, calculations and the results of testing. It includes all raw data obtained in the analysis. An electronic system, such as LIMS, can also be used.

6.34 The analytical worksheet contains documentary evidence either to confirm that the sample being examined is in accordance with the requirements or to support an out-of-specification result.

6.35 A unique analytical worksheet should be used for each numbered sample or group of samples.

6.36 Completed analytical worksheets from different units relating to the same sample should be combined.

6.37 The analytical worksheet should provide the following information:

- registration number of the sample;
- page numbering, including the total number of pages (including annexes);
- date of the test request;
- dates on which the analysis was started and completed;
- name and signature of the analyst;
- a description of the sample received;
- references to the specifications and a full description of test methods by which the sample was tested, including the limits, if applicable; as an alternative, a traceable reference to the test method is acceptable;
- identification of the test equipment used;
- reference substances used (including the provider, lot number, potency or content);
- results of the system suitability test, if applicable, as well as any analytical acceptance criteria;
- identification of reagents, solvents and columns (if applicable) employed;
- results obtained, including those obtained from another internal analytical section or external laboratory, if applicable;

- interpretation of the results and the final conclusions (whether or not the sample was found to comply with the specifications), approved and signed by designated qualified personnel;
- further comments, for example, any deviation from a prescribed procedure, which should be approved and reported or treated as nonconforming work (see subsection 6.11), or whether the sample had been forwarded to another unit or contract laboratory for a specific analysis, and the dates on which it was transferred and the result was received.

6.38 All values obtained from each test, including blank results, should immediately be entered on the analytical worksheet, and all graphical data, whether obtained from recording instruments or plotted by hand, should be attached or be traceable to an electronic record file or document.

6.39 The completed analytical worksheet should be signed by the responsible analyst and reviewed and approved by designated qualified personnel (either in paper format or electronically). Calculations and data transfers should be checked in an appropriate and systematic manner or controlled by a validated electronic system.

6.40 Any changes made to original records, either in paper or electronic format, should be traceable to what was changed, who was responsible, when it was performed, and why. The deletion of data is not acceptable.

6.41 When a mistake is made in an analytical worksheet or when data or text need to be amended, the correction must be traceable.

6.42 The analytical worksheet and any attachments, including calculations and recordings of instrumental analyses, should be archived together with the specification (*4*).

6.43 Detailed recommendations are provided in the WHO *Guideline on data integrity* (*4*) and should be implemented.

6.5 Testing

6.44 Testing of production samples from pharmaceutical manufacturers may be conducted entirely in the laboratory or, for some with high output, as a combination of in-process controls (as for real-time release testing), using process analytical technology, and laboratory testing. Samples for laboratory testing are taken and analysed throughout the production process and tested as soon as possible. Samples received by an NQCL are stored appropriately before being included in the laboratory workplan.

6.45 Pharmaceutical manufacturers apply testing methods that have been approved by the medicine licensing authority, whereas NQCLs apply, whenever available, the monograph of the appropriate pharmacopoeia when testing for compliance with the specification. Otherwise, the approved testing methods of the manufacturer are applied.

6.46 The sample should be stored appropriately in a dedicated sample storage facility within a controlled environment until testing can be performed according to the workplan of the laboratory.

6.47 When a test method included in the specification is not within the scope of the laboratory, the sample may be outsourced to a contract laboratory having the test method within its scope (see subsection 4.2). The responsible analyst prepares the request and arranges to transfer the required number of units (bottles, vials or tablets). Each of these units should bear the correct registration number. When the analytical test report contains the results of the tests performed by the contract laboratory, these results should be identified as such in the final report.

6.48 Detailed guidance on pharmacopoeial requirements is usually given in the general notices and specific monographs of the pharmacopoeia. Test procedures should be described in detail and should provide sufficient information to allow trained analysts to perform the analysis in a reliable and reproducible manner. System suitability criteria defined in the method should be fulfilled. The implementation of any deviation from the test procedure should be approved and documented and, where applicable, addressed as nonconforming work (see subsection 6.11).

6.49 Compliance with internal quality control criteria should be ensured (see subsection 6.11).

6.50 Detailed recommendations on chromatographic testing and processing are provided in the WHO guidance on *Good chromatography practices* (*22*) and should be followed.

6.6 Evaluation of test results

6.51 Quantitative test results, particularly those obtained in the manufacture of a finished dosage form of a pharmaceutical product, should be recorded in such a way that trends are detectable and, where practical, should be reviewed and evaluated statistically after completion of the tests. The evaluation should take into consideration established action and rejection limits to decide if the product meets the acceptance requirement.

6.52 For compliance testing, the product should meet all the acceptance requirements of the analytical tests included in the approved specification. Test results are compared with the specification limits to ascertain if the sample meets the requirements, and a conclusion is prepared as to the conformance of the test result with the specification.

6.53 Any test result should be traceable to a suitable primary reference substance, either of a pharmacopoeia or of a manufacturer or, if appropriate, to a certified reference material.

6.54 Atypical results should be investigated.

6.55 Neither pharmacopoeias nor NMRAs require the assay value found to be expressed with its associated uncertainty, as the upper and lower limits set already take into account the uncertainty of the measurement and, hence, no further tolerances are to be applied to the limits specified. However, for investigative testing in an unknown sample, it may also be necessary to report the content with its associated uncertainty.

6.56 Test results should be reviewed and approved or rejected by designated qualified personnel according to the competency master list or matrix (see subsection 5.1).

6.7 Measurement uncertainty

6.57 The uncertainty of measurement results is an essential component of the overall assessment and interpretation of analytical data. Understanding and appropriately addressing the measurement uncertainty is fundamental to ensuring the accuracy, reliability and reproducibility of the analytical results.

6.58 The requirements for measurement uncertainty apply to all quantitative tests performed by NQCLs.

6.59 When compliance testing is conducted using pharmacopoeial analytical procedures and analytical procedures described in the marketing authorization documentation, the requirements for evaluation of measurement uncertainty are considered to be met if all critical sources of uncertainty are controlled. In such cases, there is no obligation to report the measurement uncertainty. The decision on whether to estimate and take account of the measurement uncertainty in the statement of conformity with a specification limit rests with the laboratory. The decision is made on a case-by-case basis, and should be documented in advance.

6.60 When compliance testing is performed by internally developed analytical procedures that have undergone appropriate validation for their intended use, the specification limits, which must account for estimated measurement uncertainty, must be such that an unquestionable decision on compliance can be reached.

6.61 A thorough assessment of the measurement uncertainty may be required, for instance, when:

- employing ad hoc methods such as screening, analysis of unknown products or trace analysis;
- using methods with limited uncertainty information;
- confirming out-of-specification results, particularly if the test cannot be repeated;
- establishing limits for performance tests of measurement apparatus and critical parameters of methods.

6.62 If an analytical procedure is frequently employed in a laboratory and its measurement uncertainty has already been established and verified, there is no requirement to evaluate the measurement uncertainty for each individual result. However, the laboratory must be able to demonstrate that the critical factors that affect the measurement uncertainty have been properly managed and controlled. By ensuring that these influential factors are under control, the laboratory can have confidence in the previously established measurement uncertainty and its applicability to subsequent results obtained using the same analytical procedure.

6.63 Applying the concept of measurement uncertainty to compliance testing enables managing the risk of making the wrong acceptance or rejection decisions, provided the following elements of the concept of uncertainty are implemented:

- the decision rule on compliance of pharmaceutical products with specifications is defined;
- the laboratory evaluates the uncertainty of the analysis results.

6.64 The laboratory has the discretion to conduct an assessment of the measurement uncertainty as an internal quality control measure, when deemed appropriate.

6.65 The pharmacopoeial decision rule should be applied to all specification limits stated in the pharmacopoeial monographs and marketing authorization documentation.

6.66 The pharmacopoeial decision rule is based on the following principles:

- analytical variation typical of normal (routine) analytical practice is taken into account in the specified limits;
- the decision on compliance is made only on the basis of whether the result of the analysis meets the specified limits. No further tolerances (for example, obtained by evaluation of measurement uncertainty or setting the acceptance and rejection zones) should be applied to the specified limits.

6.67 The pharmacopoeial decision rule is simple: accept or reject, with a guard bandwidth equal to the analytical variation typical of normal analytical practice. The analyte concentration must be within a range narrower than the specification width (by analytical variation accounted for in the specification), ensuring a low probability of rejecting a product (low manufacturer risk). The pharmacopoeial decision rule works correctly only if the actual value of the uncertainty (in practice – estimated uncertainty) is fixed – that is, does not exceed the critical value, which is the target uncertainty set for the test. A decision on compliance is considered conclusive if the estimated uncertainty is less than or equal to the target uncertainty of a reportable result (pass). If the estimated uncertainty is greater than the target uncertainty, then a decision is considered inconclusive, and an investigation is required to establish the reasons for the unacceptably high uncertainty. The laboratory should ensure that the estimated uncertainty does not exceed the target uncertainty when performing the analysis.

6.68 For an NQCL to correctly reproduce an analytical procedure described in the pharmacopoeial monograph or marketing authorization documentation, the actual analytical variability should not exceed the variability characteristic of normal analytical practice.

6.69 Target uncertainty and the maximum permissible uncertainty for standard analytical operations (for normal analytical practice) are provided in Appendix 2.

6.70 The application of the concept of standard analytical practice for the evaluation of measurement uncertainty is provided in Appendix 3.

6.8 Validity of test results

6.71 The laboratory should have a procedure for ensuring the validity of results by reviewing the following activities, as appropriate:

- reference substances or reference materials;
- verification of measuring and testing equipment;
- appropriate quality control checks;
- data analysis that does not require additional experiments (use of control charts, trend analysis and different kinds of correlation of results of the sample being tested);
- replicate tests or calibrations using the same or different methods;
- retesting of retained samples;
- review of all raw data and reported results;
- review of measurement uncertainty results, if required.

6.72 Apart from the QCL of a pharmaceutical manufacturer, the performance of the laboratory should be assessed regularly by participation in:

- proficiency testing schemes, organized both internally and externally;
- interlaboratory comparisons, such as collaborative studies.

6.73 Data from monitoring activities should be subject to management review, at least annually, to ensure that necessary actions to control and, if applicable, to improve the laboratory's activities are effective.

6.74 If the results of the analysis of data from monitoring activities are found to be outside predefined criteria, appropriate action should be taken to prevent the reporting of incorrect results.

6.9 Out-of-specification results

6.75 An out-of-specification result is a result that does not comply with the acceptance criteria of any test in the specification, found in drug master files, company documentation, approved marketing submissions, or official compendia (*6*, *23*).

6.76 When a suspected out-of-specification result has been identified, a review of the different procedures applied during the testing process should be undertaken by the supervisor with the analyst or technician by using a checklist and before any retesting is performed. The investigation should ensure that:

- if stable, original sample preparations are not discarded until the investigation is complete;
- the appropriate procedures were applied and followed correctly, including requirements for validation and verification, and internal quality control tools;

- examination of the raw data is undertaken to identify possible discrepancies;
- all calculations are checked;
- the equipment used was qualified and calibrated, and system suitability tests were performed and were acceptable;
- the appropriate reagents, solvents and reference substances were used;
- the correct glassware was used.

6.77 The identification of an error that caused an aberrant result invalidates the result, and a retest of the sample will be necessary, which should be conducted by the same technician or analyst.

6.78 Suspected out-of-specification results can be rejected only if they are clearly due to an identified error. When an investigation is inconclusive, a confirmatory determination is to be performed by another trained analyst. A similar result would indicate a confirmed out-of-specification result. If comparable results are not obtained by the second analyst, the lack of consistency should be investigated. Further confirmation using another validated method, if available, may be advised and, if performed, should be fully documented.

6.79 If available, hypothesis testing should be considered in order to better define the root cause.

6.80 A standard operating procedure should be in place for the conduct of an investigation into a suspected out-of-specification test result. All investigations and their conclusions should be recorded. In the event of an error, root cause analysis should be performed, and any corrective actions should be documented, implemented, and recognized as risks and as opportunities for improvement.

6.81 All test data should be recorded and retained. If no error was identified, all test results should be reported. The standard operating procedure defined above should also consider the general rules to report this type of result.

6.82 All conclusions should be recorded (either on the analytical worksheet or in another support) by the analyst and reviewed and approved by the supervisor.

6.83 A critical review of the nature, number and root cause of out-of-specification results obtained within a given period, either confirmed or not confirmed, should be conducted during the management review (see subsection 3.10).

6.10 Reporting of results

6.84 The analytical test report (hard copies or by electronic means) is a compilation, by the study supervisor, of the analytical test results obtained for approval by the quality manager, laboratory director or designated person. Subsequently, the dossier containing all the information pertaining to the sample, including the origin, chain of custody and analytical data, is archived.

6.85 Any amendments or changes to the original analytical test report will require the issue of a new corrected document, where:

- any change of information should be clearly identified and dated;
- the reason for the change should be included in the new corrected document;
- the new report should be uniquely identified and contain a reference to the original document it will replace.

6.86 When using pharmacopoeial methods and manufacturer's approved methods for compliance testing, it is not required that the expanded uncertainty be reported.

6.87 The laboratory decides when to report the uncertainty of a result and how conformance to specifications was evaluated (see recommendations in subsection 6.7).

6.88 The analytical test report should provide the following information:

- a title (for example, "test report", "analytical test report", or another suitable title);
- the laboratory registration number of the sample;
- the laboratory test report number;
- the name and address of the laboratory testing the sample;
- the name and address of the originator of the request for analysis;
- the name, description and batch number of the sample, where appropriate;
- an introduction giving the background to and the purpose of the investigation, if applicable;
- a reference to the specifications used for testing the sample or a detailed description of the procedures employed (sample for investigative testing), including the limits;

- the results of all the tests performed or the numerical results, with the standard deviation of all the tests performed (if applicable);
- when applicable, the expanded measurement uncertainty of the reportable result with reference to its assessment and an explanation of how it was used in making the compliance decision;
- a discussion of the results obtained, where appropriate;
- a conclusion as to whether or not the samples were found to be within the limits of the specifications used, or, for a sample for investigative testing, the substances or ingredients identified;
- a statement to the effect that the results relate only to the items tested, calibrated or sampled;
- a clear identification when results are from external providers;
- the date on which the tests were completed;
- the signature of the laboratory director or other authorized person reviewing and authorizing the report;
- the name and address of the original manufacturer and, if applicable, those of the repacker or trader;
- whether or not the samples comply with the requirements;
- if applicable, opinions and interpretations, adequately supported by evidence and issued by authorized personnel;
- the date on which the sample was received;
- the expiry date or retest date, if applicable;
- a statement indicating that the analytical test report, or any portion thereof, cannot be reproduced without the authorization of the laboratory.

6.89 A certificate of analysis is prepared for each batch of a substance or product. The certificate of analysis contains the same information as the analytical test report.

6.90 For NQCLs, the issuance of a certificate of analysis is not obligatory as long as the analytical test report is adequately issued and remains at the laboratory as an internal document.

6.91 The laboratory is responsible for all the information provided in the report, except when the customer provides the information.

- Data provided by the customer should be clearly identified.
- In addition, a disclaimer should be included in the report when the information is supplied by the customer, which could compromise the validity of the results.

- Where the laboratory has not been responsible for the sampling stage (for example, the sample has been provided by the customer), the report should state that the results apply to the sample as received.

6.11 Nonconforming work

6.92 The term "nonconforming work" refers to any instance where analytical activities deviate from established procedures, internal requirements, or the analytical specifications that have been agreed upon with the customer. Such deviations encompass a range of issues, including equipment, environment conditions, internal quality control criteria and system suitability criteria. All instances of nonconforming work must be duly recorded, addressed and managed. Essentially, nonconforming work represents a technical or analytical deviation from the specified limits.

6.93 Managing nonconforming work follows the same rationale as described in subsection 3.7 and can be treated under the same system, ensuring that:

- actions (including the halting or repeating of work and withholding of reports, as necessary) are based upon the risk levels established for the affected activity;
- an evaluation is made of the significance of the nonconforming work, including an analysis of the impact on previous results;
- a decision is taken on the acceptability of the nonconforming work;
- where necessary, the customer is notified, and work is recalled;
- the responsibility for authorizing the resumption of work is defined.

6.94 Records of the nonconforming work are retained, as well as all defined actions.

6.95 Corrective actions (see subsection 3.7) should be implemented if the evaluation indicates that there is a possibility that the nonconforming work could recur or there is a doubt about the conformity with the QMS.

6.96 Analysis of the data obtained from nonconforming work should be performed, addressing specifically those issues for which a trend is observed throughout time (for example a systematic nonconforming work obtained for the same testing method, which may indicate a possible cause when trend analysis is performed). The results from this analysis and possible impacts on the identified risks and opportunities should be reviewed periodically (see subsection 3.10), and an assessment should be made of the impact of the nonconforming work on the reported results.

6.12 Retained samples

6.97 Samples should be retained (see subsection 6.2) as required by legislation or by the originator of the request for analysis (*24*).

6.98 The minimum amount of sample to be delivered for testing to the laboratory should be communicated to the authority, the manufacturer or the person responsible for sampling. There should be a sufficient amount of retained sample to allow at least two reanalyses.

6.99 The retained sample should be contained in its original packaging.

6.100 Sample disposal criteria should be established, according to national legislation or applicable international recommendations, or, if required, by the originator of the request for analysis.

7. Safety rules

7.1 Environmental health and safety policies should be followed to protect the staff, the public and the environment. A documented laboratory safety policy, which should include general and specific safety instructions reflecting identified risk, should be available to and applied by each member of staff. A staff member should be given the responsibility of overseeing the policy and ensuring compliance by all staff.

7.2 A waste management system conforming to local legislation should be in place to ensure the safe disposal of chemicals, solvents and other relevant materials.

7.3 General and specific safety procedures reflecting identified risk should be made available to each staff member. Seminars on safety-related issues should be held at predefined intervals, as specified in QMS documentation.

7.4 General rules for safe working should be included in standard operating procedures in accordance with national regulations and normally include the following requirements.

- Safety data sheets should be available to staff before testing is carried out.
- Smoking, eating and drinking in the laboratory should be prohibited.
- Staff should be familiar with the use of firefighting equipment, including fire extinguishers, fire blankets and gas masks.

- Staff should wear laboratory coats or other suitable protective clothing, as required, including eye protection.
- Special care should be taken, as appropriate, in handling highly potent, infectious or volatile substances.
- Highly toxic or genotoxic samples should be handled in a specially designed facility to avoid the risk of contamination.
- All containers of chemicals should be appropriately labelled and include prominent warnings (for example, "poison", "flammable", "radioactive"), whenever appropriate.
- Adequate insulation and spark-proofing should be provided for electrical wiring and equipment, including refrigerators.
- Rules on the safe handling of cylinders of compressed gases should be observed and staff should be familiar with the relevant colour identification codes.
- Staff should not work alone in the laboratory.
- First-aid materials should be provided, and staff instructed in first-aid techniques, emergency care and the use of antidotes.

7.5 Protective clothing should be available, including eye protection, masks and gloves, and should be fit for purpose. Safety showers (eyes and full body) should be installed at a suitable location and should be fit for purpose. Rubber suction bulbs should be used on manual pipettes and siphons. Staff should be instructed in the safe handling of glassware, corrosive reagents and solvents, including the use of safety containers or baskets to avoid spillage from containers. Warnings, precautions and instructions should be incorporated, when appropriate, in standard operating procedures for work with violent, uncontrollable or dangerous reactions when handling specific reagents (for example, mixing water and acids or acetone–chloroform and ammonia), flammable products, and oxidizing or radioactive agents. Peroxide-free solvents should be used. Staff should be aware of methods for the safe disposal of unwanted corrosive or dangerous products by neutralization or deactivation and of the need for safe and complete disposal of mercury and its salts.

7.6 A standard operating procedure for the storage and handling of controlled substances complying with applicable national legislation should be available and enforced.

7.7 Poisonous or hazardous products should be identified, labelled appropriately and kept separately from other products.

7.8 Unnecessary contact with reagents, especially solvents and their vapours, should be avoided. The use of known carcinogens and mutagens as reagents should be limited or totally excluded.

7.9 Replacement of toxic solvents and reagents with less toxic materials or reduction of their use should always be the aim, particularly when new techniques are developed and validated.

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Appendix 1

Equipment for a first-stage and medium-sized pharmaceutical quality control laboratory

A list of equipment considered by the Expert Committee to be adequate, either for a first-stage or medium-sized pharmaceutical quality control laboratory, is given in Table 1.

This list does not represent any requirements that should be fulfilled to comply with these guidelines. National medicines regulatory authorities (NMRAs) or laboratories wishing to perform pharmaceutical analyses may consider the following list in the establishment or upgrading of their testing facilities. For budgetary reasons it is necessary, besides the cost of equipment, to take into consideration the cost of reference materials, reagents, solvents, glassware, other laboratory commodities and personnel. Experience has shown that, for sustainability, a laboratory should allow a margin of 10–15% per year of the purchasing expenditure on equipment to cover the cost of maintenance.

Table 1
Equipment for a first-stage and medium-sized pharmaceutical quality control laboratory

First-stage laboratory	
Equipment and major instruments	**Quantity**
Top-loading balance	1
Analytical balance (5 digits)	1 or 2
Melting-point apparatus	1
pH meter (with assorted electrodes)	1
Microscope	1
Polarimeter	1
High-performance liquid chromatograph with ultraviolet detector	2
Ultraviolet/visible spectrophotometer	1
Infrared spectrophotometer with pellet press	1
Karl Fischer titrator (semi-micro determination of water)	1

First-stage laboratory *(continued)*	
Equipment and major instruments	**Quantity**
Agate mortar with pestle	1
Equipment for thin-layer chromatography	1
Temperature and humidity probe	1
Thin-layer chromatography spotter	1
Developing chambers	6 + 1[a]
Atomizers	6
Ultraviolet viewing lamp	1
Disintegration test equipment (1 basket for 6 tablets)	1
Dissolution apparatus	1
Soxhlet extraction apparatus (60 mL)	3 + 1[a]
Micrometer calipers	1
Pycnometers	2
Burettes/pipettes (10 mL and 25 mL/1, 2, 5, 10, 20, 25, 50 mL)	3 of each
Desiccator	1 + 1[a]
Centrifuge (table-top model, 4-place swing rotor)	1
Water bath (20 litres)	1
Hot plates with magnetic stirrers	3
Vacuum pump (rotary, oil)	1
Drying oven (60 litres)	1
Vacuum oven (17 litres)	1
Muffle furnace	1
Refrigerator (explosion-proof)	1
Water distilling apparatus (8 litres/hour)	1
Water deionizer (10 litres/hour)	1
Dehumidifier (where needed)	1
Fume hood	1

First-stage laboratory *(continued)*	
Optional items	**Quantity**
Analytical microbalance	1
Flame photometer (including air compressor)	1
Refractometer	1
Viscometer	1
Vortex mixer	1
Shaker (wrist-action)	1
Pipette rinser	1
Constant temperature water bath	1
Ultrasonic cleaner (5 litres)	1
Medium-sized laboratory	
Equipment and major instruments	
Top-loading balance	1 or 2
Analytical balance (5 digits)	2
Analytical microbalance	1
Microscope	1 or 2
Equipment for thin-layer chromatography	1
Thin-layer chromatography multispotter	1
Developing chambers	6
Atomizers	6
Ultraviolet viewing lamp	1
Temperature and humidity probe	2
Potentiometric titrimeter	1
Micro Kjeldahl equipment (including fume flasks)	1
Soxhlet extraction apparatus (60 mL)	3
Densimeter, combined with viscometer	1
Burettes/pipettes (10 mL and 25 mL/1, 2, 5, 10, 20, 25, 50 mL)	6 of each
Micrometer calipers	1

Medium-sized laboratory *(continued)*	
Equipment and major instruments	**Quantity**
Heating mantles for flasks (assorted sizes: 50, 200 and 2000 mL)	6
Sieves (assorted sizes)	1 set
Centrifuge (floor model)	1
Shaker (wrist-action)	1
Vortex mixers	2
Water bath (electrical, 20 litres)	2 or 3
Hot plates with magnetic stirrers	3 or 4
Vacuum pump (rotary, oil)	2
Vacuum rotary evaporator	1
Drying oven (60 litres)	2 or 3
Muffle furnace (23 litres)	1
Vacuum oven (17 litres)	1
Desiccators	2
Refrigerator (explosion-proof)	2
Freezer	1
Ultrasonic cleaners (5 litres)	2
Laboratory glassware washing machine	1
Water distilling apparatus (8 litres/hour)	1
Water deionizing equipment (10 litres/hour)	1
Fume hoods	2
Melting-point apparatus	1
Polarimeter	1
pH meters (with assorted electrodes)	2
High-performance liquid chromatograph with variable wavelength:	
Ultraviolet/visible detector	2 or 3
Ultraviolet/visible spectrophotometer, double-beam	1
Diode array	1 or 2

Medium-sized laboratory *(continued)*	
Equipment and major instruments	**Quantity**
Infrared spectrophotometer (MIR, NIR) with pellet press	1
Agate mortar with pestle	1
Gas chromatograph (flame ionization, direct and static head space injection)	1
Karl Fischer titrators (1 semi-micro and 1 coulometric for microdetermination of water)	2
Disintegration test equipment (1 basket for 6 tablets)	1
Dissolution test equipment (for 6 tablets/capsules)	1
Oxygen flask combustion apparatus	1
Optional items	
Refractometer	1
Atomic absorption spectrophotometer (flame, furnace)	1
Spectrofluorometer	1
High-performance liquid chromatograph detectors:	1
Fluorescence	1
Mass spectrometric (MS)	1
Evaporative light scattering (ELSD)	1
Charged aerosol (CAD)	1
Refractive index	1
Gas chromatograph detectors:	1
Electron capture detector (ECD)	1
Nitrogen/phosphorous (NPD)	1
Mass spectrometric (MS)	1
Capillary electrophoresis equipment	1
Thin-layer chromatography scanner	1
Hardness tester	1
Friability tester	1

Medium-sized laboratory *(continued)*	
Optional items	**Quantity**
Ice machine	1
Solvent recovery apparatus	1
Equipment for microbiology unit	
pH meter	1
Ultraviolet/visible spectrophotometer, single-beam	1
Microscopes (for bacteriology)	1
Membrane filter assembly for sterility tests	2
Colony counter with magnifier	1
Laminar air flow unit	1
Hot-air sterilizer	1
Incubators, 60 litres	1
Anaerobic jar	2 or 3
Zone reader	1
Centrifuge	1
Water bath (thermostatically controlled)	1
Autoclaves (100 litres, top-loading)	2
Refrigerators (340 litres)	2
Deep freeze	2
Laboratory glassware washing machine	1
Equipment for pharmacognosy/phytochemistry unit	
Grinder/mill (for preparation of sample of herbal materials)	1
Top-loading balance	1
Sieves	1
Microscope[b]	1 set
Soxhlet extraction apparatus	1
Water bath	2 or 3
Heating mantles for flasks	1

Equipment for pharmacognosy/phytochemistry unit *(continued)*	
	Quantity
Hot plates with magnetic stirrers	1 or 2
Equipment for thin-layer chromatography	2
Developing chambers	1 or 2
Desiccators	3 or 4
Rotary vacuum apparatus	2
Distillation equipment	1
Conical percolators	1
Apparatus for determination of water content by azeotropic method[b]	2 or 3
Apparatus for determination of volatile oils[b]	1
Apparatus for determination of arsenic limit test[c]	1

[a] Needed in the case that herbal medicines are also tested.

[b] Quality control methods for herbal materials. Geneva: World Health Organization; 2011 (https://apps.who.int/iris/bitstream/handle/10665/44479/9789241500739_eng.pdf?sequence=1, accessed 19 January 2024).

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Appendix 2

Recommendations for the target uncertainty and the maximum permissible uncertainty for normal analytical practice

To effectively apply the concept of uncertainty to compliance testing in the pharmaceutical sector, the following key recommendations should be formulated (see subsection 6.7):

- recommendations for the target uncertainty for pharmacopoeial tests;
- recommendations for the maximum permissible uncertainty for standard analytical operations (recommendations for normal analytical practice).

Recommendations for the target uncertainty for pharmacopoeial tests

To assess the risk of making an incorrect decision on compliance, the estimated uncertainty (U^{est}) should be compared with the target uncertainty (U^{tg}).

For the assay of an API or excipient, the minimum value of measurement uncertainty usually comprises (*1–3*):

- 1.0% for volumetric titration of the conjugate acids, non-aqueous and acid–base titrations;
- 1.5% for redox and argentometric titrations;
- 2.0% for complexometric titrations;
- 2.0% and 3.0% for ultraviolet spectrophotometry assays, using the reference substance and specific absorbance, respectively;
- 2.0% for liquid chromatographic assays.

U^{tg} is an expanded uncertainty, expressed as a 90% two-sided confidence interval, which is equivalent to a 95% one-sided confidence interval.

The minimum value of U^{tg} corresponds to the minimum width of content limits for assay. Therefore, the minimum value of U^{tg} = 2.0% means that the metrologically correct content limits should not be narrower than 98–102%.

For finished pharmaceutical products, the following requirements for U^{tg} can usually be applied (*4*).

- For assay, the target uncertainty should be insignificant compared to the half-width of the symmetrical two-sided content limits, U^{tg} = (UCL – LCL)/2 × 0.32, where UCL and LCL are upper and lower content limits, respectively.
- For assay with a one-sided content limit (known as "not less than …"), U^{tg} = 6.4%. This requirement can also be applied to APIs and excipients with a one-sided content limit.
- For tests for dissolution and uniformity of dosage units, U^{tg} = 3.0%.
- For related impurities and residual solvents, U^{tg} = 16.0% (the found quantity of impurity is used only for comparison with the specification limit). This requirement can also be applied to APIs or excipients.

Recommendations for the maximum permissible uncertainty for normal analytical practice

The approach of normal (routine) analytical practice (NAP) establishes the maximum permissible level of uncertainty from standard analytical operations (U_i^{tg}) U^{tg} and reflects the minimum pharmacopoeial requirements that should be met by all laboratories performing compliance testing (see subsection 6.7). Adherence to NAP is assumed when performing analytical procedures outlined in monographs (*5*–*7*) and marketing authorization documentation (*8*).

Currently, most of the analytical procedures described in pharmacopoeias and marketing authorization documentation have been validated without the use of the concept of uncertainty; hence, without considering that when the procedures are reproduced in another laboratory, the actual uncertainty of the analytical result (in practice, the estimated uncertainty, or U^{est}) can be as large as the maximum permissible value (NAP recommendations), which can be greater than that achieved during the analytical procedure development or validation. Therefore, some sources of variation, which may become significant when reproducing the analytical procedure in another laboratory, may not be accounted for, since they were insignificant in the developer's laboratory (and in the interlaboratory trials for pharmacopoeial analytical procedures).

Thus, the classic approach to quality assurance does not consider the "worst case", that is, when the laboratory meets the NAP recommendations minimally, which may result in approving metrologically incorrect analytical procedures for which reproducibility problems may occur with an unacceptably high risk.

To control the risk of obtaining an unacceptably large value of U^{est}, it is reasonable to carry out the bottom-up evaluation of measurement uncertainty during the development of a procedure based on the NAP recommendations (that

is, perform an uncertainty estimation for the "worst case"). If the uncertainty estimated for the worst case (U^{NAP}) exceeds U^{tg}, then there is a high risk that U^{est} will also exceed U^{tg} when reproducing the procedure, and the laboratory will not be able to make a conclusive decision on compliance. In such a case the analytical procedure needs optimization of measurements and sample preparation steps.

Here and below, measurement uncertainty is an expanded uncertainty, expressed as a 90% two-sided confidence interval, which is equivalent to a 95% one-sided confidence interval.

Typically, variability sources can be divided into measurement related (for example, random variability of an analytical signal) and associated with sample preparation operations (weighing, dilution).

The requirements for the maximum permissible uncertainty (target uncertainty) for standardized analytical operations (NAP recommendations – U_i^{tg}) may be specified directly in the analytical procedure (as a requirement for the suitability of the analytical system) or other regulations (for example, as a requirement for the qualification of analytical equipment in the pharmacopoeias).

The example of a variability source for which U_i^{tg} is harmonized between pharmacopoeias is the random variability of the analytical signal for assay by separation technique of an API (or excipient) where the value is 100% for a pure substance (*2*, *9*, *10*). This approach assumes that random variability from the analytical signal is the main component of uncertainty associated with measurements. Requirements for the maximum permitted relative standard deviation (%RSD_{max}) for the given assay upper content limits are set so that a 90% two-sided confidence interval (equal to a 95% one-sided interval), calculated for the uncertainty component of the analysis result related to the precision of measurements, does not exceed 0.5 of U^{tg}.

The recommendations for %RSD_{max} for assay by separation technique for finished pharmaceutical products with symmetrical assay content limits are shown in Table 1 (*11*). These requirements are set so that a 95% one-sided confidence interval calculated for the uncertainty component of the analysis result related to the precision of measurements does not exceed U^{tg}. It is recommended that U^{tg} for finished pharmaceutical preparations should comprise not more than 0.32 of the half-width of symmetrical content limits.

Table 1
Requirements for maximum permitted relative standard deviation (%RSD_{max}) of the analytical signal for assay by separation technique for finished pharmaceutical products with symmetrical assay content limits

	Number of individual injections *n*[a]						
	2	3	4	5	6	7	8
(UCL – LCL)/2[b]	%RSD_{max}						
5	0.25	0.67	0.96	1.19	1.38	1.54	1.69
7.5	0.38	1.01	1.44	1.78	2.06	2.31	2.53
10	0.51	1.34	1.92	2.37	2.75	3.08	3.38
15	0.76	2.01	2.88	3.56	4.13	4.62	5.07
20	1.01	2.68	3.85	4.75	5.50	6.16	6.76

[a] Assuming that the same number of repetitive injections is made for the test and reference solutions.

[b] UCL and LCL are upper and lower content limits, respectively, expressed in per cent in relation to the nominal content value.

For spectrophotometric assays the next recommendations can be used as NAP recommendations (*12*):

- for a series of measurements of the absorbance with cuvette withdrawal RSD ≤ 0.52%;
- not less than three measurements for the test and reference solutions.

NAP recommendations for individual operations with volumetric glassware ISO class A are shown in Tables 2–4 (*1*, *4*). It should be noted that these estimates of uncertainty exceed the maximum permissible deviation from the nominal volume under the requirements for ISO class A volumetric glassware, as the NAP recommendations additionally account for the random variability introduced by the analyst in routine analysis.

Table 2
Target uncertainties typical of NAP due to the use of volumetric flasks ISO class A of different volumes

Volumetric flask volume, mL	Target uncertainty, mL	Target uncertainty, %
10	0.05	0.50
20	0.057	0.28

Table 2 *continued*

Volumetric flask volume, mL	Target uncertainty, mL	Target uncertainty, %
25	0.0575	0.23
50	0.085	0.17
100	0.12	0.12
200	0.20	0.10
250	0.20	0.08
500	0.35	0.07
1000	0.50	0.05

Table 3

Target uncertainties typical of NAP due to the use of transfer pipettes ISO class A of various volumes

Transfer pipette volume, mL	Target uncertainty, mL	Target uncertainty, %
1.0	0.010	0.98
2.0	0.012	0.61
5.0	0.018	0.37
10.0	0.025	0.25
20.0	0.037	0.18
25.0	0.037	0.15
50.0	0.061	0.12

Table 4

Target uncertainties typical of NAP due to the use of graduated pipettes ISO class A of different volumes

Graduated pipette volume, mL	Target uncertainty, mL	Target uncertainty, %[a]
0.5	0.0061	1.23
1.0	0.0074	0.74
2.0	0.012	0.62
5.0	0.037	0.74

Table 4 *continued*

Graduated pipette volume, mL	Target uncertainty, mL	Target uncertainty, %[a]
10.0	0.062	0.62
25.0	0.123	0.49

[a] Indicated in relation to the total volume of the pipette.

For weighing operations, it is recommended to use U^{tg} = 0.2 mg as the NAP recommendation (*1*, *4*). This recommendation reflects typical minimum requirements for balances in NQCLs.

If the NQCL has a balance of a higher class, then to estimate uncertainty in line with NAP recommendations when reproducing the analytical procedure, it becomes essential to employ a criterion for the balance qualification (maximum permissible uncertainty).

For the initial reproduction of the analytical procedure in an NQCL, it is advisable to use the bottom-up approach for the uncertainty estimation as per the NAP recommendations. The text of the procedure and a priori knowledge of the analytical technique indicate the significant sources of variability.

Often the risk of obtaining an unacceptably large U^{est} can be mitigated by increasing the accuracy of the concentration of the test and reference solutions. This can be achieved by increasing the test portions or volumes of the volumetric glassware used, without changing the final concentration of the test and reference solutions. Such an adjustment of the approved analytical procedure is allowed by pharmacopoeial practice (*13*).

However, the actual uncertainty in a particular NQCL may be greater than the NAP recommendations. Therefore, it is necessary to confirm experimentally that actual uncertainties from variability sources regulated by NAP do not exceed the recommended value of U_i^{tg} during the real analysis. That is, the uncertainty estimation for the "worst case" (NAP recommendation) does not override the estimation of uncertainty in the laboratory, as described, for example, in (*8*).

An example of the uncertainty estimation based on NAP recommendations for chromatographic assays of an API is provided in Appendix 3.

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Appendix 3

Examples of the uncertainty estimation for compliance with normal analytical practice (the "worst case") for assay of pharmaceutical substances by chromatography

The pharmacopoeias state that the normal (routine) analytical practice (NAP) or (routine) analytical errors are considered in pharmacopoeial acceptance criteria (*1*–*3*). This means that the laboratory can reproduce a pharmacopoeial analytical procedure only if the actual uncertainty for the standard analytical operations (NAP operations) does not exceed that accounted for in the specifications. The same statement is correct regarding analytical procedures from marketing authorization because, here, the same decision rule is used (hence, the same approach to the construction of criteria) (*4*).

The recommendations for the permissible uncertainty associated with standard analytical operations can be found in the *European Pharmacopoeia* (*5*), Table 1, and the *State Pharmacopoeia of Ukraine* (*6*). The recommendations for maximum permissible uncertainty for standard analytical operations in a routine analysis (sample preparation – weighing and dilution using volumetric glassware ISO class A, and measurements) are given in Appendix 2.

The uncertainty estimation for the case of minimum compliance with NAP (the "worst case") is based on the text of the analytical procedure without the use of any experimental data. This allows the developer to optimize the text of the analytical procedure before its approval or the reproduction of an already approved procedure in the laboratory (to reduce the uncertainty of the preparation of solutions or measurements). This enables mitigation of the risk of obtaining an unacceptably large actual value of uncertainty, which could lead to inconclusive decisions on compliance during the reproduction of an analytical procedure.

It is important to highlight that when estimating uncertainty for NAP compliance (for the "worst case" scenario), the resulting uncertainty estimation applies universally to any laboratory required to meet pharmacopoeial requirements. Conversely, the general procedure for estimating uncertainty aims to provide a real estimation of uncertainty within a specific laboratory environment, which may vary for different laboratories performing the same analytical procedure. The uncertainty estimation for NAP compliance should not be considered a substitute for the generally accepted practice of individual uncertainty estimation in each laboratory to determine the actual uncertainty.

The uncertainty estimation for NAP compliance is based on the premise that:

- the significant sources of variation are usually identified in the text of the analytical procedure (primarily, they follow from the calculation formula). Such sources of variation are present in any laboratory and, therefore, need to be standardized and controlled;
- "unexpected" and non-standardized sources of variation (such as incomplete analyte extraction during sample preparation, or interference of excipients with measurements) are absent or insignificant. This should be ensured at the development and validation stages of the analytical procedure.

The purpose of uncertainty estimation for the case of NAP compliance is to calculate the expanded uncertainty for a reportable result (combined uncertainty) based on the maximum permissible uncertainties (according to the NAP) for standard analytical operations (given in Appendix 2). The rules for combined uncertainty estimation are determined by how the parameters that are sources of variation are included in the calculation formula for the reportable result (X). It is supposed that all sources of variability are independent, and there is no correlation between them.

Here and below, measurement uncertainty is an expanded uncertainty expressed as a 90% two-sided confidence interval, which is equivalent to a 95% one-sided confidence interval.

Sources of uncertainty for the assay can be grouped as follows: (group 1) measurement uncertainty (U_{Meas}); (group 2) sample preparation uncertainty (U_{SP}), which is subdivided into (group 2.1) weighing uncertainty ($U_{m,i}$) and (group 2.2) dilutions uncertainty ($U_{V,i}$); and (group 3) uncertainty of the value assigned to a reference substance (U_{RS}).

The typical formula for the assay is:

$$X = \frac{r}{r_0} \times \frac{m}{m_0} \times \frac{V_{01} \times V_{02} \times V_{03} \ldots V_{0n}}{V_1 \times V_2 \times V_3 \ldots V_n} \times \frac{P_{RS}\%}{100\%} \times K$$

1	2		3	4
	2.1	2.2		

Where:

r and r_0 are analytical signals (peak area, peak height, or their ratio) for the test solution and the reference solution;

m and m_0 are the test portions of the test sample and reference substance;

V is the nominal volume for volumetric flasks and pipettes used for making dilutions;

P_{RS} is the analyte content in the reference substance, expressed as a percentage;

K is the coefficient for converting the concentration into a reportable result (in most cases for assay of API, $K = 1$).

All sources of variation from the calculation formula, except for U_{MEAS}, are expressed as intervals (not as standard deviations). Therefore, for uncertainty estimation, it is reasonable to directly combine uncertainties from individual sources of variability as intervals without converting them to standard deviations and then back to intervals (*6*). This approach leads to the same uncertainty estimates as the classical approach (*4*).

For the assay by chromatographic methods, for a typical case, all sources of variability are reflected in the calculation formula as a product or quotient. Therefore, the combined uncertainty for X can be estimated as the square root of the sum of the squares of the partial components of the uncertainty (in this case, expressed as a percentage).

The typical sources of variability arising from measurements (group 1) and sample preparation (group 2) are standardized (Appendix 2); they are the primary focus for the uncertainty estimation for NAP compliance.

For the uncertainty estimation, it is acceptable to assume that for pharmacopoeial reference substances, U_{RS} is insignificant compared to the U^{tg} and may not be considered in the uncertainty estimation. The U_{RS} is insignificant for any pharmacopoeial applications if it does not exceed 0.5% (*7*).

1. An example of uncertainty estimation for NAP compliance for a chromatographic assay of API

For metrologically correct analytical procedures for a chromatographic assay of API, the upper content limit is not less than 102.0%; therefore, $U^{tg} = 2.0\%$ (Appendix 2).

Uncertainty for the analytical signal. Following the harmonized approach (*8*), the uncertainty for the analytical signal (U^{tg}_{Meas}) is (Appendix 2):

$$U^{tg}_{Meas} = 0.5 \times U^{tg} = 0.5 \times 2.0\% = 1.0\%.$$

Sample preparation uncertainty. It is rational to make requirements that the combined uncertainty of sample preparation (U^{tg}_{SP}) also be not more than 0.5 of U^{tg}:

$$U^{tg}_{SP} = 0.5 \times U^{tg} = 0.5 \times 2.0\% = 1.0\%.$$

2. An example of the analytical procedure for which an uncertainty estimation for NAP compliance is made

An amount of 50.0 mg of the substance being tested (m) or reference substance (m_0) is dissolved in the diluent and diluted to 50.0 mL (V_1 and V_{01}). Then, 1.0 mL of this solution (V_2 and V_{02}) is diluted to 10.0 mL (V_3 and V_{03}).

The calculation formula for the substance content in % w/w (without calculation to dry/volatile solvent-free substance) is as follows:

$$X = \frac{r}{r_0} \times \frac{m}{m_0} \times \frac{V_{01} \times V_{02}}{V_1 \times V_2} \times \frac{P_{RS}\%}{100\%}.$$

Uncertainty related to the sources of variation during sample preparation (group 2) is estimated as in Table 1.

Table 1
Uncertainty related to the sources of variation during sample preparation

Variability sources	Associated expanded uncertainty (%)
Test solution	
1. Taking a test portion of 50.0 mg of the substance being tested	= 0.2 mg[a]/50mg × 100% = 0.4%
2. Dilution to 50.0 mL (V_1)	0.17%[b]
3. Taking an aliquot of 1.0 mL (V_2)	0.74%[c]
4. Dilution to 10.0 mL (V_3)	0.50%[b]
Reference solution	
5. Taking a test portion of 50.0 mg of reference substance	= 0.2 mg[a]/50 mg × 100% = 0.4%
6. Dilution to 50.0 mL (V_{01})	0.17%[b]
7. Taking an aliquot of 1.0 mL (V_{02})	0.74%[c]
8. Dilution to 10.0 mL (V_{03})	0.50%[b]

[a] 0.2 mg is the recommended target uncertainty for the weighing operation (normal analytical practice recommendation, Appendix 2).

[b] Appendix 2, Table 2.

[c] Appendix 2, Table 4.

In this case, it is better to use a graduated pipette of 1.0 mL because formally it assures lower uncertainty than a transfer pipette of 1.0 mL.

The uncertainty for sample preparation according to NAP recommendations (U_{SP}^{tg}) can be estimated as follows:

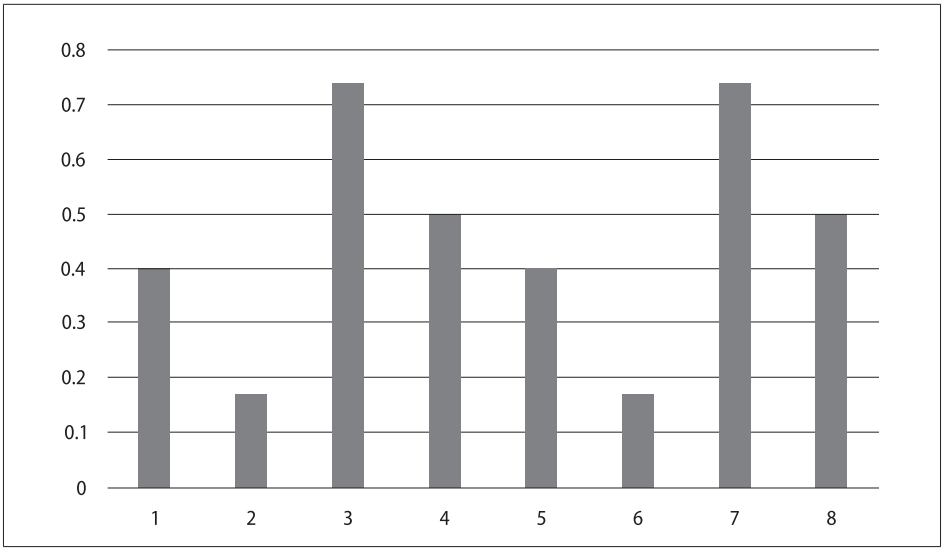
$$U_{SP}^{tg} = \sqrt{(0.4^2 + 0.17^2 + 0.74^2 + 0.5^2) \times 2} = 1.40\%.$$

U_{SP}^{tg} exceeds critical value $U_{SP}^{tg} = 1.0\%$; therefore, this analytical procedure creates an unacceptably high risk of obtaining too high uncertainty of X at reproduction of this analytical procedure in a laboratory, which complies with pharmacopoeial requirements at the minimum level (NAP recommendations).

It is recommended to optimize the accuracy of the test and reference solutions preparation.

The efficacy of sample preparation can be visualized as in Fig. 1: the x-axis shows the number of the sample preparation operation (numbers 1–8); the y-axis shows associated uncertainty (%).

Fig. 1
Relative contribution of the uncertainty of sample preparation operations (1)



The uncertainty estimates tend to decrease and converge with the optimization of the sources of variation.

Operations of the second dilution, numbers 3 and 7 (taking an aliquot of 1.0 mL) need optimization first, and then operations numbers 4 and 8 (dilution to 10.0 mL).

Using glassware of standard volumes, the modification of the second dilution without changing the final concentration can be proposed as follows: 5.0 mL of solution (V_2 and V_{02}) is diluted to 50.0 mL (V_3 and V_{03}).

Then, the uncertainty of sample preparation operations is estimated as in Table 2.

Table 2

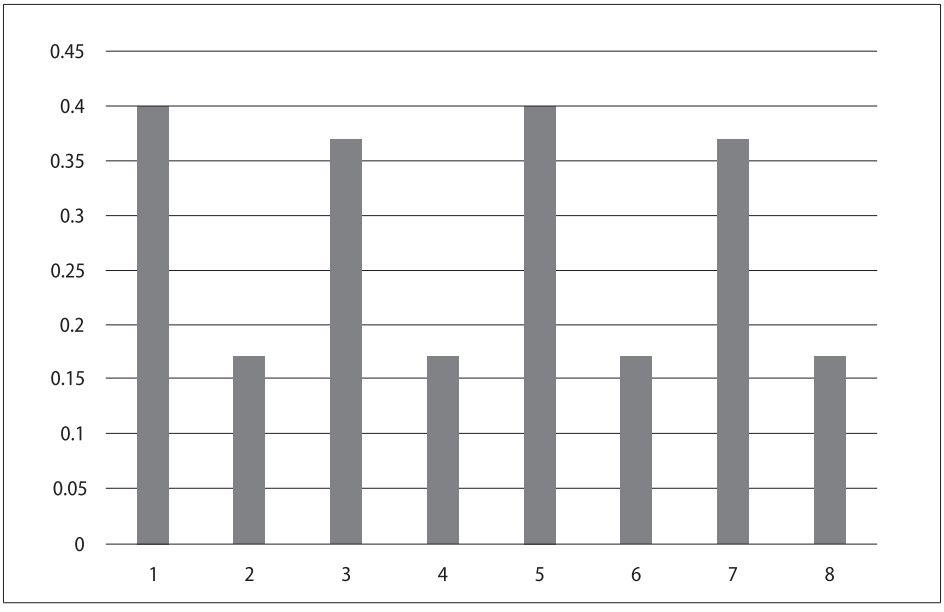
Uncertainty related to the sources of variation during sample preparation: second dilution

Variability sources	Associated expanded uncertainty (%)
Test solution	
3. Taking an aliquot of 5.0 mL (V_2)	0.37%
4. Dilution to 50.0 mL (V_3)	0. 17%
Reference solution	
7. Taking an aliquot of 5.0 mL (V_{02})	0. 37%
8. Dilution to 50.0 mL (V_{03})	0. 17%

The ratio for estimated uncertainties is shown in Fig. 2.

Fig. 2

Relative contribution of the uncertainty of sample preparation operations (2)



The estimated uncertainty for sample preparation (U_{SP}^{tg}) can be calculated as follows:

$$U_{SP}^{tg} = \sqrt{(0.4^2 + 0.17^2 + 0.37^2 + 0.17^2) \times 2} = 0.84\%.$$

As can be seen, after optimizing the accuracy of the preparation of solutions, U_{SP}^{tg} does not exceed the critical value U_{SP}^{tg} = 1.0%. Therefore, this analytical procedure does not lead to an unacceptably high risk of obtaining too high uncertainty of X and can be approved by the developer or used by NQCLs.

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Annex 5

WHO/UNFPA female condom generic specification

Contents

Abbreviations

AQL	acceptance quality limit
CFU	colony-forming unit
ISO	International Organization for Standardization
ISO/TC 157	ISO Technical Committee 157 for non-systemic contraceptives and STI barrier prophylactics
ppb	parts per billion
STED	summary of technical documentation
STI	sexually transmitted infection
TC	Technical Committee
UNFPA	United Nations Population Fund
WHO	World Health Organization

1. Introduction

This annex contains the World Health Organization (WHO)/United Nations Population Fund (UNFPA) specification for female condoms that is suitable for the bulk procurement of female condoms for use in social marketing, public sector programmes for family planning and the prevention of sexually transmitted infections.

Whereas a standard usually specifies the minimum requirements for the key properties that determine the safety and effectiveness of a product, a specification is a statement of the buyer's requirements and covers all the attributes and features of the product. Some of these requirements, such as packaging and labelling, may be unique to the buyer and not specified in the International Organization for Standardization (ISO) standard ISO 25841 (*1*).

The WHO/UNFPA specification is based on the performance requirements for female condoms specified in the international standard ISO 25841: Female condoms – Requirements and test methods (*1*). This standard, which was developed by the ISO Technical Committee 157 for non-systemic contraceptives and sexually transmitted infection (STI) barrier prophylactics (ISO/TC 157), was first published in July 2011. The standard has subsequently been updated to reflect the introduction of new types of female condom designs and changes in the availability of control condoms for conducting clinical studies. This updated standard was published as ISO 25481:2017. An amendment to the standard, ISO 25841:2017/Amd 1:2020, was published in 2020. The amendment includes verification procedures for assessing the effectiveness of

the test procedures for package integrity and freedom from holes. The current edition of the standard at the date of publication of this specification is ISO 25841:2017+A1:2020.

Throughout this specification reference to ISO 25841 (*1*) will refer to the latest edition of the standard. No significant changes to ISO 25841 (*1*) are expected until at least 2025.

Many potential designs of female condom are possible, each with its own set of design parameters and specifications. A wide range of materials can also be used to make female condoms. It is therefore not possible to establish a set of performance requirements for female condoms in the same way as it is for male latex condoms. Certain performance properties, such as burst volume and pressure, will depend upon the materials used and the design of the condom. These properties will therefore vary with condom type and design. Other performance properties, such as acceptance limits for freedom from holes, are independent of the materials and designs used. Specific limits can be set for these requirements. Whenever possible, specific limits have been set in this specification.

Female condoms also have a number of essential features that are not found in male condoms. In general terms, female condoms usually have the following components:

- a sheath that lines the vagina and may extend to cover or partially cover the external genitalia;
- an external retention feature that prevents the condom from being pushed into the vagina – commonly this is a ring or frame;
- an internal retention feature that retains the condom within the vagina and permits safe withdrawal of the penis after use – examples include rings, foam sponge devices and mucoadhesive tabs;
- a product insertion feature that facilitates insertion of the condom into the vagina. The internal retention feature may also serve this function.

For the reasons given above, it is not possible to determine the safety, efficacy and acceptability of a specific type of female condom based on its design and the materials used. Instead, it is necessary to conduct clinical investigations in humans to confirm the safety, efficacy and acceptability of any new female condom design. These investigations enable an assessment to be made of the overall performance of internal and external retention features, failure modes, safety and effectiveness of female condoms.

ISO 25841 (*1*) specifies the essential performance and safety requirements that female condoms are expected to meet and the test methods that are used

to assess compliance with these requirements. It is based on extensive research and an ongoing consultation process involving leading experts in all aspects of female condom manufacturing, research and use from around the world.

Each design of the female condom will have unique features that also may need to be agreed upon between the buyer and manufacturer. The buyer's specification must be a detailed and unambiguous statement of the buyer's requirements, describing how those requirements can be measured and assessed. The specification is generally attached to the bidding documents and forms, which are part of the supply contract. It is premature to develop a design-based specification for the public sector procurement of female condoms. Many different designs of the product are possible, each having its own unique features and specification. As a result, it has been decided to detail the scientific and technical requirements manufacturers must meet for the product to be approved for public sector distribution. These requirements incorporate the design and performance requirements of ISO 25841 (*1*).

This specification covers the generic requirements for female condoms and is largely performance based. For this reason, it is known as the *WHO/UNFPA female condom generic specification*. The *WHO/UNFPA female condom generic specification* has been developed by consensus and is based on available evidence, the details of which are catalogued in a technical basis paper. This generic specification describes the general, design, performance and packaging requirements for the product and the methods of verification. Female condoms are made and tested in lots. A lot is a collection of female condoms of the same design, colour, shape, size and formulation manufactured at essentially the same time using the same process, same specification of raw materials, common equipment, same lubricant and any other additive or dressing, and the same packaging materials. Further information about lots is given in Table A5.1.

The requirements have been divided into four categories, as follows.

- **General requirements** specify the clinical performance requirements of the product; the methods to be used by the manufacturer to set the product specifications for airburst properties; and the safety of constituent materials and other characteristics, such as shelf-life. These requirements and properties should not vary from lot to lot and therefore do not need testing on a regular basis. The general requirements are listed in subsection 3.1 of this specification.
- **Performance requirements** specify the essential performance attributes of the condoms. These must be tested on a lot-by-lot basis since the quality of these attributes may vary due to the manufacturing process. Laboratory tests are conducted to ensure that the condom and the individual containers comply with the specification. Performance requirements detailed in this specification

should not be changed. The performance requirements are listed in subsection 3.2 of this specification.

- **Design requirements** are concerned with the acceptability of the product to the end user. They are listed in subsection 3.3 of this specification. Some of these properties may be varied within certain limits to meet specific programmatic requirements by agreement with the manufacturer. Unlike the situation with male condoms, however, varying a design requirement might affect the clinical effectiveness of the female condom. Since the performance and acceptability of female condoms are established by clinical investigation, the potential impact of any change must be considered carefully. Such changes are therefore not generally feasible and users should choose from amongst the approved available designs. For each design requirement, there is a means of verification.
- **Packaging requirements** are listed in subsection 3.4 of this specification. If appropriate, purchasers may specify requirements depending upon the target population. When selecting packaging, manufacturers should consider the needs of disabled users. If consumer packaging is required, it is important to include detailed instructions in the specification and to discuss the design requirements with the manufacturer.

The *WHO/UNFPA female condom generic specification* and the WHO/UNFPA Prequalification Programme guidance are designed to ensure that a quality-assured product is purchased and distributed to the end user. This WHO/UNFPA specification should not be considered or used as a standard for regulatory purposes. For regulatory purposes, the applicable standard is ISO 25841 (*1*) or the relevant local standard, depending on the country.

2. Glossary

The definitions given below apply to the terms used in this specification. They have been aligned as much as possible with the terminology in related WHO guidelines and good practices and included in the *WHO Quality Assurance of Medicines Terminology Database: list of terms and related guideline*,[7] but may have different meanings in other contexts.

acceptance quality limit (AQL). The quality level that is the worst tolerable process average when a continuing series of lots is submitted for acceptance

[7] https://www.who.int/publications/m/item/quality-assurance-of-medicines-terminology-database.

sampling (ISO 2859-1). *Note*: Manufacturers should be consistently achieving a process average that is better than the AQL.

aseptic technique. Precautionary measures taken to prevent external contamination of materials, samples and culture media, employed during testing.

batch. Sometimes used in place of "lot" (see definition of lot; WHO recommends that "lot" be used when referring to condoms). The term can also refer to a homogeneous quantity of latex that has been compounded and is ready for dipping, from which several lots will be made, or to a quantity of individual raw materials.

bioburden. The population of microorganisms on a raw material, a component, a product, packaging or equipment.

bioluminescence. Light emitted when bacterial adenosine triphosphate reacts with firefly luciferin and luciferase. Bioluminescence tests are designed to measure the amount of light produced, which will be related to the number of microorganisms present in the sample.

CE mark. On condom packaging, a mark certifying that the product conforms to the essential requirements of European Medical Device Regulation (EU) 2017/745.

colony-forming unit (CFU). An estimate of the number of viable microorganisms per unit measured.

compliance testing. A regime of testing to verify that a lot complies with the specification.

consumer pack. A wallet or carton into which one or more individual containers are inserted for marketing purposes.

design requirements. Characteristics of the condom that are specified according to the buyer's requirements.

expiry date. The date by which the product is no longer considered acceptable for use.

exterior shipping carton. The container into which a number of inner boxes are packed.

forecast. An assessment of the future requirements of a programme, based on historical trends, research or feedback from fieldworkers on current needs.

general requirements. The general quality characteristics of condoms that are verified before supply commences and that are not expected to vary from lot to lot.

good manufacturing practice (GMP). A code of practice aimed at ensuring that the product is consistently manufactured to the required standard.

inner box. A box used to contain a convenient number of condoms in individual containers or consumer packs. Inner boxes will typically be presented as dispenser boxes containing 100 condoms.

inspection level. The degree of examination of the lot, as specified in ISO 2859-1. The higher the inspection level, the more samples will be tested, and hence the lower the risk of faulty products reaching the end user.

length. The length of the condom measured from the open end to the tip, excluding any reservoir.

lot. A quantity of condoms of a single grade, class, size and composition, manufactured under essentially the same conditions. With certain exceptions, all the condoms constituting a lot will have identical formulation (the same dimensions, colour, shape and surface texture), be manufactured on the same production line and be vulcanized under the same conditions.

lot number or code. A unique identifying alphanumeric code assigned to a lot.

Lowry method (modified). A method for determining the water-extractable protein levels in latex products.

national regulatory authority. A regulatory body with authority in a specific country to control the importation and distribution of medical products (see "regulatory authority").

non-visible hole. A hole in a female condom that is not visible under normal or corrected vision but is detected by the water leakage test specified in ISO 25841.

performance requirements. The critical tests of quality that all lots must pass to provide adequate consumer protection.

prequalification. The steps taken by the buyer to verify a manufacturer's suitability to provide condoms of the required quality. The WHO/UNFPA Prequalification Programme includes the periodic assessment of manufacturing dossiers, testing of samples and factory inspection.

preshipment compliance testing. A regimen of compliance tests conducted before a shipment leaves the supplier's factory.

process average. The long-term average percentage of non-complying condoms calculated separately for each attribute. Ideally, the process average for a specific attribute should be less than half the specified acceptance quality limit.

regulatory authority. A national or international body set up to oversee the safety, efficacy and quality of medical devices, including condoms, imported and distributed within a country or region.

rejection number. The minimum number of non-compliers (failures) in a test sample that will cause a lot to be rejected.

reservoir. A narrow portion of the condom at the closed end, designed to contain ejaculate. The reservoir is sometimes called the teat.

sampling plan. A specific plan that indicates the number of units (condoms) from each lot that are to be inspected (sample size) and the associated criteria for determining the acceptability of the lot (acceptance and rejection numbers).

shelf-life. The period of time after manufacture during which the product is considered acceptable for use.

specification. A detailed statement of a product's requirements as established by the buyer. Usually, a specification is based on an established standard.

standard. A detailed statement of the minimum acceptance requirements, as established by a national or international regulatory authority.

surrogate virus. A virus that is safer and easier to handle and can be used as a substitute for a pathogenic virus.

visible hole. A hole or tear in a female condom that is visible under normal or corrected vision before the condom is filled with water during the test for freedom from holes specified in ISO 25841.

viscosity. A fluid's resistance to flow.

3. WHO/UNFPA specification

3.1 General requirements

General requirements include the selection and safety of materials used to manufacture the condom and any insertion and retention devices. Manufacturers shall include, in their summary of technical documentation (STED), documentary evidence to confirm that the condoms comply with the requirements listed in Tables A5.1 to A5.5. Verification of conformance with

these requirements is assessed during prequalification and in response to any purchaser's doubts about whether or not the product complies with the *WHO/UNFPA female condom generic specification*.

Manufacturers are also required to include data in their STEDs supporting the shelf-life claims made for the product. Female condoms must comply with the performance requirements specified in subsection 3.2 of this *WHO/UNFPA female condom generic specification* throughout the stated shelf-life of the condom. Manufacturers must determine the shelf-life with real-time studies conducted at (30^{+5}_{-2}) °C. Pending the outcome of real-time studies, manufacturers may use appropriate accelerated studies to estimate a provisional shelf-life. The basis used to estimate the provisional shelf-life from the accelerated data must be explained in the product dossier and the appropriate validation data must be included.

Table A5.1
General requirements
(to be included in the STED and verified during prequalification)

Requirement	Further information
Clinical investigation report	Copies of clinical investigation reports shall be made available for review and included in the product dossier. The reports shall clearly identify the product variant to which they relate. Any changes made to the product since the clinical investigation was completed shall be documented. If a comparative clinical investigation against a marketed female condom has been conducted, the reports shall clearly identify the marketed female condom, including its manufacturer, the date of manufacture (if known) and the expiry date of the samples used in the study. The report shall include the test results for the condoms used in the trial, including burst test results.
Specification for minimum burst pressure and volume	Copies of reports relating to the setting of minimum burst pressure and volume specifications shall be made available and included in the product dossier. Reports shall include the original burst data on the lots of condoms used in the clinical investigations and details of how the minimum limits for burst pressure and volume were established. If the burst requirements are not based on the lots of condoms used in the clinical investigations, then a full justification is required to establish equivalence between the condom lots used to set the specification and those used in the clinical evaluation.

Table A5.1 *continued*

Requirement	Further information
Lot definition	A lot is a collection of condoms of the same design, colour, shape, size and formulation. A lot must be manufactured at essentially the same time, using the same process, same specification of raw materials, common equipment, and the same lubricant and any other additive or dressing, and must be packed in the same type of individual container, using the same packaging materials. All condoms comprising a lot will: • have an identical formulation; • have the same design, dimensions, colour, shape and surface texture; • be manufactured on the same production line; • be vulcanized under identical conditions; • be in the same packaging; • have the same lubricant; • have the same date of expiry printed on the package. Lot sizes over 500 000 are not permitted.
Materials	The condoms, retention features and any other components, such as insertion features, shall be made of suitable materials, as specified by the manufacturer. If significant changes are made to the grade or type of materials used, then the manufacturer may be required to repeat one or more of the safety, clinical and stability assessments of the product. Full details of the materials shall be given, including, if appropriate, polymer and copolymer compositions. Additional information about the material used for the sheath shall be given, including its key physical properties (tensile strength and modulus). For thermoplastic elastomers, the molecular weight and molecular weight distribution shall also be given.
Barrier properties	The barrier properties of the female condom shall be established by viral penetration studies using a suitable surrogate virus, for example bacteriophage phi X174. When tested in accordance with the method given in ISO 25841 (*1*), the volume of virus-containing medium penetrating the condom shall not exceed twice the limit of detection of the test for at least 80% of the condoms tested. A marketed male latex condom that complies with the requirements of ISO 4074 (*2*) may be used as a control in the study.

Table A5.1 *continued*

Requirement	Further information
Barrier properties *continued*	For condoms made from natural rubber latex with a sheath that has a minimum thickness of 0.055 millimetres (mm) and is made using conventional latex dipping processes, an exception from barrier testing is permissible since the barrier properties of such films in relation to viruses are well established. This exemption does not apply if the sheath is made using unusual dipping or vulcanization technology, if the sheath component or the finished condom is subjected to any subsequent treatment process other than washing, or if any additive other than the usual vulcanization ingredients and stabilizers is added to the latex. Confirmation of the viral barrier properties of the condom is normally completed prior to the submission for regulatory approval for the product. If any changes are made to the condom that could affect the barrier properties of the condom, for example changing the material used for the sheath component, the viral barrier test shall be repeated.
Biocompatibility	The condoms shall not liberate toxic or otherwise harmful substances in amounts that can be irritating, sensitizing or otherwise harmful to the user of the condom under normal conditions of use. Biocompatibility assessments shall be conducted on the whole condom, including the retention devices, any insertion device that might come into contact with the vagina and any lubricants and dressing materials, in accordance with ISO 10993-1 (*3*). Generally, tests for cytotoxicity shall be conducted in accordance with ISO 10993-5 (*4*) and tests for irritation and sensitization shall be conducted in accordance with ISO 10993-10 (*5*) and ISO 10993-23 (*6*). Manufacturers should choose accredited laboratories for these tests, and the results should be interpreted by an accredited toxicologist or other suitably qualified expert. In accordance with ISO 10993-1 (*3*), manufacturers may use existing data on identical materials instead of conducting their own tests. Expert reports shall be available for review. If there is a likelihood of systemic absorption of any components or residuals, further biocompatibility testing may be requested by regulatory authorities, such as testing for acute systemic toxicity in accordance with ISO 10993-11 (*7*) and testing for mutagenicity in accordance with ISO 10993-3 (*8*).

Table A5.1 *continued*

Requirement	Further information
Biocompatibility *continued*	The manufacturer shall also obtain, and make available on request from regulatory authorities, toxicity data on all the additives and residual monomers, solvents and known impurities used in the manufacture of the female condom. Suitable material safety data sheets shall be supplied on request for materials used in the manufacture of the condoms, retention features and lubricant. Regarding female condoms made from natural rubber latex, many latex products that have been established as safe, including male condoms and medical gloves, can exhibit a positive cytotoxic response when tested in accordance with ISO 10993-5 (*4*). Although any cytotoxic effect can be of concern, it is primarily an indication of potential for in vivo toxicity, and a female condom cannot necessarily be determined to be unsuitable for use based solely on cytotoxicity data. Manufacturers and purchasers are advised to confirm local requirements for safety testing with appropriate regulatory authorities in the countries in which the condoms are to be distributed.
Water-extractable protein levels	It is recommended that manufacturers of natural rubber latex-based female condoms determine the water-extractable levels of proteins in their products. The recommended level for soluble protein, as determined by the modified Lowry method, is less than 200 micrograms per gram (µg/g). Manufacturers should take steps not to exceed this level and should monitor production periodically. There is no specific standard for determining the protein levels in condoms. The methods described in ISO 12243 (*9*) , EN 455–3 (*10*) and ASTM D5712 (11) for determining the protein levels in medical gloves can be modified for condoms. Documentation recording protein levels should be available for review.
Bioburden levels	Condoms are not sterile devices but manufacturers should take steps to minimize the risk of contamination of the products with microorganisms. Some designs of female condoms may increase the risk of microbiological contamination because of the materials used and the additional manipulation required to assemble the finished device.

Table A5.1 *continued*

Requirement	Further information
Bioburden levels *continued*	It is recommended that bioburden levels on packed condoms are below 100 colony-forming units (CFU) and should not be allowed to exceed 500 CFU. There should be an absence of *Staphylococcus aureus* and Enterobacteriaceae, including *Escherichia coli*, *Pseudomonas aeruginosa* and all fungi. It is recommended that bioburden levels be determined periodically (for example, at least quarterly) by extracting the condoms with a neutralizing medium and determining the total viable aerobic count using appropriate test methods. Further information on the rationale for the bioburden limits, methods of determining bioburden levels and general guidelines on controlling bioburden contamination during manufacture is given in ISO 25841 (*1*). Confirmation that bioburden levels are below 500 CFU per condom will be assessed for lots of condoms submitted for prequalification testing.
Nitrosamines	Manufacturers of latex-based female condoms should take steps to minimize the formation of nitrosamines. This can be done by ensuring that condoms are adequately leached and washed by using minimum amounts of accelerators and by choosing accelerators, such as zinc dibutyldithiocarbamate, that have a preferred safety profile (*12*). For prequalification purposes, the manufacturer should be able to demonstrate that it is are able to achieve levels below 50 parts per billion (ppb) measured as per ISO 29941 (*13*). Levels should be monitored periodically, at least once a year, and following any significant change to the latex formulation.
Aromatic amines	Manufacturers using polyurethanes shall confirm that aromatic amines cannot be leached out of the female condom at levels that could be considered toxic.
Shelf-life	Condoms shall conform with the performance requirements of this *WHO/UNFPA female condom generic specification* throughout the stated shelf-life of the condom. The manufacturer shall determine the shelf-life based on the outcome of stability studies determined from the date of manufacture. The date of manufacture can be the date of sheath manufacture or the date of assembly and packaging of the female condom in individual sealed containers, depending on the procedures specified by the manufacturer. The date of manufacture shall not exceed six months from the date of sheath manufacture.

Table A5.1 *continued*

Requirement	Further information
Shelf-life *continued*	Unprocessed sheaths or unpackaged female condoms shall be stored under controlled conditions, as specified by the manufacturer, between sheath manufacture and packaging. Manufacturers shall have documented procedures for validating the storage conditions and maximum storage period. The stored sheaths or female condoms shall be protected from exposure to excessive temperature, light, ozone levels or anything else that could affect the shelf-life of the packaged female condoms. The claimed shelf-life shall be not less than three years and no more than five years, subject to confirmation by the appropriate stability data. For WHO/UNFPA prequalified manufacturers, the maximum period of time between sheath manufacture and assembly or packaging is six months, but manufacturers may use shelf-life data from stability studies with condoms that have been stored up to two years prior to packaging as specified by ISO 25841 (*1*) to support shelf-life claims. Manufacturers must commence real-time studies before lodging their applications for prequalification. Pending the outcome of the real-time studies, manufacturers may estimate a provisional shelf-life using an accelerated ageing study. If, at any time during the real-time studies, the manufacturer becomes aware that the shelf-life estimates made using the accelerated studies are incorrect, the manufacturer must notify UNFPA and the purchasers immediately.
Real-time stability studies	Shelf-life shall be confirmed by real-time stability studies conducted at 30 (+5/–2) °C according to the relevant clause in ISO 25841 (*1*). If the condom or any critical components, such as the retention features, are made from moisture-sensitive materials, and a moisture-impermeable packaging material is not used, then relative humidity shall be controlled at (75 ± 5) % during real-time stability studies. For confirmation, humidity control is not required when conducting stability studies on female condoms made from natural rubber latex packed in impermeable packaging.

Table A5.1 *continued*

Requirement	Further information
Real-time stability studies *continued*	Details about the methods of determining the shelf-lives of female condoms are given in ISO 25841 (*1*). If the female condom sheath is made from natural rubber latex by conventional dipping processes and the female condom is packed in an oxygen-impermeable individual container, for example, made from aluminium foil laminate, then the procedure used to determine a provisional shelf-life of natural latex male condoms described in ISO 4074 (*2*) can be used. For female condoms with sheaths made out of synthetic materials, the procedures described in ISO 11346 (Rubber, vulcanized or thermoplastic – Estimation of life-time and maximum temperature of use) (*14*) may be appropriate. The procedures used for accelerated stability studies shall be appropriate to the raw materials of the condom. The results of an accelerated ageing study, according to ISO 25841 (*1*), must be available at the time of submitting an application for prequalification and a real-time study must also be in progress.
Sampling	Condoms for stability studies shall be taken from three normal production lots. Sampling shall be done according to Annex A or Annex B (preferred) of ISO 25841 (*1*). The sample sizes from each lot should be adequate to complete all the tests specified in Annexes L and M of ISO 25841 (*1*) and include sufficient samples to permit retesting in full after at least one additional time point during the studies.
Conditioning	Samples shall be conditioned in their individual sealed containers according to the relevant annex of ISO 25841 (*1*). At the end of the incubation periods, withdraw the condoms and test for airburst properties, freedom from holes and package seal integrity.
Testing requirements	For real-time stability studies, all three lots of condoms shall conform to the requirements for bursting properties, freedom from holes and package integrity specified in the relevant clauses of ISO 25841 (*1*) for the full specified shelf-life of the product. For accelerated studies, suitable means of extrapolation shall be used to support the specified shelf-life.

Table A5.1 *continued*

Requirement	Further information
Stability study reports	The stability study reports should indicate the time between sheath manufacture and assembly or packaging for the lots used for the study. If a manufacturer has not recorded the required information in the stability study report, then the default position will be that the manufacturer must use the sheath manufacturing date as the date of manufacture.
Individual container	The individual container shall not adversely affect the properties of the female condom. The individual container shall be sealed and shall provide an adequate level of protection consistent with the materials used to manufacture the condom. The individual container shall not allow lubricant to leak. Individual containers for female condoms made from natural rubber latex, or other materials that can be affected by light, shall be opaque. It is unlikely that biodegradable packaging will provide sufficient product protection for female condoms made from natural rubber latex. The individual containers shall have sufficient mechanical strength to protect the condoms during shipping and storage. Purchasers may choose to specify special packaging requirements at the purchase order stage, in which case the requirements must be included in the purchase specification.

3.2 Performance requirements

The performance requirements specified here are based on the requirements in the current published edition of ISO 25841 (*1*). These requirements cannot be altered. Verification of compliance with these requirements must be done as part of the prequalification process and the lot-by-lot preshipment compliance testing of the product.

For prequalification purposes (that is, when testing fewer than five lots), the sampling plans specified in Annex B of ISO 25841 (*1*) shall be used. For lot-by-lot compliance testing (that is, when testing continuing series of lots), the sampling plans specified in Annex A of ISO 25841 (*1*) shall be used. Sample requirements for testing are summarized in Appendix 1.

Table A5.2
Performance requirements

Requirement	Further information
Bursting volume and pressure	
Sampling	In accordance with ISO 2859-1: Sampling procedures for inspection by attributes (general inspection level I) (*15*). For prequalification testing, at least code letter M as specified in Annex B of ISO 25841 (*1*) shall be used.
Testing	In accordance with the method given in the relevant annex of ISO 25841 (*1*). Condoms shall comply with the minimum burst volume and pressure requirements specified by the manufacturer, as determined according to the method described in ISO 25841 (*1*).
Requirements	The limit for nonconforming condoms is an AQL of 1.5.
Freedom from holes and visible defects, including critical visible defects in packaging	
Sampling	ISO 2859-1 general inspection level I (*15*), but at least code letter M shall be used. For prequalification testing, at least code letter N as specified in Annex B of ISO 25841 (*1*) shall be used.
Testing	Condoms shall be assessed in accordance with the method given in the relevant annex of ISO 25841 (*1*). Critical visible defects in the individual containers are also assessed at the same time using the same samples. The list of critical and non-critical visible defects for the condoms and individual containers is given in Appendix 2.
Requirements	The limits for nonconforming condoms are: • freedom from holes: AQL 0.25 • critical visible defects: AQL 0.4 • non-critical visible defects: AQL 2.5. The limit for nonconforming individual containers is an AQL of 0.4. Female condoms with non-visible holes in any position greater than 25 mm from the open end and visible holes in any position along the whole length of the sheath are considered nonconforming. Descriptions of critical visible defects and non-critical visible defects are given in Appendix 2. Exact definitions of critical and non-critical defects should be reviewed and agreed on during the contractual process.

Table A5.2 *continued*

Requirement	Further information
Package integrity (seal integrity)	
Sampling	ISO 2859-1 inspection level S-3 (*15*) . For prequalification testing, at least code letter H as specified in Annex B of ISO 25841 (*1*) shall be used.
Testing	In accordance with the method given in the relevant annex of ISO 25841 (*1*).
Requirements	The limit for nonconforming individual containers is an AQL of 2.5.

3.3 Design requirements

Since the approval of female condoms is based on a satisfactory outcome from the clinical investigation, any change in the design of the condom or the materials used requires a detailed evaluation to ensure that the safety and effectiveness are not compromised. A full risk assessment using, for example, the procedures described in ISO 14971 (*16*) shall be conducted following any significant change to the design, formulation, manufacturing process, equipment used and packaging. As a consequence of the risk assessment, further clinical investigation of the product or retesting may be required. Approval from relevant regulatory and notified bodies may be required before the changes can be implement. A prequalified manufacturer implementing such changes must inform the UNFPA Prequalification Programme about the changes.

For the design requirements listed in Table A5.3, the nominal specified requirements shall be the same as those for the samples of condoms submitted for clinical investigation. All condoms tested in the sample shall fall within the tolerances specified for the specified mean nominal value. Any variation in the specified tolerances may be acceptable at the time of prequalification, subject to a full justification for the variation and agreement with UNFPA.

Table A5.3
Design requirements

Requirement	Further information
Sampling	Unless otherwise stated, all design requirements shall be assessed using a sample size of 13 female condoms.
Requirements	Unless otherwise stated, all samples shall conform to specification.

Table A5.3 *continued*

Requirement	Further information
Essential features	
Verify by visual inspection	A female condom will normally have the following essential features: • A sheath component that lines the vagina and may extend to cover or partially cover the external genitalia. • An external retention feature to prevent the condom from being pushed into the vagina. Commonly this is a ring or a frame. • An internal retention feature that retains the condom within the vagina and permits safe withdrawal of the penis after intercourse. Examples include rings, foam sponge devices and mucoadhesive tabs. • A product insertion feature that facilitates insertion of the condom into the vagina. The internal retention feature may also serve this function.
Minimum burst properties	The minimum burst volume and pressure for the condom shall be based on results obtained by testing at least 2000 female condoms from the lot or lots used in the clinical trial (if more than one lot was used the samples shall be drawn across all lots in proportion to the size of each lot). The minimum burst pressures and volume limits shall be set at 80% of the 1.5 percentile values of the measured airburst volumes and pressures. Round the bursting volume limit to the nearest 0.1 cubic decimetre (dm^3) if the value is 14.9 dm^3 or below, and to the nearest 0.5 dm^3 if the value is greater than 14.9 dm^3. Round the bursting pressure to the nearest 0.05 kilopascal (kPa). After a period of essentially continuous production of at least 30 full-scale manufacturing lots, the limits should be re-evaluated to confirm that they are still applicable.
Requirements	All condoms in the sample shall have the essential features and components specified by the manufacturer, which shall be the same as those for the condoms used in the clinical investigation. These requirements include: • the materials used for the sheath and all retention features; • the method of manufacture of the female condom in including the sheath and the retention features; • the dimensions of the sheath and retention features; • the physical properties of the materials used for the sheath and retention features; • the type and amount of lubricant used.

Table A5.3 *continued*

Requirement	Further information
Requirements *continued*	If any of these critical design requirements are changed for any reason, a full risk assessment must be completed to demonstrate that the safety and effectiveness of the product has not been compromised. A further clinical investigation may be necessary to confirm this.
Colour	
Pigment	If any pigment is used to colour the condom, it shall be suitable for use in medical devices. Full details of any pigments used shall be supplied along with the relevant material safety data sheets.
Colour assessment	A sample of female condoms from each lot shall be inspected visually for colour (colour may be assessed on the same sample of condoms used to assess other design requirements). Reference samples or colour charts may be used to define and assess colour. Exact colour matches may not be possible.
Odour and flavour	
Verify by visual inspection and smell	The condoms shall not give off an unpleasant odour when the package is opened at any time after manufacture and during the shelf-life of the product. (Many materials, including natural rubber latex, have a characteristic odour. Often the odour tends to dissipate quickly once the package is opened. A mild odour that dissipates quickly is acceptable.) It is suggested that appropriate reference samples be retained by the testing laboratory to help resolve disputes over odour. It is recommended that the retained samples be kept for the duration of the shelf-life of the condom. Purchasers may, by agreement with the manufacturer, specify the addition of a suitable fragrance or flavour. Such fragrances and flavours must be non-toxic and non-irritant and must not adversely affect the performance and acceptability of the condom. If a fragrance or flavour is included, full details of the fragrance or flavour, including a material safety data sheet, shall be included in the STED and data sheet.

Table A5.3 *continued*

Requirement	Further information
Testing	See Appendix 3 for guidance on odour testing. If a masking agent or fragrance is used, odour testing should become part of the lot-by-lot preshipment compliance testing. Odour testing should be included in ageing studies. Evaluation of odour is inherently subjective, and a degree of tolerance is required when assessing products for conformance with the specification.
Width	
Testing	Samples from each lot shall be assessed in accordance with the method given in the relevant section of ISO 25841 (*1*). The width of a female condom is unique to each design. The manufacturer shall specify the nominal width of female condoms at each of the measurement locations given in the relevant annex of ISO 25841 (*1*). The maximum tolerance for width requirements shall be ± 2 mm around the specified width.
Length	
Testing	Samples from each lot shall be assessed in accordance with the method given in the relevant annex of ISO 25841 (*1*).
Requirements	The length of a female condom is unique to each design. The manufacturer shall specify a nominal length for the female condom consistent with the length of the female condoms used in the clinical investigation. The maximum tolerance shall be ± 5 mm if the nominal length is 150 mm or less and ± 10 mm if the nominal length is greater than 150 mm.
Thickness	
Testing	A sample from each lot shall be tested in accordance with the method given in the relevant annex of ISO 25841 (*1*). The thickness of a female condom is unique to each design. The manufacturer shall specify a nominal thickness of the female condom at each of the measurement locations specified in the relevant annex of ISO 25841 (*1*). The thickness shall be consistent with the thickness of the female condoms used in the clinical investigation. The tolerance shall be ± 0.01 mm. For female condoms made from natural rubber latex with sheath thicknesses greater than 0.1 mm, a tolerance of ± 0.015 mm shall apply.

Table A5.3 *continued*

Requirement	Further information
Quantity of lubricant including powder	
Testing	Samples from each lot shall be tested in accordance with the method given in ISO 25841 (*1*). The design of a female condom may include lubrication in any of the following forms: • lubricant preapplied directly to the female condom during packaging; • lubricant supplied in a separate container to be applied to the female condom by the user; • lubricant both preapplied to the female condom and supplied in a separate container. The type and amount of lubricant is unique to each female condom design. The manufacturer shall specify the amount of lubricant, which shall be the same as that used in the clinical investigation.
Requirements	The manufacturer shall specify the amount of lubricant, which shall be the mean amount of lubricant used in the clinical investigation. All female condoms in the sample tested shall be within ± 15% of the specified mean. Manufacturers shall specify test methods as appropriate to verify the design and to ensure the quality and consistency of the lubricant. The specification for the lubricant should include viscosity. If the lubricant is supplied separately from the female condom, then manufacturers shall provide full details on how the lubricant should be used. These details shall be consistent with the instruction given with the clinical investigation samples. The quantity of lubricant supplied in the container shall be not less than the amount supplied with the clinical investigation samples. The containers for the lubricant shall not leak. An inspection level of S-3 and an AQL of 1.5 are recommended for assessing lubricant container integrity. Consult the purchase order and specification to determine if additional packaging requirements apply to the lubricant container.

Table A5.3 *continued*

Requirement	Further information
Retention features and other additional components	
Sampling	A sample of 13 female condoms shall be tested from each lot.
Testing	The dimensions of all retention features and any other ancillary components, such as insertion features, shall be measured using the methods specified by the manufacturers. Manufacturers are required to specify mechanical properties for the retention features that are relevant to the correct function of the feature. Examples could include stiffness and elastic memory parameters for rings, resilience and recovery times for foams and adhesion properties for adhesive pads. The specification requirements shall be based on the lots used in the clinical investigation. Periodically, purchasers and other interested parties may assess the physical properties specified for the internal and external retention devices.
Requirements	The dimensions of the retention features and other ancillary components for every condom tested shall comply with those specified by the manufacturer. The specified dimensions for retention features shall be the same as those for the clinical investigation samples within a tolerance of ± 5%. The mean mechanical properties of the retention features shall be the same as those used for the clinical investigation samples within a tolerance of ± 10%. All samples tested shall comply.
Individual container markings	
Sampling	A sample of 13 individual containers and, if appropriate, 13 consumer packs shall be taken from each lot.
Testing	The individual containers are visually inspected to verify the required aspects of package marking.
Requirements	The colour, print design and identification markings, including Pantone references and font sizes, shall be as specified by the buyer and annexed to the specification for the product. All samples shall comply.

Table A5.3 *continued*

Requirement	Further information
Verified by visual inspection	The individual containers shall not adversely affect the properties of the female condom. The individual containers shall be sealed and shall provide an adequate level of protection consistent with the materials used to manufacture the condom. The individual containers shall not allow lubricant to leak. The recommended individual containers shall have sufficient mechanical strength to protect the condoms during shipping and storage.
Verified by supplier's data or independent test requirement	The lot numbers on individual containers should be printed at the time of packaging. If this is not feasible, then manufacturers shall ensure that there are adequate procedures to ensure that the correct lot number is placed on the individual containers. The individual containers shall have the following markings, which shall be clearly legible under normal and corrected vision: • the identity of the manufacturer or distributor or, if permitted by local regulations, the registered brand or trademark; • the lot number or lot identification code (printed at the time of packaging, not preprinted); • expiry date – month and year labelled expiry date in languages to be specified by the purchaser (printed at the time of packaging, not preprinted) – the year shall be written as a four-digit number and the month as a two-digit number; • instructions for use that are clearly legible in pictorial form or in languages to be specified by the purchaser (may be supplied separately if unable to print on the packaging); • the statement relating to the effectiveness of the condom, if required by the purchaser (see *Family planning: a global handbook for providers*, section 14, "Female condoms" (*17*), for information about the effectiveness of female condoms); • a warning about the risk of allergic reactions to the condom if the condom is made from natural rubber latex. Purchasers may specify the use of Braille for specific information, including the expiry date. If a separate lubricant and condom are supplied in the same package, then the expiry date shall be the shorter of the two. The expiry date shall be printed on all packages (that is, the individual condom container, the lubricant package and any outer or consumer package). All inspected individual containers and, if appropriate, consumer packs shall comply with the packaging requirements.

3.4 Packaging requirements for shipment

Inspections or verifications in this section will generally be carried out during prequalification, lot-by-lot preshipment compliance testing and periodic inspections.

Information included on all packaging shall be in the language specified by the purchaser.

Table A5.4
Packaging requirements for shipment

Requirement	Further information
Consumer packaging	No requirements for consumer packs (sometimes called wallet packs) are included in the *WHO/UNFPA female condom generic specification*. If required, the full design of the consumer pack should be specified in accordance with the requirements of the programme.
Inner boxes	The inner boxes shall be packed into plastic bags or other bags with waterproof linings, which will be placed in three-wall cartons made from weather-resistant corrugated fibreboard with a bursting test strength of no less than 1900 kPa. The inner boxes will be marked in a legible manner to facilitate identification in case of subsequent queries. The following information shall be included in the inner box marking: • A description of contents. • Lot identification number. • Month and year of manufacture (including the words "date of manufacture", "month" and "year") in languages to be specified by the purchaser. The year shall be written as a four-digit number and the month as a two-digit number. • Month and year of expiry (including the words "expiry date", "month" and "year") in languages to be specified by the purchaser. The year shall be written as a four-digit number and the month as a two-digit number. • Manufacturer's name and registered address. • Number of condoms in the box. • Instructions for storage. *Note*: all markings must be legible. Inner box markings can be specified in accordance with programme requirements.

Table A5.4 *continued*

Requirement	Further information
Interior shipping cartons	The inner boxes shall be packed into plastic bags or other bags with waterproof linings, which will be placed in three-wall cartons made from weather-resistant corrugated fibreboard with a bursting test strength of no less than 1900 kPa. The carton flaps shall be secured with water-resistant adhesive applied to not less than 75% of the area of contact between the flaps, or with water-resistant tape, 75 mm wide, applied to the full length of the centre seams and extending over the ends by not less than 75 mm. The cartons may be secured by plastic strapping in no less than two positions. Alternatively, wire-bound, cleated plywood or nailed wood boxes are acceptable when lined with a material that provides a waterproof barrier. The barrier material must be sealed at the edges with waterproof tape or adhesive, and there must be no sharp protrusions inside the boxes. In some countries, the three-wall corrugated fibreboard available is not of sufficient strength and rigidity to meet stacking requirements or to resist being cut at the corners when the plastic strapping is applied. In such cases, an inner carton of two-walled corrugated fibreboard shall be inserted into the shipping carton before packing the condoms.
Exterior shipping cartons	The exterior shipping carton, like the inner box, shall be marked with information about the contents in a clearly legible manner. Information should be printed on two adjacent sides. The information shall include: • A description of the contents. • Lot identification number. • Month and year of manufacture (including the words "date of manufacture", "month" and "year") in languages to be specified by the purchaser. The year shall be written as a four-digit number and the month as a two-digit number. • Month and year of expiry (including the words "expiry date", "month" and "year") in languages to be specified by the purchaser. The year shall be written as a four-digit number and the month as a two-digit number. • Name and address of the manufacturer or supplier. • Number of female condoms contained in the carton. • The consignee details. • Instructions for storage and handling.

Table A5.4 *continued*

Requirement	Further information
Lot traceability	Condom lots presented for inspection and acceptance must be complete and packed in their exterior shipping cartons. Provision should be made during production for sufficient additional condoms from each lot to replace those sampled for acceptance testing. Wherever practicable, lots must be shipped in their entirety and be kept whole during containerization and shipping. The manufacturer should take all reasonable steps to maintain the shipments in discrete lots as far as practicable down the distribution chain. These steps may include the use of very large letters for lot codes, colour coding and the grouping of pallets with the same lot number.

3.5 Information for the user

Table A5.5
Information for the user

Requirement	Further information
Information	If information is to be provided with the condom, in accordance with local regulations or programme requirements or specified by the purchaser, then the following instructions and information should be considered for inclusion in the inner box or the secondary or consumer carton. The language, which should be appropriate for the intended population, shall be specified by the purchaser: • how to handle the female condom carefully, including removal from the package to avoid damage to the condom by fingernails, jewellery, or other means; • how and when to insert the female condom – mention shall be made that the female condom should be inserted into the vagina before any contact occurs between the vagina and the partner's body to assist in the prevention of STIs (sexually transmitted infections) and pregnancy; • a statement instructing the user to stop and check if they feel the female condom slipping into or out of the vagina; • if the lubricant is supplied with the condom but in a separate sachet, then instructions on how to use the lubricant shall be provided along with a description of the lubricant and an expiry date;

Table A5.5 *continued*

Requirement	Further information
Information *continued*	• a statement informing the user about which type of additional lubricant can be used with that specific female condom and how the lubricant should be used; • if the female condom is made with natural rubber latex, a statement instructing the user to avoid using oil-based lubricants, such as petroleum jelly, baby oil, body lotions, massage oils, butter and margarine, as these are deleterious to the integrity of the female condom; • a statement instructing the user to consult a doctor or pharmacist about the compatibility of topical medicines and other topical products that may come into contact with the female condom; • advice on seeking medical assistance as soon as possible should a female condom fail during use; • advice to discard the female condom and use a new one from an undamaged package if the individual package is obviously damaged; • advice on withdrawing the penis soon after ejaculation, leaving the female condom in place in the vagina; • instructions for withdrawal and disposal of the female condom; • a statement that the condom is for single use only and that cleaning and reuse can compromise the integrity of the device; • explanation of any symbol used on the packaging; • if a symbol for latex is used on the packaging, a statement that the female condom is made of natural rubber latex, which may cause allergic reactions, including anaphylactic shock, if the user is allergic to latex; • the date of issue or the date of latest revision of the instructions for use; • if the product is manufactured to conform to all requirements of ISO 25841, the number of the standard (that is, ISO 25841); • for female condoms intended for distribution within the European Union, the CE mark. It is recommended that the following statement relating to the safety and effectiveness of the condom be included: "When correctly used every time you have sex, female condoms reduce the risk of unintended pregnancy, HIV and some other sexually transmitted infections. Use a new condom every time you have sex and follow the instructions carefully."

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Note: Where standards are undated the latest edition of that standard applies. All URLs accessed January 2024.

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Appendix 1

Summary tables: prequalification and lot-by-lot testing

Tables 1 and 2 summarize the testing methods and requirements for ensuring that there are no packaging defects, general requirements, performance requirements and design requirements for prequalification and lot-by-lot compliance testing. The requirements should be assessed against those specified in the manufacturer's data sheet for the specific product.

Table 1
Summary of prequalification tests (isolated lots)

Characteristics	Sampling	Verification	Requirement
Burst volume and pressure	ISO 2859-1 Level G-I Minimum code letter L (200 samples) For prequalification testing, minimum code letter M (315 samples) shall be used	Laboratory testing Comply with manufacturer's specification	AQL 1.5
Freedom from holes	ISO 2859-1 Level G-I For prequalification testing, minimum code letter N (500 samples) shall be used	Laboratory testing	AQL 0.25
Visible defects	ISO 2859-1 For prequalification testing, minimum code letter N (500 samples) shall be used	Visual inspection	Critical defects: AQL 0.4 Non-critical defects: AQL 2.5
Visible defects: individual containers	ISO 2859-1 Level G-I For prequalification testing, minimum code letter N (500 samples) shall be used	Visual inspection	Critical defects: AQL 0.4

Table 1 *continued*

Characteristics	Sampling	Verification	Requirement
Design	13 condoms per lot	Visual inspection and measurement	Comply with manufacturer's specification All samples comply
Individual container integrity	ISO 2859-1 Special inspection level S-3 For prequalification testing, minimum code letter H (50 samples) shall be used	Laboratory testing	Laboratory testing AQL 2.5
Colour	13 condoms per lot	Visual inspection	Comply with manufacturer's specification All samples comply
Scents and flavouring	13 condoms per lot	Sensory inspection	Comply with manufacturer's specification
Width	13 condoms per lot	Laboratory testing	All samples comply
Length	13 condoms per lot	Laboratory testing	Comply with manufacturer's specification
Thickness	13 condoms per lot	Laboratory testing	Comply with manufacturer's specification All samples comply
Lubricant quantity (including powder)	13 condoms per lot	Laboratory testing	Comply with manufacturer's specification All samples comply
Retention feature properties	Special inspection level S-2	Laboratory testing	AQL 2.5

Table 1 *continued*

Characteristics	Sampling	Verification	Requirement
Odour (if necessary)	13 condoms per lot	Sensory inspection	Comply with manufacturer's specification
Inner box	ISO 2859-1 Level S-3	Visual inspection	All samples comply
Exterior shipping cartons	ISO 2859-1 Level S-2	Visual inspection	Comply with manufacturer's specification

Table 2
Summary of lot-by-lot preshipment compliance testing and requirements (continuing series of lots)

Characteristics	Sampling	Verification	Requirement
Burst volume and pressure	ISO 2859-1 Level G-I	Laboratory testing	AQL 1.5
Freedom from holes	ISO 2859-1 Level G-I Minimum code letter M	Laboratory testing	AQL 0.25
Visible defects	ISO 2859-1 Level G-I Minimum code letter M	Laboratory testing	Critical defects: AQL 0.4 Non-critical defects: AQL 2.5
Visible defects: individual containers	ISO 2859-1 Level G-I	Visual inspection	Critical defects: AQL 0.4
Individual container integrity	ISO 2859-1 Special inspection level S-3	Laboratory testing	AQL 2.5
Design	13 condoms per lot	Visual inspection	Comply with manufacturer's specification All samples comply

Table 2 *continued*

Characteristics	Sampling	Verification	Requirement
Colour	13 condoms per lot	Visual inspection	Comply with manufacturer's specification All samples comply
Scents and flavouring	13 condoms per lot	Sensory inspection	Comply with manufacturer's specification All samples comply
Width	13 condoms per lot	Laboratory testing	Comply with manufacturer's specification All samples comply
Length	13 condoms per lot	Laboratory testing	Comply with manufacturer's specification All samples comply
Thickness	13 condoms per lot	Laboratory testing	Comply with manufacturer's specification All samples comply
Lubricant quantity (including powder)	13 condoms per lot	Laboratory testing	Comply with manufacturer's specification All samples comply
Retention feature properties	Special inspection level S-2	Laboratory testing	AQL 2.5
Odour (if necessary)	13 condoms per lot	Sensory inspection	Comply with manufacturer's specification All samples comply

Table 2 *continued*

Characteristics	Sampling	Verification	Requirement
Packaging and labelling	13 condoms per lot	Visual inspection	Comply with manufacturer's specification All samples comply
Inner box	ISO 2859-1 Level S-3	Visual inspection	Comply with manufacturer's specification All samples comply
Exterior shipping cartons	ISO 2859-1 Level S-2	Visual inspection	Comply with manufacturer's specification All samples comply

Appendix 2

Workmanship and visible defects

1. Introduction

All female condoms in the sample are inspected for workmanship and visible defects as part of the freedom from holes test prior to mounting on the test equipment. The number of condoms exhibiting a visible defect is recorded and defects are classified either according to the type of defect listed below or as specified in the contract.

Visible defects are divided into (a) critical visible defects, and (b) non-critical visible defects.

The individual containers in the sample are also inspected for critical visual defects before the samples are removed for testing. Critical visible defects in the packaging that could have an adverse effect on the properties of the condom are listed in Table 1.

2. Types of visible defects in condoms

It is not possible to define all critical and non-critical visible defects, and it may be necessary to exercise some judgement about whether a particular visible defect is critical.

If the visible defect may affect the performance of the female condom, the defect is considered critical. If a defect not listed in Table 1 is considered critical by any party, the purchaser, test laboratory and manufacturer must consult with each other to agree on the classification of the defect concerned.

2.1 Critical visible defects

Critical visible defects may adversely affect the performance of the condom. Condoms with critical visible defects are therefore nonconforming.

ISO 25841 covers the most common critical visible defects. Some of the more common critical visible defects are described in Table 1.

These are evaluated by visual inspection as part of the procedure for freedom from holes testing. An acceptance quality limit (AQL) of 0.4 is applied to these defects.

Other types of critical visual defects are occasionally seen and they should be assessed for their potential effect on the performance and acceptability of the condom. If a defect can be expected to affect the performance, safety or acceptability of the condom, it should be classified as a critical defect.

Table 1
Critical visible defects: AQL of 0.4

Defect	Description
Blister or bubble	An obvious circular or teardrop-shaped thin area with a well defined border in the film (such defects may break under pressure).
Coagula (large)	For female condoms made from natural or synthetic rubber latex, rubber particles with any dimension greater than 1 mm. These may cause the condom to fail during use.
Embedded and surface particles	Any particle with any dimension of 1 mm or greater. These particles may be dirt, hair, insects, etc.
Retention features	Broken, cracked, missing, damaged or severely distorted retention features (as in ISO 25841:2011). Incomplete attachment of the sheath to the external retaining feature. Disintegrating sponge internal retention features. Presence of sharp edges on retention features that could cause discomfort or damage to the vagina or penis.
Crack marks	For female condoms made from natural or synthetic rubber latex, lines that penetrate the surface of the film, formed by shrinkage of the latex during drying. These do not include flow lines or marks from the mould.
Delamination	For female condoms made from natural or synthetic rubber latex, areas in which the individual layers of latex separate (if the condom is formed by two or more dips in the latex).
Thin areas	Small areas of the condom that are visibly thin. These can show up as bulges with well-defined edges on the freedom from holes test. Condoms that look asymmetrical when filled with water are not necessarily in this category.
Seams	For female condoms made by welding, poorly welded or creased seams that could fail during use or cause discomfort. Large lumps of material within the seam that could potentially cause discomfort or damage to the vaginal mucosa.
Pleat or crease	The film sticks to itself and the pleat or crease cannot be removed by gentle stretching of the adjacent film, and unintentional adhesion to retention features.
General	Any defect that can be seen to adversely affect the performance or safety of the product.

2.2 Non-critical visible defects

Non-critical visible defects are considered minor defects as they may not cause the female condom to fail to meet the specification. Nevertheless, they are undesirable from the user's standpoint. If non-critical visible defects are specified in a purchase specification, an AQL of 2.5 is recommended. Inspection for non-critical visible defects is conducted on the samples used for freedom from holes testing.

Depending on the requirements of the specific user population, the purchaser may wish to include in the specification specific non-critical visible defects, including the most common ones, as listed in Table 2. Detailed descriptions of the non-critical visible defects should be discussed with the manufacturer and included in the contract.

Other types of non-critical defects should be assessed to determine if they will affect the acceptability of the product.

Table 2
Non-critical visible defects: recommended AQL of 2.5

Defect	Description
Small coagula and embedded particles	Small coagula and embedded particles that are not considered to pose any risk of causing the condom to fail during use.
Faulty retention features (minor)	Uneven, partially distorted or otherwise minor defects in the internal and external retention features.

3. Imperfections

Occasionally, imperfections can be seen in female condoms that do not affect the performance or acceptability of the condom. A list of the more common imperfections that fall into this category is given in Table 3. No action should be taken when these imperfections are seen.

Table 3
Imperfections that are not regarded as defects

Phenomenon	Description
Microcoagula	For female condoms made from natural or synthetic latex, particles of rubber with dimensions less than 1 mm.
Flow lines	Lines of denser material in the film.

Table 3 *continued*

Phenomenon	Description
Distortion due to rolling at packing	Apparent variations in condom width due to stretching during rolling.
Bulges	Large bulges or distortion of the female condom during the freedom from holes test that are due to minor differences in thickness or product design (these may or may not have well defined edges).
Uneven lubricant	A portion of the sheath part of the female condom may appear dry. This can be regarded as an imperfection if it does not interfere with the insertion of the condom into the vagina.
Seam imperfections	Minor creases close to the seams that have no impact on the airburst properties of the condom.
Uneven colour	Minor streaking of the sheath or retention features and uneven colour or discoloration.

Note: Any visible hole anywhere in the female condom, including close to the external retention feature, is not acceptable. These defects are counted as holes if they can be seen before water is added to the condom, even if they are within 25 mm of the open end.

4. Packaging defects

The main packaging defects are listed in Table 4. Additional defects are sometimes detected only after shipment.

4.1 Individual containers

The requirements for individual containers are specified in Table A5.3 of the *WHO/UNFPA female condom generic specification*.

4.2 Consumer packs

No requirements for consumer packs are included in the *WHO/UNFPA female condom generic specification*. Purchasers should fully specify requirements in accordance with condom programme needs. Compliance should be assessed through visual inspection, using a sampling plan in accordance with ISO 2859-1 inspection level S-3. It is recommended that an AQL of 2.5 be applied for consumer pack requirements.

4.3 Cartons and marking

Purchasers should fully specify requirements in accordance with condom programme needs. Compliance should be assessed through visual inspection, using a sampling plan in accordance with ISO 2859-1 inspection level S-3. It is recommended that an AQL of 4.0 be applied for carton requirements.

Table 4
Packaging defects

Consumer packs	Cartons and markings
Empty or partially empty containers	Non-permanent markings
Discolouration	Empty cartons or cartons not filled to order
Delamination of the packaging film	Damaged cartons that may affect the integrity or the quality of the condoms inside
Illegible printing	Number of condoms not as specified
Missing manufacturer's name	Individual containers not as specified; packaging or packing materials not as specified, missing, damaged or non-serviceable
Incorrect or missing lot number	Illegible printing
Incorrect or missing date of manufacture	Missing manufacturer's name
Incorrect or missing expiry date	Incorrect or missing lot number
	Incorrect or missing date of manufacture
	Incorrect or missing expiry date
	Shipping cartons inadequately closed and secured
	Poor application of internal packaging and packing material; distorted intermediate packaging

Appendix 3

Guidelines on the assessment of odour and fragrances

Odour and fragrances are best assessed by a panel. There are certain guidelines that apply when assessing the odour and effectiveness of fragrances on condoms. Following these guidelines should help provide a more consistent level of odour assessment. Recommendations include the following.

- The panel should consist of between six and 10 individuals.
- Panellists should not wear perfume, smoke or be exposed to a strong odour on assessment days.
- Panellists should be trained and should undergo periodic assessments using appropriate reference odours and samples.
- Odour assessments should not be carried out in a factory or other environment in which a strong background odour may be present.
- Odour assessments should be done blind and in a random order, without the panellists being aware of the source of the samples.
- Adequate time should be allowed between samples for the panellists' olfactory sense to recover.
- To prevent fatigue, the number of samples evaluated in one session should be limited.
- An appropriate grading system should be developed to quantify the intensity, acceptability and type of odour. For example, odour intensity can be rated on a balanced scale from 0 (no perceptible odour) to 6 (extremely strong odour).
- Control samples should be included to allow comparisons to be made between different panels and different sessions.
- The time delay between opening a condom pack and smelling the condom can be critical. This time should be standardized and preferably short.

It is recommended that manufacturers retain unopened samples for reference purposes and to help resolve disputes. Retained samples should be kept for the duration of the shelf-life of the product and stored in line with the manufacturer's recommendations.

Annex 6

WHO Biowaiver List: proposal to waive in vivo bioequivalence requirements for WHO Model List of Essential Medicines immediate-release, solid oral dosage forms

Contents

1. Introduction and background

The World Health Organization (WHO) recognizes the possibility of waiving in vivo bioequivalence studies for immediate-release, solid oral dosage forms with active pharmaceutical ingredients (APIs) belonging to classes I and III according to the Biopharmaceutical Classification System (BCS), using comparative dissolution studies as surrogate proof of bioequivalence (*1*).

The WHO solubility classification, also referred to as the WHO Biowaiver List, is a tool for national regulatory authorities and pharmaceutical manufacturing companies, suggesting medical products that are eligible for a waiver from in vivo bioequivalence studies, which are usually necessary to establish the therapeutic equivalence with the originator (comparator). For exemption from an in vivo bioequivalence study, an immediate-release, multisource (generic) product should exhibit very rapid or rapid in vitro dissolution characteristics that are comparable to those of the reference product. A risk-based evaluation should also account for the excipients used in the formulation of the finished pharmaceutical product.

In addition, the present list replaces the existing literature-based compilation published in 2006 that is reported in the *Proposal to waive in vivo bioequivalence requirements for WHO Model List of Essential Medicines immediate-release, solid oral dosage forms* (*2*) based on data extracted from the public domain (that is, solubility data published by different authors using inconsistent experimental conditions).

The WHO Biowaiver Project is organized into study cycles. Previous and current cycles are summarized below in order to provide an outline of the project development:

- 2018: cycle I, also referred to as the pilot phase
- 2019: cycle II
- 2020: cycle III
- 2021: cycle IV
- 2022/2023: cycle V – The new results presented in this updated document (in Table A6.1, highlighted in bold) originate from cycle V.

2. WHO solubility classification for biowaiver

In 2017, the Fifty-second Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP) recommended that the WHO Secretariat revise the existing list using verifiable laboratory data that are generated according to consistent WHO criteria. Acting on this directive from the ECSPP, the WHO Secretariat initiated a multicentre research project, the Biowaiver Project, aimed

at experimentally determining the equilibrium solubility profile of medicines listed in the WHO Model List of Essential Medicines, using a harmonized approach (*3*).

To classify APIs according to the BCS framework, two critical properties are usually evaluated: (a) an API's aqueous solubility; and (b) its absorption or permeability. The initial phase of the WHO Biowaiver Project centres on unambiguous experimental assessment of the solubility parameter, as only highly soluble APIs are eligible for biowaiver. Once experimental solubility data are available, the exact BCS class assignment can be determined by utilizing quantitative absorption and permeability data. However, since high solubility within an aqueous environment is a necessary prerequisite for an API to be eligible for a waiver from bioequivalence studies, the current focus on solubility is justified to guide the regulatory decision.

The WHO classification should be considered a living document and is meant to be regularly updated in accordance with new quality requirements and progress in scientific development.

3. Scope

The aim of the WHO Biowaiver List is to enable an informed decision as to whether or not a waiver from in vivo bioequivalence studies could be granted safely according to the WHO guidance *Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability* (*1*).

The WHO Biowaiver List is expected to promote access to standard-quality essential medicines by shortening the time required to develop a multisource (generic) product, thereby supporting optimized pharmaceutical development.

The WHO Biowaiver List has been recognized by WHO regional and country offices as a "global good" – a normative work essential to strengthening global health in WHO Member States.

4. Methodology

The WHO *Protocol to conduct equilibrium solubility experiments for the purpose of Biopharmaceutics Classification System-based classification of active pharmaceutical ingredients for biowaiver* (*4*) is a tool available to all participants in this research. It was developed with the purpose of providing a harmonized methodology for equilibrium solubility experiments, thereby minimizing a potential source of variability among centres and studies.

APIs studied in cycles I, II, III, IV and V were received primarily as in-kind donations from pharmaceutical manufacturers supporting WHO

in this scientific work. Equilibrium solubility experiments were conducted by universities, official national control laboratories and WHO collaborating centres.

5. Results

Table A6.1 provides an overview of the APIs studied by WHO during cycles I, II, III, IV and V. The new APIs studied in cycle V are reported in bold. Fixed dose combination products, where all APIs contained in the combination drug product were studied as monocomponents (Table A6.1), are also reported in Table A6.2.

Table A6.1

WHO solubility classification of active pharmaceutical ingredients prioritized from the WHO Model List of Essential Medicines

Medicine[a]	Therapeutic area	Indication	Highest therapeutic dose (mg)	API PQ, EOI-PQ	WHO classification[b]
abacavir (sulfate)	Antiretrovirals	Antiretrovirals (HIV)	600	Yes	I/III
aciclovir	Antiviral medicines	Antiherpes medicines	800	No	II/IV*
amlodipine (besylate)	**Cardiovascular medicines**	**Antihypertensive medicines**	**10**	**No**	**I/III**
amoxicillin (trihydrate)	Antibacterials	Antibiotics	3000	Yes	II/IV*
azithromycin (dihydrate)	Antibacterials	Antibiotics	2000	Yes	II/IV
bisoprolol (fumarate)	**Cardiovascular medicines**	**Antihypertensive medicines**	**20**	**No**	**I/III****
cefixime (trihydrate)	Antibacterials	Antibiotics	400	No	II/IV
chloroquine phosphate	Antiprotozoal medicines	Antimalarial medicines	1000 mg salt (= 600 mg base)	No	I/III
clindamycin (hydrochloride)	**Antibacterials**	**Access group antibiotics**	**450**	**Yes**	**I/III**
codeine (phosphate hemihydrate)	Medicines for pain and palliative care	Opioid analgesics	60	No	I/III
cycloserine	Antibacterials	Antituberculosis medicines	1000	Yes	I/III

Table A6.1 *continued*

Medicine[a]	Therapeutic area	Indication	Highest therapeutic dose (mg)	API PQ, EOI-PQ	WHO classification[b]
daclatasvir (dihydrochloride)	Antiviral medicines	Medicines for hepatitis C	60	Yes	II/IV**
darunavir (ethanolate)	Antiviral medicines	Antiretrovirals (HIV)	800	Yes	II/IV**
dexamethasone	1. Gastrointestinal medicines 2. Immunomodulators and antineoplastics 3. Medicines for pain and palliative care	1. Antiemetic medicines 2. Acute lymphoblastic leukaemia, multiple myeloma 3. Medicines for other common symptoms in palliative care	1, 3: 0.5 to 10 mg a day, depending on the disease being treated 2: 40 mg	Yes	I/III**
dolutegravir	Antiviral medicines	Antiretrovirals (HIV)	50	Yes	II/IV**
doxycycline (hyclate)	1. Antiprotozoals 2. Antibacterials	1. Antimalarial medicines 2. Antibiotics (access group)	100	No	I/III**
efavirenz	Antiviral medicines	Antiretrovirals (HIV)	600	Yes	II/IV
emtricitabine	Antiviral medicines	Antiretrovirals (HIV)	200	Yes	I/III**
entecavir	Antiviral medicines	Antihepatitis medicines	1	Yes	I/III**
ethambutol (hydrochloride)	Antibacterials	Antituberculosis medicines	2000	Yes	I/III

Table A6.1 *continued*

Medicine[a]	Therapeutic area	Indication	Highest therapeutic dose (mg)	API PQ, EOI-PQ	WHO classification[b]
ethionamide	Antibacterials	Antituberculosis medicines	500–1000	Yes	II/IV*
fluconazole (form III)	**Antifungal medicines**	**Cryptococcosis and candidosis**	**800**	**Yes**	**I/III**
furosemide	Cardiovascular medicines	Medicines used in heart failure	80	No	II/IV
hydralazine (hydrochloride)	**Cardiovascular medicines**	**Antihypertensive medicines (pregnancy-induced hypertension)**	**100**	**No**	**I/III**
hydroxychloroquine (sulfate)	Disease-modifying anti-rheumatic drugs (DMARDs)	Lupus erythematosus	600	No	I/III**
isoniazid	Antibacterials	Antituberculosis medicines	300	Yes	I/III
lamivudine	Antiviral medicines	Antiretrovirals (HIV)	300	Yes	I/III
levonorgestrel	Medicines for reproductive health and perinatal care	Oral hormonal contraceptives	1.5	Yes	II/IV*
mefloquine (hydrochloride)	Antiprotozoal medicines	Antimalarial medicines	1250 (as hydrochloride)	Yes	II/IV

Table A6.1 *continued*

Medicine[a]	Therapeutic area	Indication	Highest therapeutic dose (mg)	API PQ, EOI-PQ	WHO classification[b]
methyldopa (sesquidrate)	Cardiovascular medicines	Pregnancy-induced hypertension	500	No	I/III
oseltamivir (phosphate)	Antiviral medicines	Influenza virus	75 (as phosphate)	Yes	I/III**
paracetamol	Medicines for pain and palliative care, antimigraine medicines	Non-opioids and non-steroidal anti-inflammatory medicines, treatment of acute attack	1000	No	I/III
primaquine (phosphate)	Antiprotozoal medicines	Antimalarial medicines (curative treatment of *Plasmodium vivax* and *P. ovale* infections)	15	Yes	I/III
proguanil (hydrochloride)	Antiprotozoal medicines	Antimalarial medicines	200	No	I/III
pyrimethamine	Antiprotozoal medicines	Antimalarial medicines	75	Yes	II/IV
quinine (sulfate)	**Antiprotozoal medicines**	**Antimalarial medicines**	**648**	**No**	**II/IV***
raltegravir (potassium)	Antiviral medicines	Antiretrovirals (HIV in pregnant women and in second line)	400	Yes	II/IV**

Table A6.1 *continued*

Medicine[a]	Therapeutic area	Indication	Highest therapeutic dose (mg)	API PQ, EOI-PQ	WHO classification[b]
ribavirin	**Antiviral medicines**	**Viral haemorrhagic fevers**	**600**	**Yes**	**I/III****
rifampicin	Antibacterials	Antituberculosis, antileprosy medicines	750	Yes	II/IV
sofosbuvir	Antiviral medicines	Medicines for hepatitis C	400	Yes	II/IV**
tenofovir disoproxil (fumarate)	Antiviral medicines	Antiretrovirals (HIV)	300	Yes	I/III**
valganciclovir	**Antiviral medicines**	**Cytomegalovirus retinitis (CMVr)**	**900**	**Yes**	**I/III****

API: active pharmaceutical ingredient; PQ: prequalification; EOI-PQ: expression of interest for prequalification.

Note: In the table, the new APIs studied in cycle V are reported in bold text.

[a] 23rd WHO Model List of Essential Medicines (2023) (*3*).

[b] According to the WHO *Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability* (*1*), APIs belonging to classes I and III are eligible for biowaiver. Once experimental permeability data are available, the exact class attribution will be possible (that is, either class I or class III). The present solubility characterization is already sufficient to provide an indication as to whether or not an API is eligible for biowaiver.

* Change in solubility class with respect to WHO 2006 classification.

** APIs characterized for the first time within the WHO Biowaiver Project.

Table A6.2
WHO solubility classification of fixed-dose combination products prioritized from the WHO Model List of Essential Medicines

Medicine[a]	Therapeutic area	Indication	Highest therapeutic dose (mg)	API PQ, EOI-PQ	WHO classification[b]
efavirenz + emtricitabine + tenofovir disoproxil (fumarate)	Antiviral medicines	Antiretrovirals (HIV)	600 + 200 + 300	Yes	II/IV**
efavirenz + lamivudine + tenofovir disoproxil (fumarate)	Antiviral medicines	Antiretrovirals (HIV)	600 + 300 + 300	Yes	II/IV**
emtricitabine + tenofovir disoproxil (fumarate)	Antiviral medicines	Antiretrovirals (HIV)	200 + 300	Yes	I/III**

API: active pharmaceutical ingredient; PQ: prequalification; EOI-PQ: expression of interest for prequalification.

[a] 23rd WHO Model List of Essential Medicines (2023) (3).

[b] According to the WHO *Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability* (*1*), APIs belonging to classes I and III are eligible for biowaiver. Once experimental permeability data are available, the exact class attribution will be possible (that is, either class I or class III). The present solubility characterization is already sufficient to provide an indication as to whether or not an API is eligible for biowaiver.

* Change in solubility class with respect to WHO 2006 classification.

** APIs characterized for the first time within the WHO Biowaiver Project.

Establishing a new WHO Biowaiver List that is based on unambiguous verifiable experimental solubility data is a critical project with tremendous public health implications for patients, procurers, United Nations agencies, national and regional regulatory authorities, payers, ethics committees and manufacturers worldwide. The involvement and support of WHO stakeholders and partners is highly encouraged and appreciated.

References

1. Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-seventh report. WHO Technical Report Series No. 1052, Annex 8. Geneva: World Health Organization; 2023.
2. Proposal to waive in vivo bioequivalence requirements for WHO Model List of Essential Medicines immediate-release, solid oral dosage forms. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fortieth report. WHO Technical Report Series No. 937, Annex 8. Geneva: World Health Organization; 2006.
3. WHO Model List of Essential Medicines, 23rd list. Geneva: World Health Organization; 2023.
4. Protocol to conduct equilibrium solubility experiments for the purpose of Biopharmaceutics Classification System-based classification of active pharmaceutical ingredients for biowaiver. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-third report. WHO Technical Report Series No. 1019, Annex 4. Geneva: World Health Organization; 2019.

Further reading

- Guidance for organizations performing in vivo bioequivalence studies. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fiftieth report. WHO Technical Report Series No. 996, Annex 9. Geneva: World Health Organization; 2016.
- General background notes on the list of international comparator pharmaceutical products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-first report. WHO Technical Report Series No. 1003, Annex 5. Geneva: World Health Organization; 2017.
- Guidance on the selection of comparator pharmaceutical products for equivalence assessment of interchangeable multisource (generic) products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-ninth report. WHO Technical Report Series No. 992, Annex 8. Geneva: World Health Organization; 2015.
- List of international comparator products (March 2024). Geneva: World Health Organization; 2024.

Annex 7

WHO guideline on Biopharmaceutics Classification System-based biowaivers

Background

A recommendation was made to the World Health Organization (WHO) Norms and Standards for Pharmaceuticals Team by the group of experts participating at the Joint Meeting on Regulatory Guidance for Multisource Products (1–3 November 2022), as well as by other parties, including the WHO Prequalification Team, to update the WHO Biopharmaceutics Classification System (BCS)-based biowaiver requirements (associated section within the overarching WHO *Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability)* (*1*) in order to harmonize those guidelines with those stated in the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guideline M9 on *Biopharmaceutics classification system-based biowaivers*, adopted in November 2019 (*2*).

The *WHO guideline on Biopharmaceutics Classification System-based biowaivers* will supersede the BCS-based biowaiver section of the WHO *Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability* (*1*). The purpose of this document is to provide recommendations to support the biopharmaceutics classification of active pharmaceutical ingredients (APIs) and the BCS-based biowaiver of bioequivalence studies for finished pharmaceutical products (FPPs).

Contents

This text is based on the ICH guideline M9: *Biopharmaceutics Classification System-based biowaivers*, November 2019.

1. Introduction

Two finished pharmaceutical products (FPPs) containing the same active moiety of the active pharmaceutical ingredient (API) are considered bioequivalent if their bioavailabilities (rate and extent of API absorption) after administration in the same molar dose lie within acceptable predefined limits. These limits are set to ensure comparable in vivo performance (that is, similarity in terms of safety and efficacy). In in vivo bioequivalence studies, the pivotal pharmacokinetic parameters maximum concentration (C_{max}) and area under the concentration time curve (AUC) are generally used to assess the rate and extent of drug absorption.

The Biopharmaceutics Classification System (BCS)-based biowaiver approach is intended to reduce the need for in vivo bioequivalence studies, as it can provide a surrogate for in vivo bioequivalence. In vivo bioequivalence studies may be exempted if an assumption of equivalence in in vivo performance can be justified by satisfactory in vitro data. The BCS is a scientific approach based on the aqueous solubility and intestinal permeability characteristics of the APIs. The BCS categorizes APIs into one of four BCS classes, as follows:

- class I: high solubility, high permeability
- class II: low solubility, high permeability
- class III: high solubility, low permeability
- class IV: low solubility, low permeability.

This guidance provides recommendations to support the biopharmaceutics classification of APIs and the BCS-based biowaiver of bioequivalence studies for FPPs. The BCS-based biowaiver principles may be applied to bioequivalence purposes not explicitly specified in the guideline, provided they can be supported by a thorough scientific rationale.

2. Scope

BCS-based biowaivers may be used to substantiate in vivo bioequivalence. Examples include the comparison between products used during clinical development through commercialization, post-approval changes, and applications for generic products in accordance with regional regulations.

The BCS-based biowaiver is only applicable to immediate-release, solid orally administered dosage forms or suspensions designed to deliver the API to the systemic circulation. FPPs, having a narrow therapeutic index, are excluded from consideration for a BCS-based biowaiver in this guidance. Fixed-dose combination products are eligible for a BCS-based biowaiver when all APIs

contained in the combination product meet the criteria, as defined in sections 4 and 5 of this guidance.

3. Glossary

The definitions given below apply to the terms used in this document. They have been aligned to the extent possible with the terminology in related WHO guidelines and good practices included in the WHO Quality Assurance of Medicines Terminology Database – List of Terms and related guidelines,[8] but may have different meanings in other contexts.

active pharmaceutical ingredient. Any substance or mixture of substances intended to be used in the manufacture of a pharmaceutical dosage form and that, when so used, becomes an active ingredient of that pharmaceutical dosage form. Such substances are intended to provide 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.

bioavailability. The rate at and extent to which the active moiety is absorbed from a pharmaceutical dosage form and becomes available at the sites of action. Reliable measurements of active pharmaceutical ingredient concentrations at the sites of action are usually not possible. The substance in the systemic circulation, however, is considered to be in equilibrium with the substance at the sites of action. Bioavailability can therefore be defined as the rate at and extent to which the active pharmaceutical ingredient or active moiety is absorbed from a pharmaceutical dosage form and becomes available in the systemic circulation. Based on pharmacokinetic and clinical considerations, it is generally accepted that, in the same subject, an essentially similar plasma concentration time course will result in an essentially similar concentration time course at the sites of action.

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

Biopharmaceutics Classification System. The Biopharmaceutics Classification System is a scientific framework for classifying active pharmaceutical ingredients

[8] https://www.who.int/publications/m/item/quality-assurance-of-medicines-terminology-database.

based on their aqueous solubility and intestinal permeability. When combined with the dissolution of the pharmaceutical product and the critical examination of the excipients of the pharmaceutical product, the Biopharmaceutics Classification System takes into account the major factors that govern the rate and extent of active pharmaceutical ingredient absorption (exposure) from immediate-release oral solid dosage forms: excipient composition, dissolution, solubility and intestinal permeability.

biowaiver. The regulatory pharmaceutical product approval process whereby the dossier (application) is approved based on evidence of equivalence rather than through in vivo equivalence testing.

comparator product. The comparator product is a pharmaceutical product with which the multisource product is intended to be interchangeable in clinical practice. The comparator product will normally be the innovator product for which efficacy, safety and quality have been established. If the innovator product is no longer marketed in the jurisdiction, the selection principle, as described in *Guidance on the selection of comparator pharmaceutical products for equivalence assessment of interchangeable multisource (generic) products*,[9] should be used to identify a suitable alternative comparator product.

dosage form. The form of the finished pharmaceutical product (for example, tablet, capsule, suspension or suppository).

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

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

fixed-dose combination product. A finished pharmaceutical product that contains two or more active pharmaceutical ingredients.

generic product. See "multisource pharmaceutical product".

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

[9] Guidance on the selection of comparator pharmaceutical products for equivalence assessment of interchangeable multisource (generic) products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-ninth report. WHO Technical Report Series No. 992, Annex 8. Geneva: World Health Organization; 2015.

interchangeable pharmaceutical product. A product that is therapeutically equivalent to a comparator product and can be interchanged with the comparator in clinical practice.

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

4. Biopharmaceutics classification of the API

BCS-based biowaivers are applicable to FPPs where the APIs exhibit high solubility and either high permeability (BCS class I) or low permeability (BCS class III).

A biowaiver is applicable when the APIs in the test and comparator products are identical. A biowaiver may also be applicable if test and comparator products contain different salts, provided that both belong to BCS class I (high solubility and high permeability). A biowaiver is not applicable when the test product contains an ester, ether, isomer, mixture of isomers, complex or derivative of an API different from that of the comparator product, since these differences may lead to different bioavailabilities not deducible by means of experiments used in the BCS-based biowaiver concept. Prodrugs may be considered for a BCS-based biowaiver when absorbed as the prodrug.

4.1 Solubility

An API is classified as highly soluble if the highest single therapeutic dose is completely soluble in 250 millilitres (mL) or less of aqueous media over the pH range 1.2–6.8 at 37 (± 1) °C.

The applicant is expected to establish experimentally the solubility of the API over the pH range 1.2–6.8 at 37 (± 1) °C . At least three pHs within this range, including buffers at pH 1.2, 4.5 and 6.8, should be evaluated. In addition, solubility at the pH of lowest solubility of the API should be evaluated if it is within the specified pH range.

Solubility should be evaluated by a method appropriate to the properties of the API.

Equilibrium solubility experiments may be performed using a shake flask technique or an alternative method, if justified. Small volumes of solubility media may be employed if the available experimental apparatus will permit it. The pH for each test solution should be measured after the addition of the API and at the end of the equilibrium solubility study to ensure that the solubility measurement is conducted under the specified pH. The experiment should be

conducted over a suitable time frame to reach equilibrium and the pH should be adjusted during this period as necessary.

Alternatively, when an equilibrium solubility study is not feasible due to the high amount of API required for the experiment, or when it is not possible to maintain the pH of the medium with pharmacopoeial buffers, solubility experiments where the highest therapeutic single dose (or a slightly higher amount to avoid recovery problems in the experiments) is examined in a 250 mL volume, or a proportionally smaller amount examined in a proportionally smaller volume of buffer, can be considered (*3*).

The lowest measured solubility over the pH range 1.2–6.8 will be used to classify the API.

A minimum of three replicate determinations at each solubility condition or pH using appropriate pharmacopoeial media is necessary to demonstrate solubility using a suitably validated method.

In addition, adequate stability of the API in the solubility media covering the gastrointestinal transit time should be demonstrated. In cases where the API is not stable, with >10% degradation over the extent of the solubility assessment, solubility cannot be adequately determined, and thus the API cannot be classified. In addition to experimental data, literature data may be provided to substantiate and support solubility determinations, keeping in mind that peer-reviewed articles may not contain the necessary details of the testing to make a judgement regarding the quality of the studies.

4.2 Permeability

The assessment of permeability should preferentially be based on the extent of absorption derived from human pharmacokinetic studies (for example, absolute bioavailability or mass balance).

High permeability can be concluded when the absolute bioavailability is ≥ 85%. High permeability can also be concluded if ≥ 85% of the administered dose is recovered in urine as unchanged (parent drug) or as the sum of parent drug, phase 1 oxidative and phase 2 conjugative metabolites. Regarding metabolites in faeces, only oxidative and conjugative metabolites can be considered. Metabolites produced through reduction or hydrolysis should not be included unless it can be demonstrated that they are not produced prior to absorption (for example, by microbial action within the gastrointestinal tract). An unchanged drug in faeces cannot be counted towards the extent of absorption unless appropriate data support the conclusion that the amount of parent drug in faeces to be accounted for absorbed drug material is from biliary excretion, intestinal secretion or originates from an unstable metabolite (such as glucuronide, sulphate or N-oxide that has been converted back to the parent by the action of microbial organisms).

Human in vivo data derived from published literature (for example, product knowledge and bioavailability studies) may be acceptable, keeping in mind that peer-reviewed articles may not contain the necessary details of the testing to make a judgement regarding the quality of the results.

Permeability can be also assessed by validated and standardized in vitro methods using Caco 2 cells (see Appendix 1). The results from Caco-2 permeability assays should be discussed in the context of available data on human pharmacokinetics. If high permeability is inferred by means of an in vitro cell system, permeability independent of active transport should be proven as outlined in Appendix 1 on Caco 2 cell permeability assay method considerations.

If high permeability is not demonstrated, the API is considered to have low permeability for BCS classification purposes.

4.3 API stability in the gastrointestinal tract

Additional data to document the API's stability in the gastrointestinal tract should be provided if mass balance studies are used to demonstrate high permeability, unless ≥ 85% of the dose is recovered as an unchanged drug in urine. Demonstration of stability in the gastrointestinal tract is required if in vitro Caco-2 studies are used to support high permeability. Stability in the gastrointestinal tract may be documented using pharmacopoeial or simulated gastric and intestinal fluids. Other relevant methods may be used with suitable justification. API solutions should be incubated at 37 °C for a period that is representative of the in vivo contact of the API with these fluids (that is, 1 hour in gastric fluid and 3 hours in intestinal fluid). API concentrations should then be determined using a suitably validated analytical method. Significant degradation (> 10%) of an API precludes BCS high-permeability classification.

5. Eligibility of an FPP for a BCS-based biowaiver

An FPP is eligible for a BCS-based biowaiver provided that the APIs satisfy the criteria regarding solubility and permeability (BCS class I and class III), the FPP is an immediate-release oral dosage form with systemic action, and the FPP is the same dosage form and strength as the comparator product.

FPPs with buccal or sublingual absorption are not eligible for a BCS-based biowaiver application. Furthermore, the BCS-based biowaiver approach is applicable only when the mode of administration includes water. If administration without water is also intended (for example, orodispersible products), a bioequivalence study in which the product is dosed without water should be conducted.

In order for an FPP to qualify for a BCS-based biowaiver, criteria with respect to the composition (excipients) and in vitro dissolution performance of the FPP should be satisfied. The FPP acceptance criteria are described in subsections 5.1 and 5.2 below.

5.1 Excipients

Ideally, the composition of the test product should mimic that of the comparator product. However, where excipient differences exist, they should be assessed for their potential to affect in vivo absorption. This should include consideration of the API properties as well as excipient effects. To be eligible for a BCS-based biowaiver, the applicant should justify why the proposed excipient differences will not affect the absorption profile of the API under consideration (that is, rate and extent of absorption, using a mechanistic and risk-based approach). The decision tree for performing such an assessment is outlined in Figures 1 and 2 in Appendix 2.

The possible effects of excipients on aspects of in vivo absorption such as solubility, gastrointestinal motility, transit time and intestinal permeability, including transporter mechanisms, should be considered. Excipients that may affect absorption include sugar alcohols, such as mannitol, sorbitol and surfactants (for example, sodium lauryl sulfate). The risk that a given excipient will affect the absorption of an API should be assessed mechanistically by considering:

- the amount of excipient used;
- the mechanism by which the excipient may affect absorption;
- absorption properties (rate, extent and mechanism of absorption) of the API.

The amount of excipients that may affect absorption in the test and comparator formulations should be addressed during product development, such that excipient changes are kept to a minimum. Small amounts included in the tablet coating, or levels below documented thresholds of effect for the specific API, are of less concern.

By definition, BCS class I APIs are highly absorbed and have neither solubility- nor permeability-limited absorption. Therefore, they generally represent a low-risk group of compounds in terms of the potential for excipients to affect absorption, compared to other BCS classes. Consideration of excipient effects for BCS class I-containing FPPs should focus on potential changes in the rate or extent of absorption. For example, if it is known that the API has high permeability due to active uptake, excipients that can inhibit uptake transporters are likely to be of concern. For BCS class I APIs that exhibit slow absorption, the potential for a given excipient to increase absorption rate should also be

considered. These excipients that may affect absorption should be considered as detailed in Fig. 1, Appendix 2.

For BCS class I APIs, qualitative and quantitative differences in excipients are permitted, except for excipients that may affect absorption, which should be qualitatively the same and quantitatively similar (that is, within ± 10% of the amount of excipient in the comparator product). Additionally, the cumulative difference for excipients that may affect absorption should be within ± 10%.

BCS class III APIs are considered to be more susceptible to the effects of excipients. These APIs are not considered highly permeable, and may have site specific absorption, so there are a greater number of mechanisms through which excipients can affect their absorption than for BCS class I APIs. For BCS class III APIs, all of the excipients should be qualitatively the same and quantitatively similar (except for film coating or capsule shell excipients). Excipients that may affect absorption should be qualitatively the same and quantitatively similar (that is, within ± 10% of the amount of excipient in the comparator product), and the cumulative difference for these excipients should be within ± 10%. The acceptable differences in excipients are defined in Table A7.1. Examples of acceptable differences in excipients are shown in Appendix 2. Differences in colorants and flavouring may be permitted when these constitute very small amounts of the formulation. For the types of excipients not listed in Table A7.1, the same rule should be applied as for the excipients that may affect absorption.

It is known that in some cases the absolute amount of an excipient present in the gastrointestinal tract is relevant to whether that excipient will exert an effect on absorption, for example, an effect on relevant transporters. Since the allowable differences for BCS class III APIs defined in Table A7.1 are based on percentage difference relative to core weight (w/w), it is possible for absolute amounts of excipients in two formulations to differ significantly while still maintaining proportionality within the limits expressed in Table A7.1. Control over differences in absolute amount of excipients where it is known that effects on absorption can be observed (for example, amounts of surfactants) is provided in Table A7.1; however, possible effects of other excipients is not controlled. Therefore, to control for possible excipient effects based on absolute amount differences between products, the total core weight of the proposed product should not deviate by more than 20% from the total core weight of the comparator product.

It is recognized that there are limitations to the application of Table A7.1 (for example, difficulty in determining the film coat weight for the comparator product). Table A7.1 is provided as a target to give clarity to applicants. Deviations from this will require appropriate justification, based on the principles described above.

Table A7.1
Criteria expected to demonstrate quantitative similarity for products containing BCS class III APIs

Within the context of quantitative similarity, differences in excipients for FPPs containing BCS class III APIs should not exceed the following targets:	
Excipient class	Percentage of the amount of excipient in the comparator
Excipients that may affect absorption Per excipient: Sum of differences:	 10% 10%
	Percentage difference relative to core weight[a] (w/w)
Major excipients types: Filler Disintegrant Starch Other Binder Lubricant Stearates Other Glidant Talc Other	 10% 6% 2% 1% 0.5% 2% 2% 0.2%
Total % change permitted for all excipients (including excipients that may affect absorption):	10%

[a] Core does not include tablet film coat or capsule shell.

BCS-based biowaivers are applicable to fixed-dose combination products that are the same dosage form and strength. Fixed-dose combination product formulations containing only BCS class I APIs should meet criteria regarding excipients for a BCS class I API. Fixed-dose combination product formulations containing only BCS class III APIs, or BCS class I and BCS class III APIs, should meet criteria regarding excipients for a BCS class III API.

5.2 In vitro dissolution

When applying the BCS-based biowaiver approach, comparative in vitro dissolution tests should be conducted using one batch representative of the proposed commercial manufacturing process for the test product relative to the comparator product. The test product should originate from a batch of at least one tenth of production scale or 100 000 units, whichever is greater, unless otherwise justified. During a (clinical) development phase, smaller batch sizes may be acceptable, if justified. The API content or potency of the comparator product should be close to the label claim, and the difference in API content or potency between the test and comparator products should be not more than 5%. The comparative in vitro dissolution tests should use pharmacopoeial apparatus and suitably validated analytical methods.

The following conditions should be employed in the comparative dissolution studies to characterize the dissolution profile of the product.

- Apparatus: paddle or basket.
- Volume of dissolution medium: 900 mL or less (it is recommended to use the volume selected for the quality control test).
- Temperature of the dissolution medium: 37 (± 1) °C.
- Agitation: paddle apparatus – 50 revolutions per minute (rpm); basket apparatus – 100 rpm.
- At least 12 units of comparator and test product should be used for each dissolution profile determination.
- Media: three buffers: pH 1.2, pH 4.5, and pH 6.8. Pharmacopoeial buffers should be employed. Additional investigation may be required at the pH of minimum solubility (if different from the buffers above).
- Organic solvents are not acceptable and no surfactants should be added.
- The sampling intervals employed in dissolution studies should be short for a scientifically sound comparison of the performance of the test and comparator products (for example, 5, 10, 15, 20 and 30 minutes).
- Samples should be filtered during collection, unless in situ detection methods are used. For this purpose, filters should be employed in line, at the end of the sampling probe, or both during sample collection.
- The pH of each dissolution medium should be maintained throughout the test. The pH of each dissolution medium should be

measured at the beginning (prior to introduction of the testing unit) and at the end of each dissolution test.

- For gelatin capsules, or tablets with gelatin coatings where cross-linking has been demonstrated, the use of enzymes may be acceptable, if appropriately justified.

Dissolution profiles for the test and comparator products should be generated in the same laboratory by the same staff at the same time using the same equipment. Compilation of historical data is not acceptable.

When high variability or coning is observed in the paddle apparatus at 50 rpm for both comparator and test products, the use of the basket apparatus at 100 rpm is recommended. Additionally, alternative methods (such as the use of sinkers or other appropriately justified approaches) may be considered to overcome issues such as coning, if scientifically substantiated. All experimental results should be provided.

To qualify for a BCS-based biowaiver for BCS class I APIs, both the test product and comparator product should display either very rapid (≥ 85% for the mean percent dissolved in ≤ 15 minutes) in vitro dissolution characteristics, or rapid (≥ 85% for the mean percent dissolved in ≤ 30 minutes) and similar in vitro dissolution characteristics (that is, based on f2 comparison), under all of the defined conditions. In cases where one product has rapid dissolution and the other has very rapid dissolution, similarity of the profiles should be demonstrated as below.

For the comparison of dissolution profiles, where applicable, the similarity factor (f2) should be estimated by using the following formula:

$$f2 = 50 \cdot \log \{[1 + (1/n)\Sigma_{t=1}^{n} (R_t - T_t)^2]^{-0.5} \cdot 100\}.$$

In this equation f2 is the similarity factor, n is the number of time points, R_t is the mean percent comparator API dissolved at time t after initiation of the study, and T_t is the mean percent test API dissolved at time t after initiation of the study.

The evaluation of the f2 is based on the following conditions.

- A minimum of three time points (zero excluded).
- The time points should be the same for the two products.
- Mean of the individual values for every time point for each product.
- Not more than one mean value of ≥ 85% dissolved for either of the products.
- To allow the use of mean data, the coefficient of variation (%CV) should not be more than 20% at early time points (up to 10 minutes) and should not be more than 10% at other time points.

Two dissolution profiles are considered similar when the f2 value is ≥ 50. When both test and comparator products demonstrate that ≥ 85% of the labelled amount of the API is dissolved in 15 minutes, comparison with an f2 test is unnecessary and the dissolution profiles are considered similar. When the %CV for the mean data is too high based on the requirements listed above, f2 calculation is considered unreliable. In such cases, an alternative method for the assessment of similarity in dissolution profiles, such as the bootstrap 90% confidence interval of expected f2, should be employed in keeping with regional expectations for dissolution similarity assessment.

To qualify for a BCS-based biowaiver for BCS class III APIs, both the test product and comparator product should display very rapid (≥ 85% for the mean percent dissolved in ≤ 15 minutes) in vitro dissolution characteristics under the defined conditions.

For fixed-dose combination product formulations, dissolution profiles should meet the criteria for all APIs in the fixed-dose combination product. Fixed-dose combination product formulations containing only BCS class I APIs should meet dissolution criteria for a BCS class I API. Fixed-dose combination product formulations containing only BCS class III APIs should meet dissolution criteria for a BCS class III API. For fixed-dose combination products containing both BCS class I and BCS class III APIs, the dissolution criteria for the applicable BCS class for each component should be applied.

For products with more than one strength, the BCS approach should be applied for each strength. It is required that test and comparator product dissolution profiles are compared at each strength.

6. Documentation

The applicant should provide complete information on the critical quality attributes of the test APIs and FPP and as much information as possible for the comparator product, including polymorphic form and enantiomeric purity; and any information on bioavailability or bioequivalence problems with the APIs or FPP, including literature surveys and applicant-derived studies. All study protocols and reports should be provided. Information on validated test methods should be appropriately detailed according to current regulatory guidance and policies.

The reporting format should include tabular and graphical presentations showing individual and mean results and summary statistics.

The report should include all excipients and their qualitative and, where appropriate, quantitative differences between the test and comparator products.

A full description of the analytical methods employed, including validation and qualification of the analytical parameters, should be provided. A detailed description of all test methods and media, including test and comparator

batch information (unit dose (strength and assay), batch number, manufacturing date, batch size and, where known, expiry date) should also be provided. The dissolution report should include a thorough description of experimental settings and analytical methods, including information on the dissolution conditions such as apparatus, de-aeration, filtration during sampling and volume.

In addition, complete information with full description of the methods applied should be provided for the Caco-2 cell permeability assay method, if applicable (see Appendix 1).

References

1. Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-first report. WHO Technical Report Series No. 1003, Annex 6. Geneva: World Health Organization; 2017 (https://www.who.int/publications/m/item/annex-6-trs-1003 accessed 4 February 2024).
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Appendix 1

Caco-2 cell permeability assay method considerations

Permeability assays employing cultured Caco-2 epithelial cell monolayers derived from a human colon adenocarcinoma cell line are widely used to estimate intestinal drug absorption in humans. Caco-2 cells undergo spontaneous morphological and biochemical enterocytic differentiation and express cell polarity with an apical brush border, tight intercellular junctions and several active transporters as in the small intestine. Due to a potential for low or absent expression of efflux (for example, P-gp, BCRP, MRP2) and uptake (for example, PepT1, OATP2B1, MCT1) transporters, the use of Caco-2 cell assays as the sole data in support of high permeability for BCS classification is limited to passively transported drugs (see "Assay considerations" below).

Method validation

The suitability of the Caco-2 cell assays for Biopharmaceutics Classification System (BCS) permeability determination should be demonstrated by establishing a rank-order relationship between experimental permeability values and the extent of drug absorption in human subjects using model drugs of zero, low (< 50%), moderate (50–84%), and high (≥ 85%) permeability. A sufficient number of model drugs are recommended for the validation to characterize high, moderate and low permeability (a minimum of five for each), plus a zero-permeability marker; examples are provided in Table 1. Further, a sufficient number (minimum of three) of cell assay replicates should be employed to provide a reliable estimate of drug permeability. The established relationship should permit differentiation between low , moderate- and high-permeability drugs.

Caco-2 cell monolayer integrity should be confirmed by comparing transepithelial electrical resistance (TEER) measures or other suitable indicators, prior to and after an experiment.

In addition, cell monolayer integrity should be demonstrated by means of compounds with proven zero permeability (refer to Table 1).

Reporting of the method validation should include a list of the selected model drugs along with data on extent of absorption in humans (mean, standard deviation, coefficient of variation) used to establish suitability of the method, permeability values for each model drug (mean, standard deviation, coefficient of variation), permeability class of each model drug, and a plot of the extent of absorption as a function of permeability (mean ± standard deviation or 95%

confidence interval), with identification of the high-permeability class boundary and selected high-permeability model drug used to classify the test API.

In addition, a description of the study method, drug concentrations in the donor fluid, description of the analytical method and equation used to calculate permeability should be provided. Additionally, information on efflux potential (for example, bidirectional transport data) should be provided for a known substrate.

Table 1
Examples of model APIs for permeability assay method validation

Group	API
High permeability ($f_a \geq 85\%$)	Antipyrine Caffeine Ketoprofen Naproxen Theophylline Metoprolol Propranolol Carbamazepine Phenytoin Disopyramide Minoxidil
Moderate permeability ($f_a = 50–84\%$)	Chlorpheniramine Creatinine Terbutaline Hydrochlorothiazide Enalapril Furosemide Metformin Amiloride Atenolol Ranitidine
Low permeability ($f_a < 50\%$)	Famotidine Nadolol Sulpiride Lisinopril Acyclovir Foscarnet Mannitol Chlorothiazide Polyethylene glycol 400 Enalaprilat

Table 1 *continued*

Group	API
Zero permeability	FITC-Dextran Polyethylene glycol 4000 Lucifer yellow Inulin Lactulose
Efflux substrates	Digoxin Paclitaxel Quinidine Vinblastine

Assay considerations

Passive transport of the test compound should be demonstrated. This may be verified using a suitable assay system that expresses known efflux transporters, such as by demonstrating independence of measured in vitro permeability on initial drug concentration, for example, 0.01, 0.1 and 1 times the highest strength dissolved in 250 mL, or on transport direction (efflux ratio, such as ratio of apparent permeability (Papp) between the basolateral-to-apical and apical-to-basolateral directions < 2 for the selected drug concentrations).

$$\text{Efflux ratio} = P_{appBL \rightarrow AP} / P_{appAP \rightarrow BL}.$$

Functional expression of efflux transporters should be verified by using bidirectional transport studies demonstrating asymmetric permeability of selected efflux transporter substrates (for example, digoxin, vinblastine or rhodamine 123, at non-saturating concentrations).

The test API concentrations used in the permeability studies should be justified. A validated Caco-2 method used for drug permeability determinations should employ conditions established during the validation and include a moderate-permeability and a high-permeability model drug in the donor fluid along with the test drug as internal standards to demonstrate consistency of the method. The choice of internal standards should be based on compatibility with the test drug (that is, they should not exhibit any significant physical, chemical or permeation interactions). The permeability of the internal standards may be determined following evaluation of the test drug in the same monolayers or monolayers in the same plate, when it is not feasible to include internal standards in the same cell culture well as the test drug permeability evaluation. The permeability values of the internal standards should be consistent between different tests, including those conducted during method validation. Acceptance

criteria should be set for the internal standards and model efflux drug. Mean drug and internal standards recovery at the end of the test should be assessed. For recoveries < 80%, a mass balance evaluation should be conducted including measurement of the residual amount of drug in the cell monolayer and testing apparatus.

Evaluation of the test drug permeability for BCS classification may be facilitated by selection of a high-permeability internal standard with permeability in close proximity to the moderate- or high-permeability class boundary. The test drug is considered highly permeable when its permeability value is equal to or greater than that of the selected internal standard with high permeability.

Information to support high permeability of a test drug (mean, standard deviation, coefficient of variation) should include permeability data on the test API, the internal standards, in vitro gastrointestinal stability information, and data supporting passive transport mechanism.

Appendix 2

Further information on the assessment of excipient differences

Fig. 1
Biopharmaceutics Classification System class I active pharmaceutical ingredients

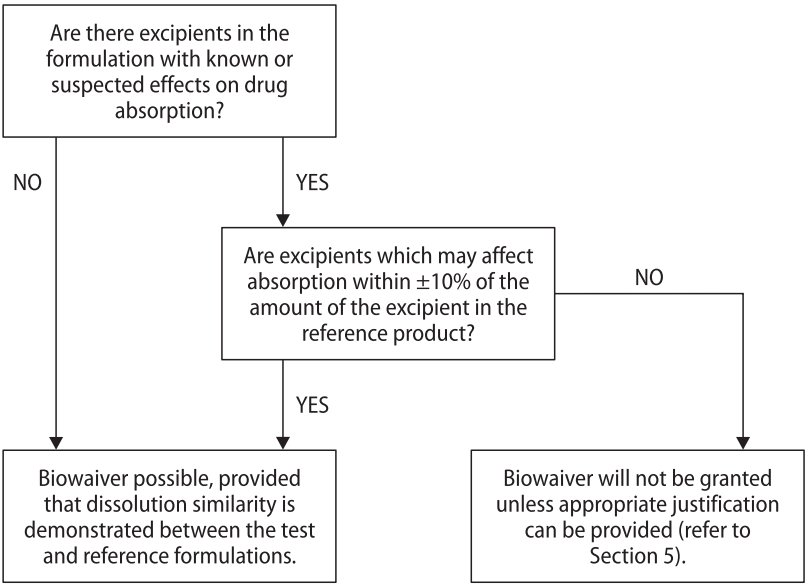
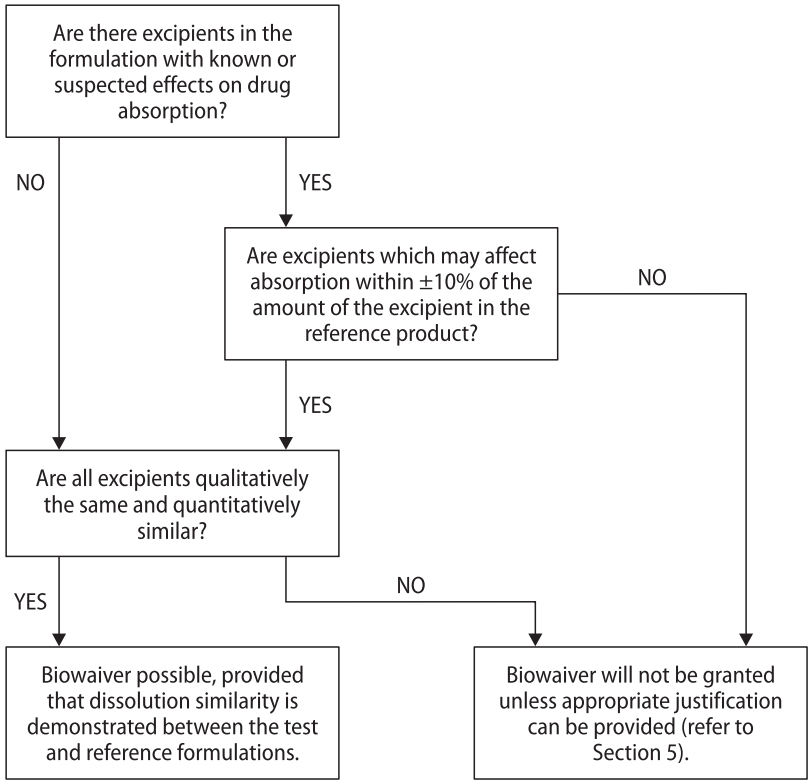


Fig. 2
Biopharmaceuticals Classification System class III active pharmaceutical ingredients



Examples of differences in excipients

Example 1. BCS class I biowaiver

The formulation of the test product is qualitatively the same as that of the comparator product. Additionally, it contains sorbitol, an excipient with known or suspected effects on API absorption. The amount of sorbitol in the test formulation is within the permitted range of 45 milligrams (mg) to 55 mg based on the amount of sorbitol in the comparator formulation (that is, 50 mg ± 10%).

Component	Amount (mg) comparator	Amount (mg) test
API	100	100
Microcrystalline cellulose (filler)	100	95

Table *continued*

Component	Amount (mg) comparator	Amount (mg) test
Sorbitol (filler)	50	55
HPMC (binder)	10	10
Talc (glidant)	5	5
Total	265	265

Example 2. BCS class III biowaiver

The test formulation is qualitatively the same as the comparator formulation. Additionally, it contains sorbitol, an excipient with known or suspected effects on API absorption. The amount of sorbitol in the test formulation is within the permitted range of 9 mg to 11 mg based on the amount of sorbitol in the comparator formulation (that is, 10 mg ± 10%). Any differences in the amount of other excipients are within the criteria outlined in Table A7.1, subsection 5.1.

Component	Comparator product		Test product		Absolute % difference relative to core weights
	Composition (mg)	Proportion relative to core weight (%w/w)	Composition (mg)	Proportion relative to core weight (%w/w)	
API	100	49.3%	100	46.5%	–
Lactose monohydrate (filler)	85	41.9%	97	45.1%	3.2%
Sorbitol (filler)	10	4.9%	9	4.2%	0.7%
Croscarmellose sodium (disintegrant)	6	3.0%	7	3.3%	0.3%
Magnesium stearate (lubricant)	2	1.0%	2	0.9%	0.1%
Total	**203**	**100%**	**215**	**100%**	
				Total change	4.3%

Example 3. Ineligible BCS class III biowaiver

The formulation of the test product is qualitatively the same as that of the comparator product. Further, the quantitative differences in excipient content between the products, based on percentage of core weight, satisfy the limits expressed in Table A7.1, subsection 5.1. However, the total core weight of the proposed product deviates by more than 20% from the total core weight of the comparator product, making the product ineligible for a biowaiver.

Component	Comparator product		Test product		Absolute % difference relative to core weights
	Composition (mg)	Proportion relative to core weight (%w/w)	Composition (mg)	Proportion relative to core weight (%w/w)	
API	8	8.0%	8	0.8%	–
Lactose monohydrate (filler)	75	75.0%	802	80.2%	5.2%
Silicon dioxide (glidant)	2	2.0%	20	2.0%	0.0%
Croscarmellose sodium (disintegrant)	13	13.0%	150	15.0%	2.0%
Magnesium stearate (lubricant)	2	2.0%	20	2.0%	0.0%
Total	**100**	**100%**	**1000**	**100%**	
				Total change	**7.2%**

Appendix 3

Equilibrium solubility experiments for the purpose of classification of active pharmaceutical ingredients according to the Biopharmaceutics Classification System

Introduction

The Biopharmaceutics Classification System (BCS) was proposed in 1995 by Amidon et al. (*1*). It is a scientific framework that divides active pharmaceutical ingredients (APIs) into four groups according to their solubility and permeability. The recommended method for determination of the solubility is described below. of the condom. If a defect can be expected to affect the performance, safety or acceptability of the condom, it should be classified as a critical defect.

Recommendations for conducting experiments for assessing solubility of APIs

Prior to the experiment, a solubility study protocol should be prepared describing the equipment and procedures in detail. The protocol should include, for example, methods of sample preparation, experimental conditions such as temperature, method and rate of agitation, method of solid/solution separation of the API, and method of sample analysis. The source and purity of the API to be used in the study should also be recorded in the protocol, as well as the methods that will be used to characterize the material.

Characterization of the solid API should be completed prior to the investigation. The depth of the characterization will depend on the existing knowledge of the solid-state properties of the API in question. For example, if it has been established that the API exists as a single polymorphic form, then less solid-state characterization is needed. In some cases, it may be necessary to characterize the solid starting material as well as the solid residue remaining after equilibrium has been reached and sampling has been completed. For a discussion of the factors that should be considered when planning the solid-state characterization studies, see Avdeef et al. (*2*).

Solubility experiments should preferably be carried out with the shake flask method, which is used to determine equilibrium solubility, although other methods are possible if justified. A discussion of the factors that should be considered when designing the study can be found in Avdeef et al. (*2*). The conditions employed should be fully described in the study protocol.

The pH solubility profile of the API should be determined over the pH range of 1.2–6.8 at 37 (± 1) °C. Measurements should be made in triplicate under

at least three pH conditions, pH 1.2, 4.5 and 6.8, as well as at the pH of any known solubility minima in aqueous media within that pH range. Pharmacopoeial buffer solutions are recommended for use in solubility experiments – see, for example, Chapter 5.5 "Dissolution test for solid oral dosage forms" in *The International Pharmacopoeia* (*3*). Factors such as common ion effects and ionic strength should be considered when selecting buffers for the study. The pH should be verified after addition of the API and at the end of the experiment with a calibrated pH meter. Samples should be taken at several time points to ensure that the equilibrium solubility has been reached. Strong agitation followed by a period of sedimentation is suggested, to achieve solubility equilibrium.

A description of the methods of solid/solution separation employed, including details such as filter type and pore size or centrifugation speed, should be provided in the study protocol. Sedimentation, centrifugation and filtration are the standard methods of separation. The factors described by Avdeef et al. (*2*) should be considered when selecting the most appropriate approach for the API under study.

A validated, stability-indicating analytical method should be employed for determination of the solubility of APIs, for example, chromatography– see Chapter 1.14.1 "Chromatography" in *The International Pharmacopoeia* (*3*) – or an alternative, validated stability-indicating assay.

A study report should be created after the experiment detailing the actual experimental conditions, results (raw data plus mean values with standard deviations), and any observations, for example, the degradation of an API as a result of pH or buffer composition. The section describing the experimental conditions should include initial and equilibrium pH of solutions and de facto buffer concentrations. If applicable, filter adsorption studies should be documented. Any deviations from the protocol should be noted and justified.

The dose–solubility ratio is calculated as follows: highest single therapeutic dose (mg) divided by solubility (mg/mL). An API is considered highly soluble when the highest single therapeutic dose is soluble in 250 mL or less of aqueous media over the pH range 1.2–6.8, that is, the dose–solubility ratio is ≤ 250.

References

1. Amidon GL, Lennemas H, Shah VP, Crison JR. A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability. Pharm Res. 1995;12:413–20.
2. Avdeef A, Fuguet E, Llinàs A, Ràfols C, Bosch E, Völgyi G et al. Equilibrium solubility measurement of ionizable drugs: consensus recommendations for improving data quality. ADMET & DMPK. 2016;4:117–78.

3. Health products policy and standards. In: The International Pharmacopoeia, 11th edition. Geneva: World Health Organization; 2023 (https://www.who.int/teams/health-product-policy-and-standards/standards-and-specifications/norms-and-standards-for-pharmaceuticals/international-pharmacopoeia accessed 5 February 2024).

Annex 8

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

Republication of *Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability*, WHO Technical Report Series No. 1003, Annex 6.

Background

Following the publication of the *WHO guideline on Biopharmaceutics Classification System-based biowaivers*, the relevant sections from this guideline have been removed, including the appendix *Equilibrium solubility experiments for the purpose of classification of active pharmaceutical ingredients according to the Biopharmaceutics Classification System*.

Contents

1. Introduction

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

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

All pharmaceutical products, including multisource products, should be used in a country only after approval by the national or regional authority.

Regulatory authorities should require the documentation of a multisource pharmaceutical product to meet the following:

- good manufacturing practices
- quality control specifications
- pharmaceutical product interchangeability.

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

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

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

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

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

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

2. Glossary

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

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

pharmaceutical dosage form and becomes available in the systemic circulation. Based on pharmacokinetic and clinical considerations, it is generally accepted that, in the same subject, an essentially similar plasma concentration time course will result in an essentially similar concentration time course at the sites of action.

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

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

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

biowaiver. The regulatory pharmaceutical product approval process whereby the dossier (application) is approved based on evidence of equivalence rather than through in vivo equivalence testing.

comparator product. The comparator product is a pharmaceutical product with which the multisource product is intended to be interchangeable in clinical practice. The comparator product will normally be the innovator product for which efficacy, safety and quality have been established. If the innovator product is no longer marketed in the jurisdiction, the selection principle, as described in *Guidance on the selection of comparator pharmaceutical products for equivalence assessment of interchangeable multisource (generic) products*, [10] should be used to identify a suitable alternative comparator product.

dosage form. The form of the finished pharmaceutical product (for example, tablet, capsule, suspension or suppository).

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

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

fixed-dose combination. A combination of two or more active pharmaceutical ingredients in a fixed ratio of doses. This term is used generically to mean a particular combination of active pharmaceutical ingredients 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. A finished pharmaceutical product that contains two or more active pharmaceutical ingredients.

generic product. See "multisource pharmaceutical product".

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

interchangeable pharmaceutical product. A product that is therapeutically equivalent to a comparator product and can be interchanged with the comparator in clinical practice.

in vitro equivalence dissolution test. A dissolution test that includes comparison of the dissolution profile between the multisource product and the

[10] Guidance on the selection of comparator pharmaceutical products for equivalence assessment of interchangeable multisource (generic) products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-ninth report. WHO Technical Report Series No. 992, Annex 8. Geneva: World Health Organization; 2015.

comparator product, typically in at least three media: pH 1.2, pH 4.5 and pH 6.8 buffer solutions.

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

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

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

pharmaceutical alternative. A products is a pharmaceutical alternative if it contains the same active pharmaceutical moiety or moieties but differs in dosage form (for example, tablets versus capsules), strength, or chemical form (for example, different salts or different esters). Pharmaceutical alternatives deliver the same active moiety by the same route of administration but are otherwise not pharmaceutically equivalent. They may or may not be bioequivalent or therapeutically equivalent to the comparator product.

pharmaceutical equivalence. Products are pharmaceutical equivalents if they contain the same molar amount of the same active pharmaceutical ingredients 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 active pharmaceutical ingredient solid-state properties, the excipients, the manufacturing process or other variables can lead to differences in product performance.

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

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

3. Documentation of equivalence for marketing authorization

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

- comparative pharmacokinetic studies in humans, in which the active pharmaceutical ingredient (API) or its metabolites are measured as a function of time in an accessible biological fluid such as blood, plasma, serum or urine to obtain pharmacokinetic measures, such as area under the curve (AUC) and Cmax, that reflect the systemic exposure;
- comparative pharmacodynamic studies in humans;
- comparative clinical trials;
- comparative in vitro tests.

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

Acceptance of any test procedure in the documentation of equivalence between two pharmaceutical products by a national regulatory authority depends on many factors, including the characteristics of the API and the pharmaceutical product. Where an API produces measurable concentrations in an accessible biological fluid, such as plasma, comparative pharmacokinetic studies can be performed. This type of study is considered to be the gold standard in equivalence testing; however, where appropriate, in vitro testing, for example Biopharmaceutics Classification System (BCS)-based biowaivers for immediate-release pharmaceutical products, can also assure equivalence between the multisource product and the comparator product (see sections 5 and 10). Where an API does not produce measurable concentrations in an accessible biological fluid and a BCS-based biowaiver is not an option, comparative pharmacodynamics studies may be an alternative method for documenting equivalence. Further, in certain cases when it is not possible to assess equivalence through other methods, comparative clinical trials may be considered appropriate.

The criteria that indicate when equivalence studies are or are not necessary are discussed in sections 4 and 5 of these guidelines.

4. When equivalence studies are not necessary

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

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

(b) When pharmaceutically equivalent products are solutions for oral use (for example, syrups, suspensions and tinctures), contain the API in the same molar concentration as the comparator product, and contain the same functional excipients in similar concentrations (if the API is BCS class I) and the same excipients in similar concentrations (for APIs from other BCS classes).

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

(d) When pharmaceutically equivalent products are gases.

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

(f) When pharmaceutically equivalent products are topical products prepared as aqueous solutions and contain the same APIs in the same molar concentration and the same excipients in similar concentrations (note that a waiver would not apply to other

topical dosage forms such as gels, emulsions or suspensions, but might be applicable to oily solutions if the vehicle composition is sufficiently similar).

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

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

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

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

5.1 In vivo studies

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

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

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

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

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

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

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

5.2 In vitro studies

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

6. In vivo equivalence studies in humans: general considerations

6.1 Provisions for studies in humans

Pharmacokinetic, pharmacodynamic and comparative clinical trials are clinical studies and should therefore be carried out in accordance with the provision and prerequisites for a clinical study, as outlined in the WHO *Guidelines for good clinical practice for trials on pharmaceutical products* (*4*), and with WHO good laboratory practices (*5*). Additional guidance for organizations performing in vivo equivalence studies is available from WHO (*6*).

All research involving human subjects should be conducted in accordance with the ethical principles contained in the current version of the Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects, including respect for persons, beneficence ("maximize benefits and minimize harms and wrongs") and non-maleficence ("do no harm"), as defined by the International Ethical Guidelines for Biomedical

Research Involving Human Subjects issued by the Council for International Organizations of Medical Sciences, or laws and regulations of the country in which the research is conducted, whichever represents the greater protection for study subjects.

6.2 Justification of human bioequivalence studies

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

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

6.3 Selection of investigators

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

6.4 Study protocol

A bioequivalence study should be carried out in accordance with a protocol agreed upon and signed by the investigator and the sponsor. The protocol and its attachments or appendices should state the aim of the study and the procedures to be used, the reasons for proposing the study to be undertaken in humans, the nature and degree of any known risks, assessment methodology, criteria for acceptance of bioequivalence, the groups from which it is proposed that trial subjects be selected, and the means for ensuring that they are adequately informed before they give their consent. The investigator is responsible for ensuring that the protocol is strictly followed. Any changes required must be agreed on and signed by the investigator and sponsor and appended as

amendments, except when necessary to eliminate an apparent immediate hazard or danger to a trial subject.

The protocol, attachments and appendices should be scientifically and ethically appraised by one or (if required by local laws and regulations) more review bodies (for example, institutional review board, peer review committee, ethics committee or national regulatory authority) constituted appropriately for these purposes and independent of the investigators and sponsor.

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

7. Pharmacokinetic comparative bioavailability (bioequivalence) studies in humans

7.1 Design of pharmacokinetic studies

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

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

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

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

7.1.1 Alternative study designs for studies in patients

For APIs that are very potent or too toxic to administer in the highest strength to healthy volunteers (for example, because of the potential for serious adverse

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

7.1.2 Considerations for active pharmaceutical ingredients with long elimination half lives

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

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

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

7.1.3 Considerations for multiple-dose studies

In certain situations multiple-dose studies may be considered appropriate. Multiple-dose studies in patients are most useful in cases where the API being studied is considered to be too potent or too toxic to be administered to healthy volunteers, even in single doses (see also subsection 7.1.1). In this case a multiple-dose, crossover study in patients may be performed without interrupting therapy.

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

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

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

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

7.1.4 Considerations for modified-release products

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

Owing to the more complex nature of modified-release products relative to immediate-release products, additional data are required to ensure the bioequivalence of two modified-release products. Factors such as the coadministration of food, which influences API bioavailability and also, in certain cases, bioequivalence, must be taken into consideration. The presence of food can affect product performance both by influencing the release of the API from the formulation and by causing physiological changes in the gastrointestinal tract. In this regard a significant concern with regard to modified-release products is the possibility that food may trigger a sudden and abrupt release of the API leading to "dose dumping". This would most likely be manifested as a premature and abrupt rise in the plasma concentration time profile. Therefore, bioequivalence studies conducted under both fasted and fed conditions are required for orally administered, modified-release pharmaceutical products. Unless single-dose studies are not possible for reasons such as those discussed in subsection 7.1.1, single-dose, crossover bioequivalence studies conducted under both fasted and fed conditions comparing the highest strength of the multisource product and the comparator product must be performed to demonstrate bioequivalence. Single-dose studies are preferred to multiple-dose studies, as single-dose studies are considered to provide more sensitive measurement of the release of API from the pharmaceutical product into the systemic circulation. In addition to single-dose studies, multiple-dose studies may be considered for extended-release dosage forms with a tendency to

accumulate; for example, after a single dose of the highest strength the AUC for the dosing interval covers < 90% of the AUC extrapolated to infinity. The comparator product in these studies should be a pharmaceutically equivalent, modified-release product. The bioequivalence criteria for modified-release products are essentially the same as for conventional release dosage forms except that acceptance criteria should also be applied to C_{min} (C_{tau}) in the case of multiple-dose studies. As release mechanisms of pharmaceutical products become more complex, as in the case of products with an immediate-release and modified-release component, additional parameters such as partial AUC measures may be necessary to ensure the bioequivalence of two products.

The fed-state bioequivalence study should be conducted after the administration of an appropriate standardized meal at a specified time (usually not more than 30 minutes) before taking the pharmaceutical product. A meal that will promote the greatest change in gastrointestinal tract conditions relative to the fasted state should be given (see subsection 7.4.4 for more recommendations on the content of the meal). The composition of the meal should take local diet and customs into consideration. The composition and caloric breakdown of the test meal should be provided in the study protocol and report.

7.2 Subjects

7.2.1 Number of subjects

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

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

The number of subjects to be recruited for the study should be estimated by considering the standards that must be met using an appropriate method – see, for example, Julious (*7*). In addition, a number of extra subjects should be recruited, dosed appropriately, and their samples analysed based on the expected rate of dropout or withdrawal, which depends on the safety and tolerability profile of the API. The number of subjects recruited should always be justified

by the sample size calculation provided in the study protocol. A minimum of 12 subjects is required.

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

7.2.2 Dropout and withdrawal

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

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

7.2.3 Exclusion of subject data

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

7.2.4 Selection of subjects

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

Generally, subjects should be aged between 18 and 55 years and their weight should be within the normal range, with a body mass index between 8 and 30 kilograms per square metre (kg/m^2). The subjects should have no history of alcohol or drug abuse problems and should preferably be non-smokers.

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

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

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

7.2.5 Monitoring the health of subjects during the study

In keeping with guidelines for good clinical practice (*4*), the health of volunteers should be monitored during the study so that the onset of side-effects, toxicity or any intercurrent disease may be recorded and appropriate measures taken. The incidence, severity, seriousness and duration of any adverse event observed during the study must be reported. The probability that an adverse event is due to the finished pharmaceutical product (FPP) should be judged by the investigator. Health monitoring before, during and after the study must be carried out under the supervision of a qualified medical practitioner licensed in the jurisdiction in which the study is conducted.

7.2.6 Considerations for genetic phenotyping

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

be important for safety reasons and for determination of sampling times and washout periods in crossover design studies.

7.3 Investigational product

7.3.1 Multisource pharmaceutical product

The multisource pharmaceutical product used in the bioequivalence studies for registration purposes should be identical to the planned commercial pharmaceutical product. Therefore, not only the composition and quality characteristics (including stability) but also the manufacturing methods (including equipment and procedures) should be the same as those to be used in the future routine production runs. Test products must be manufactured under good manufacturing practice regulations. Batch control results, lot number, manufacturing date and, if possible, expiry date for the multisource product should be stated. Samples should ideally be taken from batches of industrial scale. When this is not feasible, pilot or small-scale production batches may be used, provided that they are not smaller than 10% of expected full production batches, or 100 000 units, whichever is larger, and are produced with the same formulation and similar equipment and process to that planned for commercial production batches. A biobatch of less than 100 000 units may be accepted provided that this is the proposed production batch size, with the understanding that future scale-up for production batches will not be accepted unless supported by in vitro or in vivo data, as applicable.

7.3.2 Choice of comparator product

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

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

7.4 Study conduct

7.4.1 Selection of strength

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

7.4.2 Non-linear pharmacokinetics

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

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

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

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

7.4.3 Study standardization

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

Volunteers should not take any other medicine, alcoholic beverages or over-the-counter medicines and supplements for an appropriate interval before or during the study. In the event of emergency, the use of any non-study medicine must be reported (dose and time of administration).

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

7.4.4 Coadministration of food and fluid with the dose

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

Immediate-release formulations

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

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

Typically, a meal meeting the composition recommendations identified in the following subsection on "Modified-release formulations" should be employed in fed-state studies. The exact composition of the meal may depend on local diet and customs, as determined by the national regulatory authority. For studies conducted with immediate-release products there may be situations where it is appropriate to employ a predose meal with a different caloric or fat content from a meal meeting the composition recommendations identified in the following subsection.

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

Modified-release formulations

In addition to a study conducted under fasted conditions, food effect studies are necessary for all multisource, modified-release formulations to ensure that the interaction between the varying conditions in the gastrointestinal tract and the product formulations does not differentially impact the performance of the multisource and comparator products. The presence of food can affect product performance both by influencing the release of the API from the formulation and by causing physiological changes in the gastrointestinal tract. A significant concern with regard to modified-release products is the possibility that food may trigger a sudden and abrupt release of the API, leading to "dose dumping". In these cases, the objective is to select a meal that will challenge the robustness of the new multisource formulation to prandial effects on bioavailability. To achieve this, a meal that will provide a maximal perturbation to the gastrointestinal tract relative to the fasted state should be employed; for example, a high-fat (approximately 50% of the total caloric content of the meal), high-calorie (approximately 800 to 1000 kilocalories) test meal has been recommended (*2*). The meal selected should take into account local customs and diet. The caloric breakdown of the test meal should be provided in the study report.

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

7.4.5 Washout interval

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

7.4.6 Sampling times

Blood samples should be taken at a frequency sufficient for assessing C_{max}, AUC and other parameters. Sampling points should include a predose sample, at least

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

7.4.7 Sample fluids and their collection

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

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

7.4.8 Parameters to be assessed

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

- Area under the plasma, serum or blood concentration–time curve from time zero to time *t* (AUC_{0-t}), where t is the last sampling time point with a measurable concentration of the API in the individual

formulation tested. The method of calculating AUC values should be specified. Non-compartmental methods should be used for pharmacokinetic calculations in bioequivalence studies.

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

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

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

For additional information the elimination parameters can be calculated:

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

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

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

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

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

7.4.9 Studies of metabolites

Generally, evaluation of bioequivalence will be based on the measured concentrations of the API released from the dosage form rather than the

metabolite. The concentration–time profile of the API is more sensitive to changes in formulation performance than a metabolite, which is more reflective of metabolite formation, distribution and elimination.

In rare cases it may be necessary to measure concentrations of a primary active metabolite rather than those of the API if concentrations of the API are too low to allow reliable analytical measurement in blood, plasma or serum for an adequate length of time, or when the parent compound is unstable in the biological matrix.

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

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

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

7.4.10 Measurement of individual enantiomers

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

7.5 Quantification of active pharmaceutical ingredient

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

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

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

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

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

In general:

- The analytical method should be able to differentiate the analyte of interest and, if employed, the internal standard from endogenous components in the matrix or other components in the sample.
- The lower limit of quantification, being the lowest concentration of analyte in a sample, should be estimated to prove that the analyte at this concentration can be quantified reliably, with an acceptable accuracy and precision.
- The response of the instrument with regard to the concentration of analyte should be known and should be evaluated over a specified concentration range. The calibration curve should be prepared in the same matrix as the matrix of the intended subject samples by spiking the blank matrix with known concentrations of the analyte. A calibration curve should consist of a blank sample, a zero sample and six to eight non-zero samples covering the expected range.
- Within-run and between-run accuracy and precision should be assessed on samples spiked with known amounts of the analyte and the quality control samples, at a minimum of three different concentrations.
- Matrix effects should be investigated when using mass spectrometric methods.
- Stability of the analyte in the stock solution and in the matrix should be proven, covering every step taken during sample preparation and sample analysis, as well as the storage conditions used.

- When more than one analyte is present in subject samples, it is recommended that the stability of the analytes in the matrix be demonstrated in the presence of the other analytes under standard conditions such as freeze–thaw testing, short-term room temperature storage and long-term freezer storage.
- Where changes are made to an analytical method that has already been validated, a full validation may not be necessary, depending on the nature of the changes implemented. A partial validation may be acceptable.
- A cross-validation is needed in cases where data are obtained from different methods within and across studies or when data are obtained within a study from different laboratories applying the same method.
- Analysis of subject samples should be carried out after validation of the analytical method. Before the start of the analysis of the subject samples, the performance of the bioanalytical method should have been verified.
- Calibration and quality control standards should be processed in an identical manner and at the same time as the subject's samples from the same run.
- Reasons for reanalysis, reinjection and reintegration of subject samples should be predefined in the protocol, study plan or standard operating procedures. Reinjection of a full analytical run or of individual calibration standard samples or quality control samples, simply because the calibration or quality controls failed, without any identified analytical cause, is considered unacceptable. For bioequivalence studies, reanalysis, reinjection or reintegration of subject samples for reasons related to pharmacokinetic fit is normally not acceptable, as this may affect and bias the outcome of such a study.
- When analysing subject samples, the precision and accuracy of the method should be confirmed by reanalysing subject samples in a separate analytical run on a different day (incurred samples reanalysis). Incurred samples reanalysis should be performed for each bioequivalence trial. The extent of testing done should be based on an in-depth understanding of the analytical method and analyte used.
- The samples from one subject (all periods) should be analysed in the same analytical run if possible.

Validation procedures, methodology and acceptance criteria should be specified in the analytical protocol or the standard operating procedures.

All experiments used to support claims or draw conclusions about the validity of the method should be described in a report (method validation report).

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

7.6 Statistical analysis

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

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

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

Logarithmically transformed, concentration-dependent pharmacokinetic parameters should be analysed using analysis of variance (ANOVA). Normally, the ANOVA model should include formulation, period, sequence and subject factors. Parametric methods, that is, those based on normal distribution theory, are recommended for the analysis of log-transformed bioequivalence measures.

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

For t_{max}, descriptive statistics should be given. Where t_{max} is considered clinically relevant, the median and range of t_{max} should be compared between test and comparator to exclude numerical differences with clinical importance. A formal statistical comparison is rarely necessary. Generally, the sample size is not calculated to have enough statistical power for t_{max}. However, if t_{max} is to be subjected to a statistical analysis, this should be based on non-parametric methods and should be applied to untransformed data. A sufficient number of samples around predicted maximal concentrations should have been taken to improve the accuracy of the t_{max} estimate. For parameters describing the elimination phase ($t_{1/2}$), only descriptive statistics should be given. See subsection 7.2.3 for information on the handling of extreme data.

Exclusion of data for statistical or pharmacokinetic reasons alone is not acceptable.

Two-stage sequential design

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

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

proposed statistical plan must be clearly defined in the study protocol, including the adjusted significance level that is to be employed during each analysis.

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

This approach can be employed in both crossover and parallel study designs.

7.7 Acceptance ranges

AUC_{0-t}- ratio

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

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

C_{max} ratio

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

t_{max} difference

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

7.8 Reporting of results

The report of a bioequivalence study should give the complete documentation of its protocol, conduct and evaluation in compliance with good clinical practice and good laboratory practice rules. The relevant International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guideline (*13*) can be used in the preparation of the study report.

The responsible investigators should sign the respective sections of the report. Names and affiliations of the responsible investigators, site of the study and period of its execution should be stated.

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

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

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

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

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

7.9 Special considerations

7.9.1 Fixed-dose combination products

If the bioequivalence of fixed-dose combination products is assessed by in vivo studies, the study design should follow the same general principles as described

in previous sections. The multisource fixed-dose combination product should be compared with the pharmaceutically equivalent comparator fixed-dose combination product. In certain cases (for example, when no comparator fixed-dose combination product is available on the market) separate products administered in free combination can be used as a comparator (*3*). Sampling times should be chosen to enable the pharmacokinetic parameters of all APIs to be adequately assessed. The bioanalytical method should be validated with respect to all analytes measured in the presence of the other analytes. Statistical analyses should be performed with pharmacokinetic data collected on all active ingredients; the 90% confidence intervals of the test/comparator ratio of all active ingredients should be within acceptance limits.

7.9.2 Clinically important variations in bioavailability

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

7.9.3 Highly variable active pharmaceutical ingredients

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

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

For highly variable FPPs it is recommended that a three-way partial replicate (where the comparator product is administered twice) or a four-way fully replicated crossover bioequivalence study be conducted and reference-scaled average bioequivalence be employed to widen the acceptance interval for the C_{max} parameter, if the intrasubject variability for C_{max} following replicate administrations of the comparator product is > 30%. If this is the case, the acceptance criteria for C_{max} can be widened to a maximum of 69.84–143.19%.

The applicant should justify that the calculated intrasubject variability is a reliable estimate and that it is not the result of outliers.

The extent of the widening of the acceptance interval for C_{max} is defined based upon the intrasubject variability seen in the bioequivalence study using scaled average bioequivalence according to [U, L] = exp [± k · sWR], where U is the upper limit of the acceptance range, L is the lower limit of the acceptance range, k is the regulatory constant set to 0.760 and sWR is the intrasubject standard deviation of the log-transformed values of C_{max} of the reference product. Table A8.2 gives examples of how different levels of variability lead to different acceptance limits using this methodology.

Table A8.2
Acceptance limits for different levels of variability

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

$$CV\ (\%) = \sqrt{(e\ \text{^}(\{S\_WR\}\text{^}2\ ) -1)}$$

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

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

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

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

8. Pharmacodynamic equivalence studies

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

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

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

The following requirements must be recognized when planning, conducting and assessing the results of a study intended to demonstrate equivalence by measuring pharmacodynamic responses.

- The response measured should be a pharmacological or therapeutic effect that is relevant to the claims of efficacy and safety.
- The methodology must be validated for precision, accuracy, reproducibility and specificity.
- Neither the multisource product nor the comparator product should produce a maximal response during the course of the study, since it may be impossible to detect differences between formulations given.
- The response should be measured quantitatively, preferably under double-blind conditions, and be recordable by an instrument that produces and records the results of repeated measurements to provide a record of the pharmacodynamic events, which are substitutes for measurements of plasma concentrations. Where such measurements are not possible, recordings on visual analogue scales may be used. Where the data are limited to qualitative (categorized) measurements, appropriate special statistical analysis will be required.
- Participants should be screened prior to the study to exclude non-responders. The criteria by which responders are distinguished from non-responders must be stated in the protocol.
- In situations where an important placebo effect can occur, comparison between pharmaceutical products can only be made by a priori consideration of the potential placebo effect in the study design. This may be achieved by adding a third phase with placebo treatment during the design of the study.
- The underlying pathology and natural history of the condition must be considered in the study design. There should be confirmation that the baseline conditions are reproducible.
- A crossover design can be used. Where this is not appropriate, a parallel group study design should be chosen.

The basis for the selection of the multisource and comparator products should be the same as described in subsection 7.3.

In studies in which continuous variables can be recorded, the time course of the intensity of the action can be described in the same way as in a study in which plasma concentrations are measured and parameters can be derived that describe the area under the effect–time curve, the maximum response, and the time at which the maximum response occurred.

The comparison between the multisource product and the comparator product can be performed in two different ways:

- **Dose-scale analysis or relative potency.** This is defined as the ratio of the potency of the multisource product to that of the comparator product. It is a way of summarizing the relationship between the dose–response curves of the multisource and comparator products.
- **Response-scale analysis.** This consists of demonstration of equivalence (for at least two dose levels) at the pharmacodynamic end-point.

For either approach to be acceptable, a minimum requirement is that the study has assay sensitivity. To meet this requirement, at least two non-zero levels need to be studied and one dose level needs to be shown to be superior to the other.

Therefore, it is recommended that unless otherwise justified more than one dose of both the multisource product and the comparator product are studied. However, it is essential that doses on the steep part of the dose–response curve are studied. If the chosen dose is too low on the dose–response curve, then demonstrating equivalence between two products is not convincing, as this dose could be subtherapeutic. Equally, if a dose at the top of the dose–response curve is included, similar effects will be seen for doses much higher than that studied, and hence demonstrating equivalence at this dose level would also not be convincing.

The results using both approaches should be provided. In both cases the observed confidence intervals comparing multisource and comparator products should lie within the chosen equivalence margins to provide convincing evidence of equivalence. As for bioequivalence studies, 90% confidence intervals should be calculated for relative potency, whereas 95% confidence intervals should be calculated for the response-scale analysis. It should be noted that the acceptance range as applied for bioequivalence assessment may not be appropriate. For both approaches the chosen equivalence ranges should be prespecified and appropriately justified in the protocol.

9. Clinical equivalence studies

In some instances (see example (e) in subsection 5.1, "In vivo studies") plasma concentration time–profile data may not be suitable for assessing equivalence between two formulations. Although in some cases pharmacodynamic equivalence studies can be an appropriate tool for establishing equivalence, in others this type of study cannot be performed because of a lack of meaningful pharmacodynamic parameters that can be measured; a comparative clinical trial then has to be performed to demonstrate equivalence between two formulations.

However, it is preferable to assess equivalence by performing a pharmacokinetic equivalence study rather than a clinical trial that is less sensitive and would require a huge number of subjects to achieve adequate statistical power. For example, it has been calculated that 8600 patients would be required to give adequate statistical power to detect a 20% improvement in response to the study API compared with a placebo (*18*, *19*). Similarly, it was calculated that 2600 myocardial infarct patients would be required to show a 16% reduction in risk. A comparison of two formulations of the same API based on such end-points would require even greater numbers of subjects (*19*).

If a clinical equivalence study is considered as being undertaken to prove equivalence, the same statistical principles apply as for the bioequivalence studies, although a 95% confidence interval might be necessary for pharmacodynamic and clinical end-points in contrast to the 90% confidence level employed conventionally for pharmacokinetic studies. The number of patients to be included in the study will depend on the variability of the target parameters and the acceptance range and is usually much higher than the number of subjects needed in bioequivalence studies.

The methodology for establishing equivalence between pharmaceutical products by means of a clinical trial with a therapeutic end-point conducted in patients is not yet as far advanced as that for bioequivalence studies. However, some important items that need to be defined in the protocol can be identified as follows.

- The target parameters that usually represent relevant clinical end-points from which the onset, if applicable and relevant, and intensity of the response are to be derived.
- The size of the acceptance range has to be defined case by case, taking into consideration the specific clinical conditions. These include the natural course of the disease, the efficacy of available treatments and the chosen target parameter. In contrast to bioequivalence studies (where a conventional acceptance range is applied), the size of the acceptance range in clinical trials should be set individually according to the therapeutic class and indications.
- The currently used statistical method is the confidence interval approach.
- The confidence intervals can be derived from either parametric or non-parametric methods.
- Where appropriate, a placebo arm should be included in the design.
- In some cases it is relevant to include safety end-points in the final comparative assessments.

The selection basis for the multisource and comparator products should be the same as described in subsection 7.3.

10. In vitro equivalence testing

Over the past three decades, dissolution testing has evolved into a powerful tool for characterizing the quality of oral pharmaceutical products. The dissolution test, at first exclusively a quality control test, is now emerging as a surrogate equivalence test for certain categories of orally administered pharmaceutical products. For these products (typically solid oral dosage forms containing APIs with suitable properties), similarity in in vitro dissolution profiles, in addition to excipient comparisons and a risk–benefit analysis, can be used to document equivalence of a multisource product with a comparator product.

It should be noted that although the dissolution tests recommended in *The International Pharmacopoeia* (*20*) for quality control have been designed to be compatible with the biowaiver dissolution tests, they do not fulfil all the requirements for evaluating equivalence of multisource products with comparator products. Dissolution tests for quality control purposes, including those described in other pharmacopoeias, do not address all test conditions required for evaluating equivalence of multisource products and should not be applied for this purpose.

10.1 In vitro equivalence testing in the context of the Biopharmaceutics Classification System

The Biopharmaceutics Classification System (BCS)-based biowaiver approach is intended to reduce the need for in vivo bioequivalence studies, as it can provide a surrogate for in vivo bioequivalence. In vivo bioequivalence studies may be exempted if an assumption of equivalence in in vivo performance can be justified by satisfactory in vitro data. The BCS is a scientific approach based on the aqueous solubility and intestinal permeability characteristics of the APIs.

The BCS categorizes APIs into one of four BCS classes, as follows:

- class I: high solubility, high permeability
- class II: low solubility, high permeability
- class III: high solubility, low permeability
- class IV: low solubility, low permeability.

Guidance providing recommendations to support the biopharmaceutics classification of APIs and the BCS-based biowaiver of bioequivalence studies for FPPs can be found in the *WHO guideline on Biopharmaceutics Classification System-based biowaivers*.

10.2 Qualification for a biowaiver based on the Biopharmaceutics Classification System

Guidance providing recommendations to support the biopharmaceutics classification of APIs and the BCS-based biowaiver of bioequivalence studies for FPPs can be found in the *WHO guideline on Biopharmaceutics Classification System-based biowaivers*.

10.3 In vitro equivalence testing based on dose proportionality of formulations

Under certain conditions, approval of different strengths of a multisource product can be considered on the basis of dissolution profiles if the formulations have proportionally similar compositions.

10.3.1 Proportional formulations

For the purpose of this guidance, proportional formulations can be defined in two ways, based on the strength of dosage forms.

(a) All active and inactive ingredients are exactly in the same proportions in the different strengths (for example, a tablet of 50 milligram (mg) strength has exactly half of all the active and inactive ingredients contained in a tablet of 100 mg strength and twice what would be contained in a tablet of 25 mg strength). For immediate-release products, coating components, capsule shell, colour agents and flavours are not generally required to meet this requirement.

(b) For an FPP, where the amount of the API in the dosage form is relatively low (up to 10 mg per dosage unit or not more than 5% of the weight of the dosage form), the total weight of the dosage form remains similar for all strengths.

For (b) a waiver is considered:

- if the amounts of the different excipients or capsule contents are the same for the strengths concerned and only the amount of the API has changed;
- if the amount of filler is changed to account for the change in amount of API. The amounts of other core excipients or capsule content should be the same for the strengths concerned.

10.3.2 Qualification for biowaivers based on dose proportionality of formulations

Immediate-release tablets

A biowaiver based on dose proportionality of formulations for a series of strengths of a multisource product, when the pharmaceutical products are manufactured with the same manufacturing process, may be granted when:

- an in vivo equivalence study has been performed on at least one of the strengths of the formulation (as described in subsection 7.4.1, the strength studied will usually be the highest strength, unless a lower strength is chosen for reasons of safety or the API is highly soluble and displays linear pharmacokinetics);
- all strengths are proportionally similar in formulation to that of the strength studied;
- the dissolution profiles for the different strengths are similar at pH 1.2, 4.5, 6.8 and for the quality control media, unless justified by the absence of sink conditions.

If the different strengths of the test product do not show similar dissolution profiles owing to the absence of sink conditions in any of the above media, this should be substantiated by showing similar dissolution profiles when testing the same dose per vessel (for example, two tablets of 5 mg versus one tablet of 10 mg) or by showing the same behaviour in the comparator product.

As for the BCS-based biowaiver, if both strengths release 85% or more of the label amount of the API in 15 minutes, using all three dissolution media as recommended in the *WHO guideline on Biopharmaceutics Classification System-based biowaivers*, the profile comparison with an f2 test is unnecessary.

In the case where an immediate-release dosage form with several strengths deviates from proportionality a bracketing approach is possible, so that only two strengths representing the extremes need to be studied in vivo.

If approval of one strength of a product is based on a BCS-based biowaiver instead of an in vivo equivalence study, other strengths in the series of strengths should also be assessed based on BCS-based biowaivers as opposed to a biowaiver based on dose proportionality.

Delayed-release tablets and capsules

For delayed-release tablets, for a series of strengths of a multisource product where the strengths are proportionally similar in formulation to that of the strength studied in an in vivo equivalence study, a lower strength can be granted a biowaiver if it exhibits similar dissolution profiles, $f2 \geq 50$, in the recommended test condition for delayed-release product, for example, dissolution test in acid medium (pH 1.2) for 2 hours followed by dissolution in pH 6.8. When

evaluating proportionality in composition, it is recommended to consider the proportionality of gastro-resistant coating with respect to the surface area (not to core weight) to have the same gastro-resistance (mg/cm²).

For delayed-release capsules where different strengths have been achieved solely by means of adjusting the number of beads containing the API, similarity in the dissolution profile of the new (lower) strength to that of the approved strength ($f2 > 50$) under the test conditions recommended for delayed-release products (see above) is sufficient for a biowaiver.

Extended-release tablets and capsules

For extended-release tablets, when there is a series of strengths of a multisource product that are proportionally similar in their active and inactive ingredients and have the same API release mechanism, in vivo bioequivalence studies should be conducted with the highest proposed strength. Subsequently, lower strengths in the series can be granted a biowaiver if they exhibit similar dissolution profiles to the highest strength, $f2 \geq 50$, in three different pH buffers (between pH 1.2 and 7.5) and the quality control media by the recommended test method.

For extended-release tablets with an osmotic pump release mechanism, the dissolution profile comparison ($f2 \geq 50$) under one recommended test condition is sufficient for a biowaiver based on dose proportionality of formulation.

For extended-release beaded capsules where different strengths have been achieved solely by means of adjusting the number of beads containing the API, a dissolution profile comparison ($f2 \geq 50$) under one recommended test condition is sufficient for a biowaiver based on dose proportionality of formulation.

10.3.3 Dissolution profile comparison for biowaivers based on dose proportionality of formulations

As for biowaivers based on the BCS, a model-independent mathematical approach (for example, f2 test) can be used for comparing the dissolution profiles of two products. The dissolution profiles of the two products (reference strength and additional strength) should be measured under the same test conditions. The dissolution sampling times for both reference strength and additional strength profiles should be the same. For example:

- for immediate-release products, 5, 10, 15, 20, 30, 45 and 60 minutes;
- for 12-hour extended-release products, 1, 2, 4, 6, 8 and 12 hours;
- for 24-hour extended-release products, 1, 2, 4, 6, 8, 16 and 24 hours.

For the application of the f2 value, see Appendix 1.

10.4 In vitro equivalence testing for non-oral dosage forms

In the case of intravenous micellar solutions with the same qualitative and quantitative composition of the surfactant, but significant changes to other excipients, an in vitro comparison might avoid the need for in vivo studies if a similar micellar system and API release from the micelle after dilution of the FPP or API administration into the blood system is ensured (*21*).

Locally applied, locally acting products in the form of aqueous suspensions containing the same API in the same molar concentration and essentially the same excipients in comparable concentrations might be waived from the demonstration of equivalence by means of local availability, pharmacodynamic or clinical studies if in vitro characterization is able to ensure a similar crystallographic structure and particle size distribution as well as any other in vitro test specific for each dosage form, for example dissolution. The methodological details for the techniques mentioned below are not covered in these guidelines. Additional information regarding these techniques should be sought from guidelines produced by stringent regulatory authorities or from state-of-the-art literature.

(a) Suspensions for nebulization with the same qualitative and quantitative composition as the comparator product might be waived from in vivo studies if the particles in the suspensions are shown to have the same crystallographic structure and particle size distribution as those from the comparator product, as well as comparability in any other appropriate in vitro test, for example dissolution. In addition, the nebulized droplets should exhibit a similar aerodynamic particle size distribution to that of the comparator product.

(b) Suspensions for nebulization with different qualitative and quantitative composition might be granted a waiver if, in addition to the requirements defined above under (a), the difference in excipient composition does not alter the nebulizer efficiency (for example, by the presence or absence of a different surfactant or preservative) or the aerodynamic particle size distribution (for example, altering product hygroscopicity by the presence of a different amount of salt as isotonic agent). To this end, the appropriate state-of-the-art in vitro test should be conducted to ensure product equivalence. Any difference in excipients should be critically reviewed because certain excipients that are considered irrelevant in other dosage forms (for example, preservative, substance to adjust tonicity or thickening agent) may affect safety or efficacy of the product.

(c) Nasal drops where the API is in suspension with the same qualitative and quantitative composition as the comparator product might be waived from in vivo studies if the particles in suspension are shown to have the same crystallographic structure and similar particle size distribution to that of the comparator product, as well as comparability in any other appropriate in vitro test, such as dissolution.

(d) Nasal drops where the API is in suspension, with qualitative or quantitative differences in excipient composition with respect to the comparator product, might be waived from in vivo studies if, in addition to the requirements defined above under (c), the difference in excipient composition does not affect efficacy and safety (for example, a different preservative may affect the safety profile due to greater irritation of the nasal passages and a different viscosity or thixotropy may affect the residence time in the site of action). Therefore any difference in excipients should be critically reviewed.

(e) Nasal sprays in solution with the same qualitative and quantitative composition in excipients can be granted waivers based on a battery of in vitro tests as defined by stringent regulatory authorities (*22*).

(f) Nasal sprays in solution with qualitative and quantitative differences in the excipient composition might be waived if, in addition to showing similarity in the battery of in vitro tests referenced under (e), differences in excipients are critically reviewed as described above under (d).

(g) Nasal sprays in suspension with the same qualitative and quantitative composition in excipients might be waived if, in addition to the battery of in vitro tests referenced above under (e), the particles in suspension are shown to have the same crystallographic structure and similar particle size distribution, as well as comparability in any other appropriate in vitro test, such as dissolution.

(h) Nasal sprays in suspension with qualitative and quantitative differences in excipient composition might be waived if, in addition to the battery of in vitro tests referenced above under (e) and (g), differences in excipients are critically reviewed as described above under (d).

(i) In the case of pressurized metered-dose inhalers in solution or suspension, in vivo studies might be waived if similarity is shown in a battery of in vitro tests as described in specific guidelines produced by stringent regulatory authorities (*23*). A waiver of in vivo studies

for a dry powder inhaler is not considered feasible unless the device for the dry powder inhaler is identical to the comparator.

(j) For pharmaceutically equivalent topical gel products, equivalence can be demonstrated by means of in vitro membrane diffusion studies when the products contain essentially the same excipients in comparable concentrations and the APIs in the product are in solution (*24*).

(k) Otic and ophthalmic suspensions with the same qualitative and quantitative composition in excipients might be granted a waiver if the particles in suspension are shown to have the same crystallographic structure and similar particle size distribution, as well as comparability in any other appropriate in vitro test, such as dissolution.

(l) Products acting locally in the gastrointestinal tract containing highly soluble APIs (as defined by the BCS) in immediate-release dosage forms might be waived from in vivo equivalence studies based on the same dissolution requirements as are applied for the BCS-based biowaiver.

10.5 In vitro equivalence testing for scale-up and post-approval changes

Although these guidelines refer primarily to registration requirements for multisource pharmaceutical products, it should be noted that under certain conditions, following permissible changes to formulation or manufacturing after FPP approval, in vitro dissolution testing may also be suitable to confirm similarity of product quality and performance characteristics. More information on when dissolution testing may be used to support product variations is provided in WHO guidance on variations in pharmaceutical products.

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Further reading

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Appendix 1

Recommendations for conducting and assessing comparative dissolution profiles

The dissolution measurements of the two FPPs (for example, test and comparator or two different strengths) should be made under the same test conditions. A minimum of three time points (zero excluded) should be included, the time points for both reference (comparator) and test product being the same. The sampling intervals should be short for a scientifically sound comparison of the profiles (for example, 5, 10, 15, 20, 30, 45 and 60 minutes for an immediate-release dosage form). The 15-minute time point is critical to determine whether a product is very rapidly dissolving and to determine whether f2 must be calculated. For extended-release FPPs, the time points should be set to cover the entire duration of expected release, for example, in addition to earlier time points: samples at 1, 2, 3, 5 and 8 hours should be collected for a 12-hour release, and additional test intervals would be necessary for longer duration of release.

Studies should be performed in at least three media covering the physiological range, including pH 1.2 hydrochloric acid, pH 4.5 buffer and pH 6.8 buffer. *The International Pharmacopoeia* buffers are recommended; other pharmacopoeial buffers with the same pH and buffer capacity are also acceptable. Water may be considered as an additional medium, especially when the API is unstable in the buffered media to the extent that the data are unusable.

If both the test and reference (comparator) products show more than 85% dissolution in 15 minutes, the profiles are considered similar (no calculations required). Otherwise:

- Similarity of the resulting comparative dissolution profiles should be calculated using the following equation that defines a similarity factor (f2):

  $$f2 = 50 \text{ LOG } \{[1+1/n \sum nt =1 (Rt- Tt)2] -0.5 \times 100\},$$

  where Rt and Tt are the mean per cent API dissolved in reference (comparator) and test product, respectively, at each time point. An f2 value between 50 and 100 suggests that the two dissolution profiles are similar.
- A maximum of one time point should be considered after 85% dissolution of the reference (comparator) product has been reached.
- In the case where 85% dissolution cannot be reached owing to poor solubility of the API or the release mechanism of the dosage form,

the dissolution should be conducted until an asymptote (plateau) has been reached.

- At least 12 units should be used for determination of each profile. Mean dissolution values can be used to estimate the similarity factor, f2. To use mean data the percentage coefficient of variation at time points up to 10 minutes should be not more than 20% and at other time points should be not more than 10%.
- When delayed-release products (for example, enteric coated) are being compared, the recommended conditions are acid medium (pH 1.2) for 2 hours and buffer pH 6.8 medium.
- When comparing extended-release beaded capsules, where different strengths have been achieved solely by means of adjusting the number of beads containing the API, one condition (normally the release condition) will suffice.
- Surfactants should be avoided in comparative dissolution testing.

A statement that the API is not soluble in any of the media is not sufficient, and profiles in the absence of surfactant should be provided. The rationale for the choice and concentration of surfactant should be provided. The concentration of the surfactant should be such that the discriminatory power of the test will not be compromised.

SELECTED WHO PUBLICATIONS OF RELATED INTEREST

The International Pharmacopoeia, eleventh edition.
2022 (online)

WHO Expert Committee on Specifications for Pharmaceutical Preparations
Fifty-sixth report.
WHO Technical Report Series, No. 1044, 2022 (xiv + 412 pages)

The Selection and Use of Essential Medicines
Executive Summary of the Report of the WHO Expert Committee on the Selection and Use of Essential Medicines, 2023 (ix + 31 pages)

WHO electronic Essential Medicines List (eEML)
World Health Organization, 2023
https://list.essentialmeds.org/. Licence: CC BY 3.0 IGO

WHO Expert Committee on Biological Standardization
Seventy-seventh report
WHO Technical Report Series, No. 1048, 2023 (xiv + 137 pages)

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The Expert Committee on Specifications for Pharmaceutical Preparations works towards clear, independent and practical standards and guidelines for the quality assurance of medicines and provision of global regulatory tools. The Expert Committee develops standards through worldwide consultation and an international consensus-building process. The following new guidance texts were adopted and recommended for use:

WHO good manufacturing practices for excipients used in pharmaceutical products (revision); IAEA/WHO good manufacturing practices for in-house cold kits for radiopharmaceutical preparations (new); WHO good practices for pharmaceutical quality control laboratories (revision); WHO/UNFPA female condom generic specification (new); WHO Biowaiver List: proposal to waive in vivo bioequivalence requirements for WHO Model List of Essential Medicines immediate-release (updated), solid oral dosage forms; WHO guideline on Biopharmaceutics Classification System-based biowaivers (revision); and Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability (republished).

All of the above are included in this report and recommended for implementation.

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