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Geneva, 15–19 October 2007

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1. Introduction

The WHO Expert Committee on Specifications for Pharmaceutical Preparations met in Geneva from 15 to 19 October 2007. Dr Howard Zucker, Assistant Director-General, Health Technology and Pharmaceuticals (HTP) cluster, opened the meeting and on behalf of the Director-General of the World Health Organization welcomed all the participants to the Forty-second meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations. He expressed his appreciation of the Expert Committee for its knowledge of and expertise in the work of WHO in the area of quality assurance of medicines. He welcomed new members of the Committee, temporary advisers for prequalification, observers who were attending for the first time, and representatives of the Global Fund to Fight AIDS, Tuberculosis and Malaria, the Council of Europe (CoE), the European Medicines Agency (EMA), representatives of the Secretariats of the Pharmacopoeias of Europe, the Russian Federation and the United States of America; the Commonwealth Pharmaceutical Association (CPA), the International Pharmaceutical Federation (FIP), the European Chemical Industry Council (CEFIC/APIC), the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA), the International Pharmaceutical Excipients Council (IPEC) the Pharmaceutical Inspection Co-operation Scheme (PIC/S) and the World Self-Medication Industry (WSMI); as well as representatives from WHO Collaborating Centres in China, Hungary, South Africa, Sweden and Thailand.

Dr Zucker shared the response of Dr Margaret Chan, Director-General of WHO, to the increasingly complex and rapidly changing landscape. Dr Chan had defined a six-point agenda. The six points addressed two health objectives, two strategic needs, and two operational approaches, which were as follows:

1. Promoting development
2. Fostering health security
3. Strengthening health systems
4. Harnessing research, information and evidence
5. Enhancing partnerships
6. Improving performance

Furthermore the overall performance of WHO would be measured by the impact of its work on women's health and health in Africa. Dr Chan had stated that she wanted her leadership to be judged by the impact of the Organization's work on the health of two populations: women and the people of Africa.

Dr Zucker explained that the mission of HTP was to maintain health and reduce morbidity and mortality through access to and optimal use of available and new health technology and medicines.

The HTP vision was one of providing solutions to public health challenges by promoting the tools that build good health — safe, effective medicines and health technology. HTP would continue to support research in priority areas, and to assist national regulatory authorities and manufacturers to meet international standards for pharmaceutical and biological products.

A reliable system of quality and safety control in health care was crucial to any health system, particularly when it came to medicines, blood products and devices such as syringes. WHO assists countries to build and strengthen these quality control systems through several activities. Within HTP, all departments included a large quality and safety component in their work, which was centered on the development, harmonization and promotion of international standards. Work in this area provides governments and pharmaceutical manufacturers with the means to establish and maintain mechanisms which ensure the quality, safety, efficacy and rational use of medicines and health technologies.

Dr Zucker stressed that the Expert Committee had come to Geneva to fulfil an important task. Standards in the area of quality assurance for medicines, developed by the Committee through an international consensus-building process, would not only serve WHO, including all its specific disease programmes, but also other international, regional and national agencies and initiatives dealing with medicines.

He indicated that the Committee's activities were closely linked with important cluster activities and referred to the most important ones to set the scene for the Committee's work.

WHO's goal in relation to medicines is to help save lives and improve health by promoting access to medicines that meet quality, efficacy and safety standards. One of the tools WHO uses to achieve this goal is the Model list of essential medicines, which this year marks its thirtieth anniversary. The sixteenth meeting of the WHO Expert Committee on the Selection and Use of Essential Medicines would be held in Geneva from 24 to 25 October 2007. One of the purposes of the meeting would be to review the report of the meeting of the Subcommittee held in July 2007 and endorse, if appropriate, the proposed Model List of Essential Medicines for children.

Dr Zucker addressed the importance of the Expert Committee on Specifications for Pharmaceutical Preparations' discussion of some 10 monographs for testing medicines for children with a view to their adoption during the week ahead.

The Committee's consideration of the issue of diethylene glycol contamination and how to prevent its occurrence in the future would be of the utmost importance as it had caused many deaths over the past decades,

including those of at least 80 children in Haïti and recently of more than 20 adults in Panama. It was sad that such serious events were necessary before progress could be made. In 1937, for example, more than 100 people in the United States of America died of diethylene glycol poisoning following the use of a sulfanilamide elixir in which the chemical was used as a solvent without any safety testing. This helped to finalize pending legislation and brought about the Federal Food, Drug and Cosmetic Act with the introduction in 1938 of a pre-market notification requirement for new drugs. Unfortunately lethal events caused by diethylene glycol intoxication are still occurring in many parts of the world.

In preparation for the second Intergovernmental Working Group (IGWG) on Public Health, Innovation and Intellectual Property on 5–10 November 2007, WHO had set up a second web-based public hearing. Individuals, civil society groups, government institutions, academic and research institutions, the private sector and other interested parties were invited to contribute to the open hearing.

The WHO Commission on Intellectual Property Rights, Innovation and Public Health concluded its report in April 2006. Its recommendations were considered by the 59th World Health Assembly which adopted Resolution WHA59.24: “Public health, innovation, essential health research and intellectual property rights: towards a global strategy and plan of action”. This resolution requested the Director-General of WHO to convene an IGWG, open to all interested Member States, to draw up a global strategy and plan of action aimed at securing an enhanced and sustainable basis for needs-driven, essential health research and development relevant to diseases that disproportionately affect developing countries. This would be submitted to the 61st World Health Assembly in May 2008.

Counterfeit medical products are a major public health risk for all communities. The phenomenon had grown in recent years due to counterfeiting methods becoming more sophisticated and to the increasing amount of merchandise crossing borders and frontiers.

Reports of counterfeit and substandard medicines were constantly increasing both in developing and in developed countries. Trade in counterfeits appeared to be extremely lucrative, thus making it particularly attractive to criminal networks. This was not a problem concerning one person, but a problem of all people. It was not a problem of one country, but a problem of all nations. The solution, therefore, could not simply be left in the hands of doctors, or national regulators, district police officers, individual customs officials or companies — nor, indeed, in the hands of WHO alone. As a complex, global problem, it requires global solutions involving all stakeholders.

Dr Zucker emphasized that unfortunately, the current situation was that anyone, anywhere in the world, could have access to medicines that were seemingly packaged correctly, in the form of tablets or capsules that looked right, but which did not contain the correct ingredients and, in the worst case, might be filled with highly toxic substances. In some countries this is a rare occurrence; in others, it is an everyday reality. Counterfeit drugs lead to a loss of confidence in the entire health system; they affect the image of manufacturers, pharmacists, doctors, and private and government institutions alike. This is why each and every sector affected must be actively involved in finding a solution.

WHO has responded to this challenge by creating a global coalition of stakeholders called IMPACT (International Medical Products Anti-Counterfeiting Taskforce). The taskforce, created in 2006, has been active in promoting international collaboration to seek global solutions to this global challenge and in raising awareness of the dangers of counterfeit medical products.

Three major conferences were scheduled during the next four months to discuss various aspects of the problem of counterfeiting:

- International Conference: Developing Effective Legislation to Combat Counterfeit Medical Products, Lisbon, Portugal, 10–11 December 2007;
- Annual General Meeting: Providing the Results of IMPACT's First Year, Lisbon, Portugal, 12–14 December 2007; and
- International Conference Using Technology to Combat Counterfeit Medical Products: technology developers meet manufacturers and regulators, Singapore, 13–15 February 2008.

Dr Zucker also indicated that ultimately, the best solution would be to strengthen the ability of drug regulators to help themselves. Donor countries should not only provide good-quality medicines to developing countries, for example, but also local capacity-building. In the long run, this was the only solution that would be sustainable.

Evidence showed that where problems regarding the quality assurance of pharmaceuticals persisted, vigorous implementation of good manufacturing practices and good distribution practices were prerequisites for prevention. Poor-quality medicines and counterfeit drugs are a waste of money for the people who buy them, can prolong duration of treatment, exacerbate the conditions being treated, increase the emergence of drug resistance and can even cause death.

Dr Zucker said that the statutory advice and recommendations provided by this Expert Committee could help national authorities — in particular drug regulatory authorities and procurement agencies, as well as major

international bodies and institutions, such as the Global Fund, and international organizations such as UNICEF — to combat problems of counterfeit and substandard medicines. Ultimately, legal texts and sound standards were needed to be able to prove that a medicine is either counterfeit or substandard.

The prequalification of medicines and laboratories could not function without the guidelines, standards and specifications adopted by this Committee after passage through the usual, rigorous consultative process. In return colleagues working at all levels within the WHO-managed Prequalification Programme for priority essential medicines provided valuable feedback to the Expert Committee. Another valuable aspect of the Prequalification Programme was that participating members of drug regulatory authorities obtained “hands-on” experience in joint inspections and joint regulatory assessment activities with the participation of both developed and developing countries. This practical side is later taught in training workshops.

Dr Zucker added that the world was changing. An increase in trade, the trend towards new technologies and different lifestyles, all have immediate implications for public health. New supply routes for medicines required new approaches to quality assurance in production and distribution worldwide. He said that it was of the utmost importance for WHO to maintain its normative role if it were to meet the needs and expectations of its 193 Member States.

He concluded his remarks by saying that WHO relied on the experience of the Expert Committee members to lead and assist WHO in coordinating international efforts to define and harmonize clear, independent and practical standards and guidelines for medicines. Patients’ health, and especially children’s health, should not be compromised through bad medicines, the quality of medicines being only too often taken for granted. Public and private resources should not be wasted on medicines that might be inefficient or even harmful.

In his opening remarks Dr Hans V. Hogerzeil, Director, Department of Policy of Medicines and Standards, also welcomed the participants from all six WHO Regions, several international organizations, nongovernmental organizations, institutions and WHO Collaborating Centres. He also thanked those who had made major contributions with technical expertise as well as practical laboratory studies. He explained that the Expert Committee meeting was the top of the pyramid of much work throughout the year. Dr Hogerzeil indicated that the Expert Committee on Selection and Use of Essential Medicines was moving towards an evidence-based approach. Development of standards may be a lengthy process. A guidelines review committee had been created to streamline and harmonize the procedure for developing WHO guidelines.

The WHO Technical Report Series is the highest level of normative work. Dr Hogerzeil emphasized the importance of the normative work carried out by this Expert Committee with its very technical and scientific remit. There was a need to have core documents available in many languages to make the most of the Committee's efforts. He drew attention to the 4th edition of *The International Pharmacopoeia*, the publication of which had generated a tremendous amount of work. He mentioned that an information booklet was being developed to explain what the Expert Committee does and has done. Dr Hogerzeil also mentioned that the WHO Prequalification Programme applied WHO's standards to assess priority medicines to be procured by United Nations agencies. He thanked the members of the Committee, other organizations, clusters, institutions, bodies and authorities for their contributions and expressed appreciation for the work done in the Prequalification Programme.

The Coordinator, Quality Assurance and Safety: Medicines team welcomed everyone to the meeting. He was pleased with the work of the Committee and mentioned that paediatrics had been on HTP's agenda for some time.

The Secretary of this WHO Expert Committee explained the administrative process of appointment of experts and the working procedures related to the Expert Committee meeting.

She also provided a historical overview of the establishment of Expert Committees. The history of this Committee and that of *The International Pharmacopoeia* dated back to 1874 when the need to standardize terminology and to specify dosages and composition of drugs led to attempts to produce an international pharmacopoeial compendium. The first conference, called by the Belgian Government and held in Brussels in 1902, resulted in the Agreement for the Unification of the Formulae of Potent Drugs, which was ratified in 1906 by 19 countries. A second agreement, the Brussels Agreement, was drawn up in 1925 and ratified in 1929. This 41-article agreement stipulated that the League of Nations would be responsible for the administrative work to produce a unified pharmacopoeia, and a permanent secretariat of an international organization would coordinate the work of national pharmacopoeial commissions. In response to repeated calls from pharmaceutical experts in various countries that the Brussels Agreement be revised and extended to cover an international pharmacopoeia, the Health Organization of the League of Nations set up a Technical Commission of Pharmacopoeial Experts in 1937. In 1947 the Interim Commission of WHO took over the work on pharmacopoeias previously undertaken by the Health Organization of the League of Nations, and set up an Expert Committee on the Unification of Pharmacopoeias to continue the work of the League's Technical Commission. In 1948, the First World Health Assembly approved the establishment of the Expert Committee by the

Interim Commission. In 1951, this became the Expert Committee on the International Pharmacopoeia; and subsequently, in 1959, the Expert Committee on Specifications for Pharmaceutical Preparations. The panel has always been named the WHO Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations.

The Secretary mentioned that the Expert Committee was an official advisory body to the Director-General of WHO and was governed through rules and procedures. The report of the Expert Committee consisted of a summary of the discussions, recommendations to WHO and its Member States and included newly adopted guidelines. The report is presented to the WHO Governing Bodies for final comments, endorsement and implementation by Member States and constitutes WHO technical guidance. The development of a set of WHO guidelines is mainly based on recommendations by the World Health Assembly resolution, Executive Board resolutions to the Director-General based on advice from experts, the International Conference of Drug Regulatory Authorities, other WHO programmes and clusters or the recommendations proposed by the Committee itself.

The Expert Committee consultation process involves several steps, i.e. preliminary consultation and drafting, circulation of the first draft for comments, revision of the draft, discussion of the draft by the WHO Expert Committee and finally, once adopted, publication in the Expert Committee report as an annex, and submission to the WHO Governing Bodies and recommendation to Member States for implementation. Partners in the Expert Committee on Specifications for Pharmaceutical Preparations include: national and regional authorities; international organizations (e.g. Joint United Nations Programme on HIV/AIDS (UNAIDS), United Nations Children's Fund (UNICEF), United Nations Population Fund (UNFPA), World Bank, World Customs Organization (WCO), World Intellectual Property Organization (WIPO), and World Trade Organization (WTO); international professional associations; nongovernmental organizations (including consumer associations, Médecins sans Frontières; the pharmaceutical industry: including International Federation of Pharmaceutical Manufacturers Associations (IFPMA), International Generic Pharmaceutical Alliance (IGPA), International Pharmaceutical Federation (FIP), World Medical Association (WMA); and World Self-Medication Industry (WSMI)), members of the WHO Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations; specialists from all quality assurance-related areas, including regulatory, academic, pharmaceutical industry; WHO Collaborating Centres — usually national quality control laboratories; pharmacopoeia commissions and secretariats; national institutions and institutes; and regional and interregional regulatory harmonization groups (such as the Association of Southeast Asian Nations (ASEAN) and the International Conference on Harmonisation (ICH)).

2. General policy

2.1 Collaboration with international organizations and agencies

2.1.1 *The Global Fund*

An update on the Global Fund Quality Assurance Policy Implementation was presented to the Expert Committee. The Committee noted that about 48% of grant funds were for procurement of medicines and health products. Access to and continued availability of quality-assured medicines and health products were essential to fight acquired immunodeficiency syndrome (AIDS), malaria and tuberculosis (TB). The Global Fund does not perform procurement but elaborates procurement policies for quality-assured medicines and health products. The Committee was informed that the Global Fund encouraged companies to have their products prequalified by WHO and/or to be registered by a stringent drug regulatory authority.

The Global Fund Procurement and Supply Management Policies have three basic principles: to procure quality-assured products at the lowest price; to adhere to national and international laws; and to conduct procurement in a transparent and competitive manner. Procurement is based on the decisions of the Global Fund Board. The policy outlines what Principal Recipients (PRs) need to do. The Global Fund Quality Assurance Policy is based on the principles listed in Table 1.

Table 1

Principles of the Global Fund Quality Assurance Policy

Multisource pharmaceutical products	Single- and limited-source pharmaceutical products
<ul style="list-style-type: none">• Products generally off-patent and product standards are available in the public domain (e.g. Ph Int, BP and USP)• Products tend to be available from a wide range of manufacturers• Must comply with quality standards and requirements of drug regulatory authority in the recipient country	<ul style="list-style-type: none">• Products for which there are no publicly available QA standards, analytical methods, and reference substances for the finished dosage form (No monograph in Ph Int, BP or USP)• Products tend to be available from one or a limited number of manufacturers• Must procure single- or limited-source pharmaceutical product that meets the criteria approved by the Global Fund Board• Must comply with quality standards and requirements of DRA in the recipient country.

Ph Int, *The International Pharmacopoeia*; BP, *British Pharmacopoeia*; USP, *United States Pharmacopoeia*; QA, quality assurance; DRA, drug regulatory authority.

Pharmaceuticals procured with Global Fund resources are subject to authorization by the national drug regulatory authority (NDRA) in the

country in which they are used, following its standard practices for drug registration (or other forms of authorization, such as authorizations for special use) for pharmaceutical products.

For products that have passed the WHO Prequalification Project review, NDRA's are encouraged to expedite registration by accepting this WHO prequalification inspection and supporting assessment of the dossiers in lieu of national requirements.

For products that have been authorized by stringent drug regulatory authorities, NDRA's are encouraged to expedite registration by accepting, in lieu of national requirements, the Executive Summary of the Common Technical Document (CTD) or summary parts for quality, safety and efficacy together with all information necessary to perform quality control testing of products and the requisite reference standards.

Monitoring product quality is also a requirement endorsed by the Board. For all multisource products and single- and limited-source products classified as A (prequalified) or B (registered by a stringent NDRA) a product's PR is responsible for organizing at random intervals the quality control of the drugs received. PRs are encouraged to send the samples to WHO-recognized laboratories in cases where the NDRA has no capacity for this testing activity.

For single- and limited-source products classified as Ci or Cii products, as per the classification defined in the Global Fund Quality Assurance Policy (Board decision in April 2005), the quality control, before any shipment to the recipient country, is under the responsibility of the Global Fund Secretariat. WHO's Quality Assurance and Safety: Medicines team participated in the selection of the laboratories.

It was acknowledged that collaboration with WHO's Quality Assurance and Safety: Medicines team was crucial to achieve responsible quality assurance policies and to achieve the mission of the Global Fund. The Global Fund expressed appreciation of, trust in and support for the collaboration and expertise in the areas of the WHO Prequalification Programme, publication of monographs on medicines (e.g. antiretroviral medicines, artemisinin combination therapy and medicines used in the treatment of tuberculosis) and other technical expertise.

2.1.2 ***Pharmacopoeial Discussion Group***

The Committee was updated on the general method texts signed off by the Pharmacopoeial Discussion Group (PDG) in May 2007. The PDG is *the European Pharmacopoeia, the Japanese Pharmacopoeia and the United States Pharmacopoeia*. It was noted that harmonized texts would be published in the respective pharmacopoeias. A new version of the working procedure

for dealing with the revision of harmonized texts was agreed. A number of International Conference on Harmonisation (ICH) Expert Working Group Q6A general chapters were still under study.

The Expert Committee noted that a replacement batch of endotoxin standard was presently being established with the participation of WHO, the *European Pharmacopoeia*, the *Japanese Pharmacopoeia* and the *United States Pharmacopoeia*.

Of the method texts published in Methods of analysis: sections 1 to 3 of the 4th edition of *The International Pharmacopoeia*, there were some for which a corresponding internationally harmonized text was signed off by the PDG partners and published in all three above-mentioned pharmacopoeias. The Expert Committee endorsed the recommendations made during the consultation process, which includes circulation for, and receipt, review and discussion of comments as follows: the relevant method texts of *The International Pharmacopoeia* should be reviewed alongside the finalized harmonized PDG texts in order to identify any differences and to ascertain to what extent it might be appropriate to revise the text of *The International Pharmacopoeia*. Any proposed changes would then be circulated in accordance with the usual WHO consultation process. Once the suggested actions were identified and agreed by the WHO Expert Committee on Specifications for Pharmaceutical Preparations, the WHO Secretariat should contact the PDG, as appropriate, with regard to its decision on the use of PDG harmonized tests.

As an example of such a review, the Secretariat had carried out an examination of *The International Pharmacopoeia* method 2.3 Sulfated ash.

The Expert Committee endorsed the recommendation made during the consultation process that the PDG text be included in *The International Pharmacopoeia* and that it be used for application to new and revised monographs. However, it recommended that the current *International Pharmacopoeia* method be retained as an interim measure for application to the existing monographs. This precautionary approach was considered advisable in view of the large number of monographs affected.

2.1.3 **European Medicines Agency**

The Expert Committee was updated on the paediatrics initiatives of the European Medicines Agency (EMA) and on the main activities carried out by EMA in the last few months, which included two major events.

The new Paediatric Regulation entered into force in January 2007 and the new Paediatric Committee (PDCO) started its activities in summer 2007. One of the main tasks of the committee was to evaluate the Paediatric Investigation Plans (PIPs), plans for the development of medicines for the

paediatric population, which would be mandatory for new products from July 2008. The PDCO can also grant waivers on the submission of PIPs for medicines that are unlikely to benefit children.

A joint European Commission (EC)/EMA conference on the European Union (EU) Clinical Trials Directive was held on 3 October 2007 as part of an extensive consultation process started by the EC, following receipt of some criticism on the Directive. The main purpose of the conference was to discuss the possibility of amending the Directive, to make it more suitable for the stakeholders' needs. Among the criticisms, problems were reported on the compliance with the Directive and associated guidelines, and on some lack of harmonization of implementation of the Directive in EU Member States. Representatives of sponsors (pharmaceutical industry, contract research organizations (CROs), noncommercial research and academia), ethics committees, patients' organizations and regulators were present. A report on the conference would shortly be published on the EMA web site.

On topics relating to quality, EMA informed the Committee that a revision of the EU guidelines on radiopharmaceuticals had been published on the EMA web site for a 6-month external consultation period, and that the revision of the current guidelines on near infrared spectroscopy was continuing. Work on implementation in the EU of the ICH documents, Q8 (Pharmaceutical development), Q9 (Quality risk management) and Q10 (Pharmaceutical quality system) was also continuing.

Concerning good manufacturing practices (GMP), EMA reported that the work on the revision of various annexes to the EU-GMP guide was progressing. In particular the revision of Annex 1 (sterile manufacture) was now finalized and the revised Annex 2 (biologicals), had been published on the EMA web site for external consultation.

2.1.4 Council of Europe/European Directorate for the Quality of Medicines and HealthCare

The Committee was informed that Dr Susanne Keitel had been newly appointed Director of the European Directorate for the Quality of Medicines and HealthCare (EDQM). During the past year EDQM had undertaken a number of new activities. The Council of Europe Committee on Blood Transfusion and Organ Transplantation had been transferred to EDQM and to reflect this EDQM had had its name changed from the European Directorate for the Quality of Medicines to the European Directorate for the Quality of Medicines and HealthCare.

EDQM had also become the repository for the International Standards for Antibiotics and had taken on responsibility for their replacement and distribution. The Committee was informed that the 6th Edition of the

European Pharmacopoeia had been published in July 2007 and would become effective as of 1 January 2008. Many monographs had undergone editorial revision in order to bring them in line with the present style, in particular with regard to the Related substances test. It was also reported that three supplements would be published annually, following each session of the Commission. A new edition of the *European Pharmacopoeia* would be published every three years. An expert group on Traditional Chinese medicine had also been newly established and it was also intended to cover Ayurvedic products.

A symposium was held on the new EDQM premises entitled “New frontiers in the quality of medicines” to coincide with the publication of the 6th Edition of the *European Pharmacopoeia* and the move to the new building, which was inaugurated in March 2007.

2.1.5 **International Conference on Harmonisation**

The Committee was provided with an overview of activities on ICH quality guidelines including ICH Q8 (Pharmaceutical development), ICH Q9 (Quality risk management) and ICH Q10 (Pharmaceutical quality system). The documents were available on the ICH web site (www.ich.org).

During the meeting of the ICH held in Brussels in 2003, experts agreed on a new quality vision: “Develop a harmonised pharmaceutical quality system applicable across the lifecycle of the product emphasizing an integrated approach to quality risk management and science”. This has culminated in the three following guidelines: Q8: Pharmaceutical development (step 5), Q9: Quality risk management (step 5) and Q10: Pharmaceutical quality system (step 2).

This new vision or paradigm considers the medicinal product during its lifecycle, i.e. starting from development through technical transfer to routine manufacturing, putting emphasis on a better understanding of product and process and on deriving specifications from this understanding. The whole should be achieved by taking a more systematic approach to development, by using risk management tools and by working within a Q10-type quality system. This could result in some opportunities, for instance in the manufacturing area (e.g. design space, real-time release). In addition, experience gained through monitoring during routine manufacturing could be optimized in the light of the scientific understanding obtained during development studies (knowledge management).

Q8 has defined several concepts like Process Analytical Technology (PAT), design space, real-time release, control strategies and systematic approach to development. If Q8 addresses the drug product, experts agree that the same principles and concepts described there would also be applicable to the drug substance, whether derived chemically or by biotechnological

methods. It is the complexity of the product rather than the type of product itself which will have an impact on the implementation of these concepts.

According to current opinion in ICH, testing alone does not assure quality. However it was felt that end-product testing would still be part of a risk management assessment and that this might be a good topic for consideration at a future meeting of the Expert Committee. The Committee recommended that the Secretariat should continue to monitor the developments in ICH quality topics in order to assist the Committee to formulate a future strategy.

2.1.6 ***International Conference of Drug Regulatory Authorities***

The Committee was informed of plans that were under way for the 13th ICDRA that would be hosted by the Swiss Agency for Therapeutic Products (SwissMedic), to be held in Berne, Switzerland from 16 to 19 September 2008. The programme was still under development.

It was anticipated that the pre-ICDRA meeting would focus on paediatric medicines.

2.2 **Cross-cutting pharmaceuticals — quality assurance issues**

2.2.1 ***Quality assurance***

The Committee was pleased to note the continued cooperation with other WHO departments and programmes.

2.2.2 ***Herbal medicines***

The Committee received a report on WHO's policy and activities in the field of traditional medicine. The Traditional Medicine team (TRM) provided information on the International Regulatory Cooperation on Herbal Medicines (IRCH) and support provided to Member States for the integration of traditional medicine/complementary and alternative medicine (TM/CAM) into national health care systems, including the contribution of traditional medicine to primary health care. The IRCH was created in early 2006. Membership was open to the regulatory authorities responsible for herbal medicines. Currently IRCH had 19 Members.

The following new publications were presented to the Committee:

- *WHO monographs on selected medicinal plants*, Vol. 3, which provided 32 additional monographs on medicinal plants.
- *WHO guidelines on good manufacturing practices (GMP) for herbal medicines*, consisting of two independent annexes in the WHO Technical Report Series of publications, i.e. *GMP main principles for manufacture of herbal medicines* and *GMP supplementary guideline for manufacture of herbal medicines* (updated). These guidelines were compiled and

printed in order to promote GMP in this particular field and to provide core technical guidance in a more user-friendly manner. This booklet would be used as key training material for national capacity building in this field.

- *WHO guidelines on assessing quality of herbal medicines with reference to contaminants and residues*, which was reviewed by past Expert Committees and was now in press.
- A WHO technical document *Key technical issues of quality impacting on safety of homoeopathic medicines* was reviewed and finalized during the usual consultative process. WHO thanked over 400 reviewers, including the national regulatory authorities of 100 countries, who were involved in the preparation of this technical document.
- *WHO guidelines for basic training and safety in herbal medicines therapy* was finalized in November 2006, and was currently being edited.
- WHO Second Global Survey on national policy on traditional medicine and regulation of herbal medicines. The Committee was informed about the plan to conduct a second global survey to assess and measure the impact of the implementation of WHO's strategies. It was expected to provide WHO with updated and more comprehensive information from each Member State, and to enable WHO to identify new needs for technical support.

The Committee was also briefly informed about WHO's future direction in the field of traditional medicine, in the context of the WHO Medium-term Strategic Plan (MTSP): 2008–2013.

2.2.3 **Malaria**

The Committee was informed by the Coordinator, Policy, Access and Rational Use (PAR), of the continued collaboration between the Quality Assurance and Safety: Medicines (QSM) team and the Global Malaria programme to facilitate access to antimalarial products.

WHO's aim was to improve access to essential medicines for all people in need. In living up to this aspiration, PAR was very much aware of the critical role of product quality tools: specifications, test methodology and reference standards. In the area of access to antimalarials, PAR had the privilege of working closely with QSM and with the Expert Committee, especially on the monotherapies, to develop appropriate specifications, test methodology and reference standards. With the advent of artemisinin-based combination therapies (ACTs) PAR had moved to work on the supportive quality tools. The Coordinator was delighted to note that this session of the Committee would consider some of the documents related to this work.

PAR's work encompassed development of policies and guidance in the area of medicines supplies management. The team was starting to consolidate

its guidance on quality assurance in the supply chain, including monitoring and evaluation of performance of the delivery systems.

The issues discussed by the Committee relating to risk analysis and management, within the context of pharmaceutical quality systems, were equally applicable to supply chain management. PAR looked forward to the outcomes of the Committee's deliberations in this area as it would, in the near future, be sharing with the Committee its thinking on how these concepts and approach might strengthen medicines supplies management.

PAR was also pleased to note that the Committee was considering the guidance on GMP as it related to active pharmaceutical ingredients (APIs) as well as to prequalification of APIs. PAR looked forward to seeing this work completed as the team believed it would enhance the tools provided by WHO in assisting national programmes to assure quality of products circulating in domestic markets. It hoped the Committee would be able to facilitate the sharing of information emanating from the prequalification of APIs as widely as possible.

2.2.4 **Biologicals/vaccines**

The Expert Committee was informed that following the discussions at its forty-first meeting, further consideration had been given to the development of a draft policy to guide the transition from biological to chemical assay for the quality assurance of medicines. The issue had been discussed at the recent meeting of the Expert Committee on Biological Standardization. It was recognized that the transition from a biological approach, using biological assay methods reporting in International Units (IU), to a chemical approach, using physicochemical assay methods reporting in SI units, was an evolutionary step, based on an increased understanding that links structure with function, and made possible by the continuing development and increasing utility of physicochemical methods such as high-performance liquid chromatography (HPLC). Appropriate scientific evidence should be available to justify placing reliance on a chemical assay. The amount and type of evidence required might depend on the purpose of the assay (e.g. product characterization, routine quality control, pharmacopoeial compliance). Such transitions usually proceeded gradually as evidence was acquired and confidence was built. The process had, for example, been completed for drugs such as steroids, thyroid drugs and adrenergic agents, and largely completed for antibiotics. The transition had also been made for a number of peptide and small protein drugs.

Both Expert Committees recognized that the implications of such a transition might be complicated by considerations of labelling and dose regimens. The question of how dosage of any particular medicine was expressed and hence the manner in which strength was stated on the product

label required broad consultation. Once a switch had been made to the assay method specified in the relevant pharmacopoeia, the content limits in a pharmacopoeial monograph for a substance should be expressed in appropriate terms. However, an equivalence statement should normally be included to permit the continued labelling of the corresponding formulated preparations in IU.

The Expert Committee on Biological Standardization had recommended that WHO should develop a framework for handling such transitions and that progress should be made jointly by the two Expert Committees by means of an informal consultation. While acknowledging that once a biological assay was no longer required and the International Standard would no longer strictly be needed, the Expert Committee on Biological Standardization had advised a cautionary approach. This Expert Committee endorsed both these recommendations. It advised that, in cases where it was deemed necessary to continue to label products in biological units for the purposes of dosage, a mechanism should be found to maintain the International Unit. Concern was expressed that for some substances the use of different units of biological activity would give rise to problems of non-equivalence.

It was suggested that those antibiotics that were still assessed by means of microbiological assay should also be considered during the consultation process.

2.2.5 *Blood products*

The Committee was informed about WHO's work in the area of blood products and related biologicals. A summary was presented on the priority projects agreed upon at the recent meeting of the Expert Committee on Biological Standardization. It was noted that these included the development of guidelines for the production, control and regulation of antivenoms and anti-rabies immunoglobulins, guidelines for GMP for the production of blood products and the development of WHO Biological Reference Materials for the control of in vitro diagnostic tests used in assessing blood safety.

2.2.6 *Risk of transmitting animal spongiform encephalopathy agents via medicinal products*

The Committee noted that the Expert Committee on Biological Standardization had adopted an update of the major categories of infectivity for transmissible spongiform encephalopathies (TSEs) in human and animal tissues that might be used in the manufacture of medicinal products. WHO publishes authoritative information on the assignment of infectivity for TSEs aimed to assist national regulatory authorities and manufacturers in conducting risk assessment studies and selecting measures to reduce the risk

of transmitting TSE through medicinal products. New scientific information had emerged since the most recent guidance from WHO was published in 2006. Because of the rapid evolution of the scientific information, the updates of the Major Categories of infectivity for TSEs would only be published on the web site (www.who.int/bloodproducts).

The Committee noted that this was why the relevant text included in *The International Pharmacopoeia* invoked the “current version” of this guidance.

2.3 Essential medicines for children

The Committee was informed that the 60th World Health Assembly in May 2007 adopted a resolution on “Better medicines for children”. Article 2 of the WHA Resolution requested the Director-General: “(2) to ensure that all relevant WHO programmes, including but not limited to that on essential medicines, contribute to making safe and effective medicines as widely available for children as for adults;” and “(3) to promote the development of international norms and standards for quality and safety of formulations for children, and of the regulatory capacity to apply them”.

WHO was already working on the creation of a medicines list specifically tailored to children’s needs. As noted in a Press Release of 16 April 2007, some new entries for medicines for children had been added to the 15th Model List of Essential Medicines (EML). These were either oral liquids or chewable/dispersible tablets. They included the following medicines used in the treatment of epilepsy: carbamazepine oral liquid, chewable carbamazepine tablets, phenobarbital oral liquid, phenytoin oral liquid, chewable phenytoin tablets, valproic acid oral liquid and crushable valproic acid tablets. Moreover a WHO Model List for children had been suggested at a first subcommittee meeting (9–13 July 2007) and would be discussed at the 16th meeting of the Expert Committee on the Selection and Use of Essential Medicines (24–25 October 2007).

The subject of quality and safety of children’s medicines was covered at an informal consultation held in Geneva in November 2006, with a view to providing WHO guidance and training on pharmaceutical (quality) aspects of paediatric formulations. A joint WHO/FIP pilot training workshop for manufacturers was held in South Africa in April 2007 on pharmaceutical development (with an emphasis on paediatric medicines). A first draft on points to be considered was being prepared.

With respect to *The International Pharmacopoeia*, several monographs for specific paediatric formulations were in preparation as final texts and others were under development. It was noted that dosage form monographs in *The International Pharmacopoeia* were generally designed to cover a range

of strengths. In principal, therefore, they could accommodate both adult and paediatric products. Thus, where a paediatric medicine was developed by simply providing a lower strength of an adult formulation (e.g. a capsule, tablet or injection) which was the subject of a monograph in *The International Pharmacopoeia*, the paediatric medicine would be covered by that monograph. In such cases the strength(s) available for paediatric use could be added under Additional information.

2.4 Counterfeit medicines

The Committee was provided with an update by the International Medical Products Anti-Counterfeiting Taskforce (IMPACT). It summarized the work to date and the planned meetings at which discussion on available technology would continue. Most importantly WHO/IMPACT was establishing ongoing dialogue between drug regulatory authorities, manufacturers, distributors and technology providers in order to permit assessment of recent trends in anticounterfeit technology. IMPACT had five committees: legislative and regulatory structure; regulatory implementation; enforcement; communication; and technology.

The outcomes of the efforts of working groups would be combined in a toolkit. Additional information could be found on the relevant web site (<http://www.who.int/impact>).

3. Quality control—specifications and tests

3.1 *The International Pharmacopoeia* (4th edition)

The Committee was pleased to note that the 4th edition of *The International Pharmacopoeia* had been published and distributed and that *The International Pharmacopoeia* web site was now presented in a more user-friendly format. The improved layout was demonstrated using, as an example, medicines included in the WHO Prequalification Programme. Work was already under way on the first Supplement which would be published in book form and as a replacement CD-ROM and on-line version of the 4th edition. Approximately 30 monographs adopted by the Expert Committee were ready for inclusion in the first Supplement. The final texts of the monographs were available on the WHO Medicines web site (<http://www.who.int/medicines/publications/pharmacopoeia/overview/en/index.html>).

The Experts also complimented WHO on the new on-line connection to the 4th edition of *The International Pharmacopoeia* available at: <http://www.who.int/phint>.

3.2 Proposed new work plan

The Committee noted the good progress being made with the current work plan.

The Secretariat had recently carried out a review of the most recent Model List of Essential Medicines — the 15th — in order to identify entries in the list for which a monograph is neither published in the 4th edition of *The International Pharmacopoeia* nor included in the current work plan. The findings of the study formed the basis of the Secretariat's proposal for a new work plan.

The Committee reviewed and endorsed the proposals for the new work plan. These proposals were based on an analysis of:

- the review of the 15th Model List referred to above;
- current WHO priorities and focus issues, e.g. paediatrics, women's health, pain relief and various expressions of interest within the Prequalification Programme;
- suggestions made by colleagues in WHO's specific disease programmes and obtained from consultation meetings;
- certain classes or subclasses of medicines of particular importance in developing countries, e.g. anti-infectives (including antibacterials, antifungals, antiprotozoals and antivirals);
- focus on most common dosage forms — capsules, tablets, oral liquids and injections;
- need for a realistic work programme.

The Expert Committee agreed to the proposed work programme for the development of monographs for *The International Pharmacopoeia*; the proposals would be made available on the WHO Medicines/*International Pharmacopoeia* web site.

3.3 **Specifications for medicines, including children's medicines**

3.3.1 **Medicines for HIV and related conditions**

The progress of the draft monographs on antiretrovirals was presented to the Expert Committee for discussion and consideration.

It was noted that draft monographs for efavirenz capsules, nevirapine oral suspension and nevirapine tablets were in preparation. Draft texts had been circulated for comment in May 2007 and the comments received discussed at an informal consultation. Revised drafts were in preparation.

The Committee was pleased to note that work on a number of other monographs was in progress.

The current concern relating to the presence of "alkyl mesitates" in medicines was discussed. It was agreed that the statement in the manufacture section of the related monographs, such as that on nelfinavir mesilate, should be revised to make reference to a suitable method of control and possibly

to include an acceptance limit after checking with national and regional authorities.

3.3.2 ***Antimalarial drugs including combination products***

The following monographs were adopted subject to some minor modifications and inclusion of comments:

- lumefantrine
- artemether and lumefantrine tablets.

The monograph for artemether and lumefantrine capsules would be circulated again for comment. The Committee was pleased to note that the development of a number of other monographs was in progress.

3.3.3 ***Antituberculosis drugs including combination products***

The following monographs were adopted subject to some minor modifications and inclusion of comments:

- rifampicin, isoniazid and ethambutol tablets
- rifampicin and isoniazid dispersible tablets (for paediatric use)
- rifampicin, isoniazid and pyrazinamide dispersible tablets (for paediatric use).

The Committee was pleased to note that the development of a number of other monographs was in progress.

3.3.4 ***Oral rehydration therapy***

It was recalled that preparation of the draft monographs listed below had been initiated because zinc supplementation was included in the revised WHO/UNICEF recommendations for the management of diarrhoea as an adjunct to oral rehydration therapy and was included in the 15th Model List of Essential Medicines.

The following monographs were adopted subject to some minor modifications and inclusion of comments:

- zinc sulfate
- zinc sulfate oral solution, paediatric
- zinc sulfate tablets, paediatric.

3.3.5 ***Magnesium sulfate injection***

It was recalled that preparation of a monograph for magnesium sulfate injection had been initiated in view of the potential for errors in dosage due to confusion concerning the strength of this injection. The injection is included in the Model List of Essential Medicines and within the “Making pregnancy safer” programme of the WHO Family and Community Health Cluster. The

draft monograph was adopted subject to some minor modifications and inclusion of comments.

3.3.6 **Other medicines**

The Expert Committee noted that other monographs were in preparation and that draft texts had been circulated for comment, for example, for oseltamivir phosphate and for oxytocin. The latter was an example of a substance in transition from biological to chemical assay.

3.4 **Revision of texts**

3.4.1 **Storage**

As agreed by the WHO Expert Committee on Specifications for Pharmaceutical Preparations at its forty-first meeting in October 2006, the Secretariat had carried out a review of the monographs of *The International Pharmacopoeia* in which reference was made to storage “in a cool place” or “at a temperature not exceeding 15 °C” with a view to revising these statements, wherever possible.

The amendments recommended at an informal consultation were discussed and it was agreed that the relevant monographs would be revised accordingly for inclusion in the first Supplement to the 4th edition.

3.4.2 ***Oxytetracycline dihydrate: water***

During the preparation of the protocol for the first test in the 4th series of the External Quality Assurance Assessment Scheme for national quality control laboratories, a need for revision was identified. The Committee recommended that the limits for water be amended to “not less than 60 mg/g and not more than 90 mg/g” for inclusion in the first Supplement to the 4th edition.

3.4.3 ***Chewable mebendazole tablets***

At the meeting of the Expert Committee in October 2006 it was agreed that the monograph for mebendazole tablets should be revised to apply to chewable tablets in accordance with the entries included in the WHO Model List of Essential Medicines and Model Formulary. A revised monograph text was discussed; the points raised would be incorporated before circulation for comment.

3.5 **General monographs for dosage forms and associated method texts**

3.5.1 ***New general monographs — liquid preparations for oral use***

The need for a general monograph for “Liquid preparations for oral use” had been confirmed by the WHO Expert Committee on Specifications

for Pharmaceutical Preparations at its October 2006 meeting. It was required inter alia for use in conjunction with individual monographs for oral solutions of antiretrovirals, which had been adopted by the Expert Committee and for other monographs for oral liquids that were in preparation.

The Committee endorsed the inclusion of a statement mentioning paediatric preparations under “Additional information” and of a boxed text headed “Safety concerns” at the end of the section on Manufacture to highlight the importance of ensuring the quality of starting materials in view of the continuing incidents of diethylene glycol poisoning associated with oral liquids.

The text of the general monograph was discussed and adopted for inclusion in the first Supplement to the 4th edition subject to some minor modifications and inclusion of comments.

Supplementary information chapter: Guidance on the pharmaceutical development of paediatric formulations

The draft monograph for Liquid preparations for oral use that was circulated for comment included a suggestion that guidance on the pharmaceutical development of paediatric formulations could be provided in future in the Supplementary information section of *The International Pharmacopoeia* and a preliminary draft outline had been included in the text.

During the usual consultative process, the inclusion of such a guidance text had been recommended. It had been suggested that brief guidance on key issues of formulation could be given. The focus would be to provide guidance concerning the types of paediatric formulations that would be suitable for use. In view of other activities in this field (see sections 2.3 and 14.1) it had been recommended that preparation of a Supplementary information chapter should await the outcome of these initiatives.

The Expert Committee endorsed these recommendations.

3.5.2 ***Efficacy of antimicrobial preservation***

In light of the comments received on the draft general monograph the Expert Committee recommended that a text on Efficacy of antimicrobial preservation (containing a suitable test method together with criteria for judging the preservative properties of the formulation) be developed for inclusion in *The International Pharmacopoeia*. It was suggested that the first step should be a review of the different approaches adopted in various pharmacopoeias.

3.5.3 **Review of published general monographs**

The following general monographs for dosage forms have been published in the 4th edition of *The International Pharmacopoeia*:

- capsules
- ophthalmic preparations
- parenteral preparations
- suppositories
- tablets
- topical semi-solid dosage forms.

The following general monographs for dosage forms have been prepared for addition to *The International Pharmacopoeia*:

- oral powders (final text on Medicines web site)
- liquid preparations for oral use (text adopted).

The Committee agreed that, with the publication of the 4th edition, it would be timely for these (published) general monographs to be reviewed and revised as necessary. It endorsed the addition of a submonograph for Dispersible tablets to the general monograph for Tablets to include a Definition and a requirement for Disintegration.

3.5.4 **Additional general monographs**

It was recommended that the basis for preparing further general monographs for inclusion in *The International Pharmacopoeia* should be the need to support individual dosage form monographs recommended for addition to the work plan.

3.5.5 **Review of published pharmaceutical method texts**

The Expert Committee agreed that, with the publication of the 4th edition, it would be timely to review the general method texts for Pharmaceutical technical procedures (Methods of analysis section 5) to ascertain whether any revision was considered necessary or advisable. It was noted that there were some for which a corresponding internationally harmonized text had been signed off by the PDG partners (*European Pharmacopoeia*, *Japanese Pharmacopoeia* and *United States Pharmacopoeia*) and had been published in the three pharmacopoeias.

The Committee recommended that, in these cases, the relevant method texts of *The International Pharmacopoeia* should be reviewed alongside the harmonized texts to identify the differences and to ascertain to what extent it might be appropriate to align *The International Pharmacopoeia* text with the PDG text. Where relevant, the WHO Secretariat would contact the PDG requesting permission to use the relevant texts with due reference.

**Uniformity of content and mass for single-dose preparations
(5.1 and 5.2 in *The International Pharmacopoeia*, 4th edition)**

The *International Pharmacopoeia* tests together with the PDG harmonized text had been considered during the usual consultative process. The Expert Committee discussed the proposals. It was noted that the harmonized test differed in several fundamental ways from those in *The International Pharmacopoeia*. The Expert Committee agreed that the existing established tests in *The International Pharmacopoeia* provided adequate confirmation of uniformity and had the advantage of being straightforward, transparent and suitable for application in a wide variety of compliance settings. It was therefore decided that these tests should be retained in the Methods of analysis section of *The International Pharmacopoeia*.

It was also agreed to include the harmonized tests within the Supplementary information section of *The International Pharmacopoeia*. Providing information in this way concerning tests that might be used by manufacturers to demonstrate that the manufacturing process yielded a suitable product with respect to uniformity might be helpful to users of *The International Pharmacopoeia*.

It was suggested that, during the review of texts on methods, consideration might be given to the inclusion in “5.1 Uniformity of content” of an additional acceptance criterion in terms of a standard deviation.

Dissolution test for solid oral dosage forms (5.5 in *The International Pharmacopoeia*, 4th edition)

The Committee recommended that any discrepancies between the descriptions (e.g. the dimensions) of the dissolution apparatus should be eliminated by aligning the text of *The International Pharmacopoeia* with the harmonized PDG text. It was noted that this work would be carried out during the review of the general methods.

**Test for Extractable volume for parenteral preparations
(5.6 in *The International Pharmacopoeia*, 4th edition)**

The Committee noted that the approach used in *The International Pharmacopoeia* and PDG tests were similar. It was recommended that the comparison carried out by the Secretariat form the basis of a review of text of the method given in *The International Pharmacopoeia*.

3.5.6 General texts for performance of finished dosage forms

The Committee agreed that it would be helpful to users of *The International Pharmacopoeia* (especially manufacturers but also regulatory authority assessors and inspectors) to provide guidance concerning certain tests that may be used by manufacturers to demonstrate that the manufacturing process

yields a suitable product with respect to particular physical attributes. Such non-mandatory test methods could be described within the Supplementary information section of *The International Pharmacopoeia*. Reference could then be made to the method text under the heading Manufacture, in the relevant general monographs.

The following general methods were agreed to be relevant in relation to the general monographs of *The International Pharmacopoeia*:

- friability of uncoated tablets;
- resistance to crushing of tablets;
- measurement of consistency by penetrometry; and
- determination of softening time of lipophilic suppositories.

It was recommended that these methods should be included in the Supplementary information section of *The International Pharmacopoeia*. This could be carried out alongside any revision of the relevant general monographs.

The WHO Secretariat would contact the *European Pharmacopoeia* and PDG requesting permission to use these texts with due reference.

3.6 Radiopharmaceuticals

The Expert Committee noted the progress made in the development of monographs on radiopharmaceuticals in cooperation with the International Atomic Energy Agency (IAEA). Following consultation and discussion, it had been agreed that this work should include inter alia revision of the general monograph in *The International Pharmacopoeia* and the preparation of monographs for individual radiopharmaceuticals. Meanwhile, for the main volumes of the 4th edition of *The International Pharmacopoeia*, published in December 2006, the section on Monographs for radiopharmaceuticals consisted of the general monograph for Radiopharmaceuticals as included in the 3rd edition.

A draft revised general monograph for Radiopharmaceuticals had now been prepared by the IAEA together with a first set of individual draft monographs for a first series of about 30 radiopharmaceutical preparations (more drafts were in preparation) for addition to the 4th edition of *The International Pharmacopoeia*. The Expert Committee was pleased that these texts had now been circulated by WHO for comment in line with the usual consultative process for monograph development. As noted within the documents however, the WHO Secretariat had not, as yet, adapted these texts to the format and style of *The International Pharmacopoeia*. This would be carried out at a later stage. Meanwhile, a “skeleton text” had been prepared to provide an indication of the format and style that would be used for the monographs for the individual radiopharmaceutical preparations.

Comments had, therefore, been invited on the technical content of the draft monograph texts.

In addition to publishing these monographs in the section on Radiopharmaceuticals in a future Supplement to *The International Pharmacopoeia*, it was intended that they also form part of a joint IAEA/WHO publication that would also include other texts relevant to the manufacture and use of radiopharmaceuticals. In including the monographs in such a “stand-alone” publication, it would be necessary to supplement them with relevant supporting texts from *The International Pharmacopoeia*. These would include, for example, the General notices, the general monographs for Parenteral preparations and capsules and selected Methods of analysis.

3.7 Dissolution tests for addition to specific monographs

At its meeting in October 2006, the Expert Committee agreed the general format for the test for inclusion in relevant monographs for products containing highly soluble APIs. As suggested, the proposals for addition to the specific monographs had been circulated for comment. In addition to comments relating to the analytical aspects of the dissolution test proposed for addition to a specific monograph, some of the comments received raised questions concerning the overall approach to dissolution testing in *The International Pharmacopoeia* as represented in the circulated document.

Following discussion it was recommended that, for inclusion in the relevant monographs of *The International Pharmacopoeia* for tablets and capsules containing highly soluble APIs, the standardized criteria should be amended as follows:

(Using six tablets) the amount in solution for each of the tablets is not less than 80% of the amount declared on the label. If the amount obtained for one of the six tablets is less than 80%, repeat the test using a further six tablets; the average amount for all 12 tablets tested is not less than 75% of the amount declared on the label and the amount in solution for none of the tablets is less than 60% of the amount declared on the label.

It was agreed that, for pharmacopoeial purposes, the disintegration test was generally satisfactory for products containing highly soluble APIs (class I and III). It was, therefore, recommended that in monographs for tablets or capsules containing such highly soluble APIs, if the proposed standardized dissolution test was to be included, it should be as an alternative to disintegration. The approach adopted in the monograph for isoniazid and ethambutol hydrochloride tablets was recommended for application to

all the relevant monographs but using the amended criteria as shown in Box 1.

Box 1. Isoniazid and ethambutol hydrochloride tablets

Dissolution/disintegration

- Either test A or test B may be applied

A. Dissolution. Carry out the test as described under 5.5 Dissolution test for solid oral dosage forms, using as the dissolution medium, 500 ml of dissolution buffer, pH 6.8, TS and rotating the paddle at 75 revolutions per minute. At 30 minutes withdraw a sample of 10 ml of the medium through an in-line filter. Allow the filtered sample to cool to room temperature and dilute 5 ml to 20 ml with water [solution (3)]. Determine the content of isoniazid, $C_6H_7N_3O$, and ethambutol hydrochloride, $C_{10}H_{24}N_2O_2 \cdot 2HCl$ as described below under Assay using solution (3) in place of solution (1).

For each of the six tablets tested, calculate the total amount of isoniazid, $C_6H_7N_3O$, and ethambutol hydrochloride, $C_{10}H_{24}N_2O_2 \cdot 2HCl$ in the medium from the results obtained. For both substances the amount in solution for each of the tablets is not less than 80% of the amount declared on the label. For either substance, if the amount obtained for one of the six tablets is less than 80%, repeat the test using a further six tablets; the average amount for all 12 tablets tested is not less than 75% of the amount declared on the label and the amount in solution for none of the tablets is less than 60% of the amount declared on the label.

B. Disintegration. Comply with 5.4 Disintegration test for tablets and capsules, operating the apparatus for 10 minutes. If the tablets do not comply, carry out test A above.

It was recognized that, for application to the monographs for tablets and capsules containing less soluble APIs identified as requiring a dissolution test, the standardized test conditions might need to be modified. It was appreciated that work was being carried out by the Collaborating Centre on the development of such monograph-specific tests. It was agreed that it would be timely to review the situation.

The Expert Committee endorsed the recommendations to:

- apply a standardized dissolution test to tablets and capsules containing highly soluble APIs
 - as an alternative to disintegration (using format as shown above)
 - subject to amendment of the criteria;
- add the test thus modified to the relevant monographs by means of the first Supplement to the 4th edition;
- review the development of additional dissolution tests.

4. **Quality control — International Chemical Reference Substances and International Infrared Reference Spectra**

4.1 **Annual report of the WHO Collaborating Centre**

The Committee noted with appreciation the work carried out by the WHO Collaborating Centre for Chemical Reference Substances as presented in the report for 2006, and by the collaborating laboratories. It was noted that the total number of International Chemical Reference Substances (ICRS) distributed from the Centre in 2006 was 1579 which was an increase from 1360 reported in 2005. The five most frequently requested substances were in order of demand: didanosine, artesunate, phenacetin melting point (MP), didanosine for system suitability and vanillin melting point (MP).

The lists of all ICRS and International Infrared Reference Spectra available from the Collaborating Centre are attached as Annex 1. The Centre was complimented for its efforts and support to *The International Pharmacopoeia*.

4.2 **Adoption of new International Chemical Reference Substances**

Twelve International Chemical Reference Substances were established in 2006, including the following seven new substances:

- abacavir sulfate
- anhydrotetracycline hydrochloride
- 4-epianhydrotetracycline hydrochloride
- 4-epitetracycline hydrochloride
- medroxyprogesterone acetate
- nevirapine impurity B
- pyrazinamide.

The Committee adopted the report and the seven new ICRS and expressed support for the continuation of the activities of the Collaborating Centre. Annex 1 includes the current list of all ICRS.

4.3 **Infrared Reference Spectra**

Developments, maintenance and publication

It was noted that the Collaborating Centre in Sweden was working on the preparation of infrared reference (IRR) spectra in a form suitable for publication. Of the 202 spectra required, 125 were now available and 75 had yet to be prepared. It was noted that these spectra were as included in the relevant analytical reports appended to the annual reports previously presented to the Expert Committee and that they could, therefore, be

considered as “adopted”. In order to prepare the remaining spectra, the Collaborating Centre was seeking suitable samples of the substances concerned and would appreciate assistance with this task. Such samples should generally be suitably qualified for preparing the relevant ICRS.

The Expert Committee :

- noted that 125 reference spectra were available for inclusion in *The International Pharmacopoeia* and on the web site;
- approved the text for inclusion in *The International Pharmacopoeia* and on the web site together with the IRR spectra.

5. Quality control — national laboratories

5.1 External Quality Assurance Assessment Scheme

With a view to continuing the promotion of quality assurance in drug quality control laboratories in WHO Member States, the first test series of Phase 4 of a proficiency testing scheme had commenced. To date 49 laboratories had been contacted with a view to enlisting their participation.

This External Quality Assurance Assessment Scheme (EQAAS) aimed to give each laboratory the opportunity to measure its performance through a confidential system of testing of blind samples and to determine its ability to perform a given analytical procedure within a network of governmental control laboratories. The system was aimed at reinforcing mutual confidence within a network of governmental control laboratories.

In this 4th phase, performance would be evaluated in the five following analytical procedures:

- titration
- water content by Karl-Fischer titration
- dissolution test
- determination of glucose by polarimetry
- high-performance liquid chromatography assay.

The Committee noted the recently received preliminary report on the first test carried out in Phase 4 of this Scheme. The results reported were moderately satisfactory since only 66% of the laboratories had obtained z -scores lower than two. Nevertheless there seemed to have been an improvement compared to the previous proficiency testing scheme on water determination by Karl-Fischer titration, in which only 58% of the laboratories reported satisfactory results. However, the laboratories participating in this testing scheme were not all the same as those that had previously participated. Thus, it seemed that the overall performance of laboratories performing this technique was still poor.

The Expert Committee discussed mechanisms to improve the overall performance of the laboratories and in particular that of the poorer performers. Suggestions included standardized protocols, communication via an established web site or discussion forum, capacity building and educational opportunities. It might be helpful if these suggestions could be implemented on a regional basis. It was also suggested that WHO could send out samples to the poorly performing laboratories with detailed protocols and advice on where things could go wrong to assist in improving the laboratories' techniques.

The Committee recommended that:

- training with “hands-on” workshops should be organized, based on the gap analysis in order to enhance the effects of the EQAAS; and
- there should be a link with capacity projects in target countries.

The WHO Secretariat informed the Expert Committee that the above recommendations had already been taken into account in recent WHO activities. Workshops which would include participants from more than 20 WHO Member States had been organized in collaboration with the WHO Regional Offices for Africa and the Eastern Mediterranean and with EDQM, namely in Morocco and in the United Republic of Tanzania, which would include participants from more than 20 WHO Member States.

The Expert Committee noted the outcome of the first series of results, as well as examples of tests undertaken in the various phases and series and thanked both the United Nations Children's Fund (UNICEF) for the provision of samples and the Collaborating Centre in Sweden for the provision of ICRS.

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

6.1 **Good manufacturing practices for active pharmaceutical ingredients**

6.1.1 ***Proposal for revision: WHO GMP for APIs***

Based on feedback received during informal consultations and from the WHO Prequalification Programme, discussions had been held on new approaches and risk evaluation for manufacture of medicines and specifically as to whether the current WHO GMP for APIs should be revised to bring them into line with the ICH GMP guide for APIs (reference ICH Q7).

Both texts were available on the following web sites:

- WHO good manufacturing practices (GMP) for active pharmaceutical ingredients (APIs). Printed version: WHO good manufacturing practices:

starting materials. In: *Quality assurance of pharmaceuticals. A compendium of guidelines and related materials, Volume 2*, 2nd updated edition. Geneva, World Health Organization, 2007:188. Available at: http://www.who.int/medicines/areas/quality_safety/quality_assurance/production/en/

- ICH GMP guide for APIs (ICH Q7) available at: <http://www.ich.org/>

Bringing the WHO guidelines into line with those of the ICH would require a stepwise approach and appropriate training provided together with other parties.

The Committee agreed that the principles of ICH Q7 should be adopted because:

- they had been adopted by numerous regulatory authorities worldwide; and
- many manufacturers of APIs already complied with ICH Q7.

The Committee thus recommended that the GMP for APIs be revised accordingly following the normal WHO consultation process.

6.2 **Good manufacturing practices for biologicals**

The Committee was informed of the process for revision of the WHO GMP for biologicals and supported collaboration between the two Expert Committees (Specifications for Pharmaceutical Preparations; and Biological Standardization) in this area.

To define a strategy for the revision, a series of workshops assembling regulators and manufacturers of biological products had been conducted to gather information on the users' needs for the interpretation and implementation of GMP. Based on a gap analysis, it was recommended that a biologicals-specific core section should be provided, in which the requirements common to all biologicals would be covered, and then a series of technical appendices covering specific topics would be added as necessary. The core set of requirements would include the procurement of biological starting materials; avoiding contamination of products through facility design, validation and qualification of inherently variable biological processes; stability concerns for labile biological materials; quality control and quality assurance for biological products; risk analysis tools for biological processes; and inspection procedures for manufacturers of biologicals. For the annexes, the topics accorded the highest priority were the GMP requirements in high-level biosafety facilities.

The Committee was reminded that the WHO GMP for biologicals were used for prequalification by the WHO Immunization, Vaccines and Biologicals Department.

The Expert Committee suggested that the currently published WHO GMP for biologicals was not really out of date and that the real issue was training of inspectors. It was suggested to keep the proposed new text simple and practical and in particular to avoid contradiction with the main principles in the main WHO GMP text. It was recalled that the GMP for biologicals was a special section of the WHO GMP text. The Committee would be kept informed and consulted once a draft document became available.

6.3 **Good manufacturing practices — new texts**

Based on the recommendations made during the forty-first meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations, discussions had taken place in informal consultations based on feedback from the Prequalification Programme during the usual consultative procedure, with a view to reviewing the possible gaps in the areas of GMP and other WHO guidance on manufacture and inspection.

The inspectors involved in the Prequalification Programme had identified the need for WHO to start the development of new GMP guidance texts covering:

- microbiological laboratories; and
- computerized systems.

After discussion, the opinion of the Expert Committee was that a new text on computerized systems would not be a priority for the time being and agreed that a new GMP text for microbiological laboratories be drafted.

7. **Quality assurance — new approaches and risk analysis**

An update on the new ICH Q10 was given. It was, however, considered that there would be no immediate impact of the new ICH Q 10 for developing countries. In addition, it was not expected that these principles could be easily adopted within small- and medium-sized industries.

It was concluded that the Q8, Q9 and Q10 were useful tools and that there was currently no need for similar WHO document application of these ICH principles which might be difficult in “non-ICH” countries. It was recommended that WHO follow the new developments in this area.

In addition the Committee made recommendations for WHO to:

- review an update of the WHO guidelines on Hazard Analysis and Critical Control Points (HACCP);

- revise the main text of the WHO GMP to include these principles of *application of risk management* by adding the following sentence: “There should be a quality risk management system”;
- develop a *WHO explanatory document* addressing issues such as Corrective and Preventive Action (CAPA), on how to conduct proper investigations, etc. and consider inclusion of these principles in the WHO GMP; and
- add a new section on “utilities” to the *main text of the GMP*.

7.1 **Technology transfer**

During the usual consultative procedure, the need for new WHO guidelines on transfer of technology was discussed. Colleagues from the WHO Prequalification Programme shared their experience of recently submitted dossiers by, and inspections carried out in, plants that had undergone technology transfer. It appeared that there was currently no international guidance available that could cover technology transfer, which was becoming increasingly popular. Technology transfer was happening worldwide both within and between companies, within the same country as well as between countries. It was noted that the International Society for Pharmaceutical Engineering (ISPE) had published a guide on technology transfer.

The Expert Committee recommended that WHO guidelines on transfer of technology be developed.

8. **Quality assurance — distribution and trade of pharmaceuticals**

8.1 **WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce**

8.1.1 ***Proposal for improvement of the Scheme***

The Committee was provided with a presentation on the WHO Certification Scheme outlining some of the problems in the current process and a proposal for improvement.

It was emphasized that new technologies and tools were available, for example, public drug regulatory authority (DRA) web databases, and increased implementation and use of the Scheme in the WHO Prequalification Programme. Reference was also made to the WHO pharmaceutical starting materials certification scheme (SMACS) (In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-eighth report*. Geneva, World Health Organization, 2004 (WHO Technical Report Series, No. 917), Annex 3).

The Expert Committee members recalled that the Scheme had originally been designed to serve as a tool for exchange of information between DRAs. However it was noted that most certificates nowadays were requested by brokers or manufacturers.

According to the European Federation of Pharmaceutical Industries and Associations (EFPIA) the current administrative procedures involved in issuing a Certificate of Pharmaceutical Product (CPP) could delay the making available of new medicines to patients. Alternatives to a CPP should be acceptable as evidence of approval by a competent authority, e.g. e-form and information available from a DRA or a letter of approval posted on a web site.

An intensive discussion took place on the problems noted with the Certification Scheme. The main problems identified and possible measures to address these problems are listed in Table 2.

Table 2

Problems with the Certification Scheme and potential solutions

Problem	Measures to be taken
Exporting countries that do not fulfil the prerequisites required by the Certification Scheme issue certificates to support export.	<ul style="list-style-type: none"> • Request countries to submit a verifiable self-assessment report before they become party to the Scheme. Alternatively: <ul style="list-style-type: none"> – consider the possibility of ISO certification; or – certification by a well-established/known regional drug regulatory authority cooperation/block, e.g. ASEAN, EU, ICH, SADC. • Require governments of Member States to submit a letter declaring that the competent authority meets the prerequisites set out in the Certification Scheme. • Establish criteria for assessment and follow a procedure for assessment for each Member State when they indicate that they wish to be part of the Scheme. • Add a clear statement on use of Scheme, certificates to be used only for their intended purpose.
Countries not party to the Scheme issue certificates to support export of pharmaceutical products.	<ul style="list-style-type: none"> • WHO should write a letter to the governments of those countries asking them to be party to the Scheme. • Inform authorities of importing countries of the names of those countries that issue certificates without being party to the Scheme. • Advise countries not to accept certificates from countries that are not party to the Scheme.

Problem	Measures to be taken
<p>There have been cases in which forged certificates have been supplied to competent authorities of importing countries.</p>	<ul style="list-style-type: none"> • Ask exporting countries to develop secured certificates by using a watermark, hologram, or any other suitable technology. • Request each exporting country to submit to WHO samples of their certificates so that WHO can compile these certificates and distribute them to Member States with the list of names of competent authorities to serve as reference material. • Avoid use of photocopies. • Promote access of certificates on secure web sites instead of a paper version (may be necessary to meet legal requirements) at least for cross-reference purposes. • Simplify use and availability. • Use legal information provided by DRA web sites.
<p>Information on who released the batch for marketing is not disclosed in certificates issued by exporting countries.</p> <p>Currently not asked for in WHO model certificate.</p>	<ul style="list-style-type: none"> • Certificates should be transparent in disclosing information that has an impact on quality of products. • A certificate issued for a product manufactured by a contract manufacturer should indicate the name and address of: <ul style="list-style-type: none"> – the product licence holder; and – the name and address of the contract manufacturer. • A certificate issued for a product intended for export only (not registered in the exporting country) should indicate: <ul style="list-style-type: none"> – the name and site address of the manufacturer who released the batch; and – the reason why it is not registered in the exporting country.
<p>Certificates are issued for products that are produced by manufacturers that do not comply with WHO GMP requirements.</p>	<ul style="list-style-type: none"> • Manufacturers producing pharmaceutical products should be required to provide a certificate of GMP compliance, e.g. issued by any known and reliable national inspectorate such as the FDA. • Importing countries should inspect any manufacturer suspected of non-compliance with WHO GMP requirements. • Address challenges in regions, e.g. for less developed DRAs, to collaborate within their region and obtain regulatory information. • Separate information on GMP inspection from dossier/marketing authorization.

Problem	Measures to be taken
Addresses of some authorities have changed.	<ul style="list-style-type: none"> • WHO should send a circular letter to countries asking them to reapply for participation in the Scheme. WHO should take countries off the list if they do not reapply. • Membership to the Scheme should have a time limit, i.e. to be renewable every 5 or 10 years.
<p>Member States issue certificates for products not manufactured under their jurisdiction, i.e. in their country.</p> <p>Current practice in many countries. Key issue: assessment of dossier for marketing authorization.</p>	<ul style="list-style-type: none"> • In principle, Member States should not issue certificates for products that are not produced under their jurisdiction, i.e. in their country. The country in which the product has been manufactured should issue the certificate. • If a certificate is issued for such a product then the name and address of the manufacturer (the one who released the batch) and the site address where the product has been manufactured should be indicated in the certificate.
Exporting countries issue other certificates such as free sale certificates.	<ul style="list-style-type: none"> • WHO should advise importing country authorities not to request or accept free sale certificates. They should request and accept only those certificates indicated in the WHO Certification Scheme. • WHO should ask exporting countries not to issue certificates other than those mentioned in the WHO Certification Scheme. • WHO should organize seminars and workshops for DRAs from time to time in order to promote the Scheme and give advice to countries.
Importing countries require legalization of certificates, additional stamps, etc.	<ul style="list-style-type: none"> • This is due to lack of confidence in the authenticity of certificates. This problem will remain until countries build up confidence in the Scheme and the certificates being issued under the Scheme. • Exporting countries should develop secured certificates and should provide samples of certificates, signature and stamp of authority to serve as reference materials.

ISO, International Standards Organization; ASEAN, Association of Southeast Asian Nations; EU, European Union; ICH, International Conference on Harmonisation; SADC, Southern African Development Community; DRA, drug regulatory authority; FDA, Food and Drug Administration of the USA; GMP, good manufacturing practices.

The Committee further reviewed the possible solutions and endorsed in principle the main strategies as follows:

- Revise the Certification Scheme to make it responsive to the needs of countries that rely on it.
- Revise criteria for membership to the Scheme.
- Prepare a list of Member States party to the Scheme.
- Create awareness and understanding of the Scheme.
- Delisting and negative publication (e.g. if a country issues a certificate without being a party to the Scheme).
- Strengthen national regulatory systems.

The Committee recommended that further discussion of the measures and steps to be taken should take place in a future consultation, taking due consideration of the comments received during the consultation phase of the discussion paper.

9. **Quality assurance — stability**

The Committee was provided with a historical perspective on WHO's stability testing guidelines and the Expert Committee's involvement in the ongoing discussions.

To date 22 parties had submitted comments on the draft guidelines on the stability testing of active pharmaceutical ingredients and pharmaceutical products, and comments were still being submitted. The Committee was informed about the major changes in the new draft guidelines. The scope of the guidelines had been expanded to include new and existing pharmaceutical ingredients and addressed information to be submitted in original and subsequent applications for marketing authorization/registration of the related pharmaceutical products for human use.

The annex listing long-term storage conditions required for marketing authorization/registration in each WHO Member State had been prepared in response to the International Conference of Drug Regulatory Authorities (ICDRA) recommendation and as endorsed by the Expert Committee at its forty-first meeting. The list included all information received by WHO from its Member States so far. Further efforts were being made by WHO to collect the missing information. It was hoped that DRAs would respond to the request to facilitate import to and export from their countries, thus avoiding creation of barriers to access to medicines.

The discussion considered the applicability of the guidelines to existing products and APIs. The Committee was provided with information on a proposal for an additional storage condition based on data climatic conditions prevailing in India and other countries. The condition was

suggested as an extension for the climatic zone IV and given as 30°C /70% RH. Global manufacturers might be faced with undertaking studies for many different stability testing conditions when exporting. Also labelling with storage conditions had already been noted as being complicated, and would become even more complex with the addition of another set of new conditions. During the discussion, the Committee recognized that more stringent conditions would normally be accepted by DRAs in place of prevailing lower conditions in use in the country.

The Committee concluded that it would be better to minimize the number of stability testing conditions necessary for global marketing. It was decided to retain the currently adopted conditions for zone IV, i.e. zone IVa at 30°C/65% RH and zone IVb at 30°C/75% RH.

The Committee also suggested asking one technical expert to assist in the revision process and prepare a consultation that would review all comments received. Several comments, e.g. on the definition of the retest date, had been made and would also be discussed during the consultation.

10. **Prequalification of priority essential medicines and devices**

The Committee was provided with the annual report for 2006 and an update on the Prequalification Programme activities in 2007. The Committee was pleased to note that the financial support from the Bill and Melinda Gates Foundation and from UNITAID had enabled the programme to expand its activities related to training, capacity building, technical assistance and quality control laboratories, and to recruit additional staff, including the opening of a rotational position for assessors for staff from national regulatory agencies. Government support from a number of countries including France and the People's Republic of China from where staff were seconded to WHO was appreciated.

The Committee recommended that any revision and new procedures for prequalification should be consistent and be in line with those adopted by this Committee. The Committee suggested harmonizing the terminology using the definitions it had already adopted in related quality assurance guidelines.

It was anticipated that the Prequalification Programme would follow the new developments in paediatrics once information was available from the Model List of Essential Medicines and specific programmes.

10.1 **Procedure for prequalification of medicines**

The experience from implementation of assessment and inspection activities in the prequalification of priority medicines and the feedback

from interested parties were reported as necessitating revision of the current procedure.

The Committee was informed about the changes envisaged to the procedure for the prequalification of medicines, which were aimed at increasing the transparency of the procedure, and clarifying the responsibilities of applicants and WHO in the evaluation process and in the maintenance activities of the prequalified medicines.

The Committee noted that the procedure was currently being discussed with the WHO Office of the Legal Counsel and would be presented again to the Committee at its next meeting in 2008.

10.2 Procedures for prequalification of intrauterine devices and condoms

Two guidelines, on prequalification of intrauterine devices (IUDs) and of male condoms, resulting from collaboration between the WHO Departments of Medicines Policy and Standards and Reproductive Health and Research, and the United Nations Population Fund (UNFPA), were presented to the Committee for discussion and review. Both procedures followed the principles and processes of the current procedure for prequalification of medicines and summarized the experience from quality evaluation carried out by agencies procuring IUDs and condoms. The agency implementing these two procedures would be the United Nations Population Fund (UNFPA).

IUDs and condoms have been proven to be effective contraceptives and were essential products included in the WHO Model List of Essential Medicines. Prequalification of IUDs and condoms was important to prevent unwanted pregnancies. Condoms were also important in preventing transmission of sexually transmitted infections including HIV. Special expertise was needed to evaluate these procedures which was to be undertaken by the WHO Reproductive Health and Research Department.

The Committee agreed, in principle, to the suggested procedures, and unless considerable critical comments were received during their external review, suggested adoption of the prequalification procedures for intrauterine devices and male condoms (Annexes 2 and 3).

It was proposed to include prequalification of these devices for discussion on the agenda for the next ICDRA meeting.

11. Prequalification of active pharmaceutical ingredients

11.1 Procedure for prequalification of active pharmaceutical ingredients

The need for quality assurance of APIs, as requested by Member States, was discussed by the Committee at its fortieth and forty-first meetings, and

this need had also been endorsed at the recent meeting of ICDRA. The Committee was given a presentation on the proposed procedure, which followed that for the finished products, and which would be implemented by the WHO Prequalification Programme. If adopted this procedure would enable procurement agencies and organizations, including WHO Member States, to validate the quality of products they were purchasing and manufacturers of finished products to choose from reliable sources and manufacturers of APIs.

Discussion by the Committee included the following points. A significant factor in the quality of the finished pharmaceutical product was the quality of the APIs used for its formulation. Under current WHO GMP guidelines, it was the manufacturer of the pharmaceutical product who was responsible for the overall operations having an impact on the quality of the medicines, including the choice of the suppliers and manufacturers of the ingredients. Pharmaceutical manufacturers had to qualify their suppliers of APIs as part of their overall quality systems. However, in the context of globalization, APIs were sourced in a worldwide market and the risk of sourcing substandard or contaminated products was high. That was why only a proper system of qualification of suppliers could ensure the continuous sourcing of APIs of appropriate quality and safeguard public health interests.

The Committee endorsed, in principle, the suggested approach. It was noted that the procedure had been distributed for comment and that it would be presented again to the Committee at its next meeting.

The Committee suggested that WHO focus on the prequalification of APIs related to HIV/AIDS, tuberculosis, malaria medicines and reproductive health, in accordance with the priorities of the Prequalification Programme.

12. **Prequalification of quality control laboratories**

The prequalification of quality control laboratories was undertaken by WHO together with UNICEF, UNAIDS, UNFPA and UNITAID and with the support of the World Bank. The Committee was informed that the 3rd Invitation for Expression of Interest (EOI) had been published in September 2007 (http://www.who.int/prequal/info_applicants/eoi/EOI-QCLabsV3.pdf). In contrast to previous EOIs, which had been limited to African laboratories, there was now no regional limitation. WHO, however, reserved the right to prioritize the assessment of national quality control laboratories or laboratories providing testing services to the government and to laboratories in areas where United Nations agencies identified the need for medicines quality testing.

The Committee was informed that at present there were four prequalified laboratories and 19 laboratories in various stages of the prequalification

procedure. In terms of capacity building WHO provided technical assistance to three laboratories and two others would be provided with assistance before the end of 2007. Two training programmes for laboratory staff had been organized and two more would be organized before the end of 2007.

The Committee was given an overview of the sampling and testing projects. The survey of the quality of antiretroviral medicines circulating in selected African countries had been finalized and the report was provided to Committee members. There were seven ongoing projects focused on antimalarials, paediatric antiretrovirals, second-line antiretrovirals, lumefantrine/artemether tablets and generic products containing nelfinavir mesilate.

13. **Active pharmaceutical ingredient master file**

The Committee was briefed by a senior assessor assisting in the Prequalification Programme about the active pharmaceutical ingredient master file (APIMF) procedure being used within the assessment process. It was suggested that this be adopted as a formal WHO guideline.

The main objective of the APIMF procedure was to allow the valuable confidential intellectual property or “know-how” of the manufacturer of the API to be protected, while at the same time allowing the applicant or holder of the prequalification dossier (PD) to take full responsibility for the finished pharmaceutical product (FPP) and the quality and quality control of the API. The Prequalification team thus had access to all the information that was necessary for an evaluation of the suitability of the use of the API in the FPP.

This guideline was intended to assist applicants and PD holders in the compilation of the API information in their dossiers for a prequalification dossier application (PDA) or a prequalification dossier variation (VPD) of an FPP. It was also intended to help APIMF holders in the compilation of their APIMFs.

Information available in master files was used in the Prequalification Programme to avoid duplication of assessment. It was acknowledged that there was currently no globally harmonized system for assessing APIMFs among WHO Member States.

The Committee agreed, in principle, to the suggested procedure, unless considerable critical comments were received during the consultation procedure (Annex 4). It was also suggested that the terminology should be harmonized using the definitions already adopted by this Committee in related quality assurance guidelines.

The Committee also recommended a review of the concept relating to the evidence on regulatory acceptance, as this did not seem to be in current

practice by any national authority. WHO was requested to promote discussion on sharing regulatory information between the DRAs to conserve resources in APIMF and dossier assessment and inspection.

14. Regulatory guidance

14.1 Specific guidance on children's medicines

Following the recommendations of the forty-first Expert Committee meeting, as well as WHO's efforts (Sections 2.3 and 3.5.1) to further enhance access to medicines for children, the Committee considered the need for specific guidance in this area.

The Committee was informed about several workshops that had been and were being conducted in various parts of the world by WHO to promote development and quality aspects of paediatric formulations. The Committee was pleased to note that a two-day pre-meeting on medicines for children was planned to take place during the 13th ICDRA.

The Committee encouraged cooperation between the different departments in WHO working on clinical and quality aspects of paediatric formulations. It was noted that the paediatric subcommittee had highlighted and mapped research gaps in the clinical area. The recommendations of the Committee with respect to advancing the development of paediatric formulations included the following steps:

1. Review literature for information and studies on dosage forms suitable for children.
2. Develop a guiding principles document on development of formulations for children's medicines.
3. Include specifications for *The International Pharmacopoeia* (this work had already started).

It was suggested to closely link the various guidance texts currently in development, e.g. the newly suggested pharmaceutical development of multisource products and proposed draft text for oral liquid formulations for inclusion in *The International Pharmacopoeia*.

14.2 Guidelines for pharmaceutical development of generics

In view of the recent developments within the ICH, assessors involved in the Prequalification Programme voiced the possibility of the need for WHO to develop a guidance document for pharmaceutical development for generics.

The main purpose of such a document would be to guide the pharmaceutical industry on what to include in the pharmaceutical development section of

the dossier and offer NDRA information on how to assess the resulting submission. Further, it would harmonize and facilitate the efforts of the prequalification applicants and assessors. The proposal included a suggested structure for a possible new WHO text on a pharmaceutical development plan for generics.

The Expert Committee discussed the proposal to create new WHO guidelines for the development of generics and concluded that this might be useful for originators and manufacturers of generic products. The Committee, therefore, recommended that preparation of a document be initiated, following the normal procedure, for consideration at the next meeting.

14.3 **Quality of herbal and complementary medicines**

The Traditional Medicine (TRM) team informed the Committee about the development of new WHO guidelines on selection of substances for quality control of herbal medicines. TRM briefed the Committee on the background to these guidelines and the development plan. The revised second draft of the guidelines would be circulated to global reviewers, including the members of the Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations.

The Expert Committee would be kept informed about progress.

14.4 **Near infrared spectroscopy**

A discussion took place on the possible need for WHO to draft guidance on near infrared spectroscopy (NIR). The issue had been raised by colleagues involved in assessment as well as in inspection in relation to the WHO Prequalification Programme.

For WHO purposes the two main issues appeared to be method and application and would involve the following:

Method: Preparation of a method text for inclusion in *The International Pharmacopoeia*.

Application: Possible WHO guidance on the use of NIR in pharmaceutical quality assurance.

The following recommendations were made by the Expert Committee:

- prepare a stand-alone, general guidance document including the methodology; and
- review existing test methods for later inclusion in the Supplementary section of *The International Pharmacopoeia*.

15. **Nomenclature, terminology and databases**

15.1 **WHO terminology used in quality assurance**

The newly updated database was presented to the Committee. The information was now available on the WHO quality assurance web site (http://www.who.int/medicines/areas/quality_safety/quality_assurance/en/). The Committee expressed its appreciation for the work done as the database could now be accessed when guidelines were prepared. This would ensure consistency in the terms used.

The Expert Committee endorsed the use of the terminology database which included definitions of all terms used in the medicines quality assurance guidelines adopted in its meetings. It was recommended that the same database be used whenever new texts in this area were developed by WHO and its Regional Offices, as this database was intended to help harmonize terminology and to avoid misunderstandings that might result from the different terms and their interpretations used in various WHO publications. The terminology database would be updated whenever new terms and definitions were adopted by this Expert Committee.

The Committee recommended that preferred terms should be identified, when different definitions had been published over time.

15.2 **International Nonproprietary Names for pharmaceutical substances**

The Secretary of the International Nonproprietary Names (INN) Programme gave an update on the selection of INNs with a special focus on selection of INNs for biological products. Annex 5 includes the main principles for selection of biologicals as agreed by the INN experts.

The Committee was also informed about the information available on the INN web site and on the INN Cumulative List no. 12 on CD-ROM.

15.3 **Pharmacopoeial references**

The Coordinator of HTP Information Management provided information on the new on-line connection for *The International Pharmacopoeia* (www.who.int/phint) and WHO's pharmacopoeial reference database.

Currently WHO has access to this database in-house. The Expert Committee recommended that this database also be made available to its members and to those directly involved in monograph development and also upon request to national quality control laboratories.

16. Miscellaneous

16.1 Diethylene glycol

In view of the numerous tragic events which have seemed to occur persistently over the past 70 years, the Expert Committee recommended the following:

1. Prepare a general paper with a different target audience:
 - public;
 - health professionals working in hospitals (including clinicians).
2. Revise monographs on glycerol and propylene glycol:
 - to include a test for absence of diethylene glycol if feasible preference should be given to a thin-layer chromatography method.
3. When the test under point 2 is finalized, include it in the *External Quality Assurance Assessment Scheme (EQAAS)* series.
4. Alert drug regulatory authorities (DRAs) with a paper including:
 - advice on tools available;
 - advice to assessors to include specifications for absence of diethylene glycol;
 - advise not to allow testing to be skipped, but that strict implementation of rules, also for excipients and especially for “risky” ones, was important. The use of excipients in herbal preparations, e.g. cough syrups, also required special attention.

In addition the Committee recommended that this topic be included on the agenda of the next ICDRA meeting and a review of which measures should be undertaken by Member States to help prevent new incidents involving diethylene glycol poisoning.

16.2 Regulatory burden — inspections

During various agenda items the topic of inspections was raised. Discussion took place to identify means to minimize the impact on manufacturers of repeated inspections, as well as that on inspectorates. It was mentioned that some manufacturers were concerned with the burden imposed by the increasing trend of multiple inspections performed in the same year by different national regulatory authorities. Concern was raised about the continuing lack of exchange of inspection reports. It was felt that sharing of information about inspection plans was also important.

The Committee was informed that the Secretariat was still collaborating with various agencies on the approach to inspections. Joint inspections were also done in some cases where possible, e.g. WHO Prequalification Programme and EDQM. WHO informed the Committee about the availability of public inspection reports (PIRs) from the inspections carried out within the

context of the Prequalification Programme and that DRAs were informed immediately in cases of serious life-threatening deficiencies found within the entities being inspected as part of the Prequalification Programme.

The Committee was informed of plans to hold a special workshop during the 13th ICDRA on information sharing and risk assessment.

The Committee requested that:

- a risk-based approach in selection of inspections be attempted based on the sharing of information;
- better cooperation on a regional basis be considered; and
- information on databases be made available where possible.

It also suggested that:

- positive reports should be published; and
- information on negative results be exchanged among DRAs and inspectorates.

17. **Summary and recommendations**

The international guidelines, specifications and nomenclature developed under the aegis of the Expert Committee serve all Member States, international organizations, United Nations agencies, regional and interregional harmonization efforts, and underpin important initiatives, including the prequalification of medicines, the Roll Back Malaria Programme, Stop TB, essential medicines and medicines for children. The advice and recommendations provided by this Expert Committee are intended to help national and regional authorities (in particular DRAs), procurement agencies, as well as major international bodies and institutions, such as the Global Fund to Fight AIDS, Tuberculosis and Malaria, and international organizations such as UNICEF — to combat problems of counterfeit and substandard medicines and to work towards access to quality medicines. Making resources available for these activities is, therefore, very cost-effective.

The activities discussed during this Expert Committee have broad inter- and intra-cluster relationship and links. This is mainly because most of the standards, such as GMP and requirements for stability testing, are broadly applicable to all groups of medicines. In addition, the Committee serves to develop specific additional guidance and specifications as needed for the various medicines recommended by WHO programmes.

The WHO-managed Prequalification Programme could not function without the guidelines, standards and specifications adopted by this Committee after passage through its rigorous, wide consultative process. Moreover,

as a result of implementing these guidelines and specifications, practical suggestions for potential revision or the need for additional guidance are communicated in return to the Expert Committee. Another valuable aspect of the link between the normative side and the Prequalification Programme is that participating members of DRAs obtain “hands-on” experience in joint inspections and joint regulatory assessment activities with the participation of both developed and developing countries. The experience gained by participating colleagues from NDRAs is shared in training workshops, thus allowing even more regulators to benefit from the outputs of this programme. Manufacturers and quality control laboratories benefit from helpful advice given in the inspection reports. National authorities benefit from the availability of public assessment and inspection reports published on the web and upon request to the Prequalification Programme.

The members of the Expert Committee work towards making available clear, independent and practical standards and guidelines for medicines. Standards in the area of quality assurance for medicines were developed by the Committee through an international consensus building process. This Committee reconfirmed the need to hold the meeting of the Expert Committee annually to allow it to respond swiftly to the international needs in this area and recommended that the annual frequency of its meetings be maintained.

In conclusion, the Expert Committee oversees activities in the area of quality assurance that it considers should continue efficiently and swiftly in order to enable Member States, international organizations, United Nations agencies, regional and interregional harmonization efforts to benefit from them. Sustainability of the activities discussed is considered essential, if WHO is to continue to be seriously committed to provide these services laid down in its Constitution.

The following new standards and guidelines were adopted and recommended for use

1. List of available International Chemical Reference Substances (Annex 1)
2. Procedure for assessing the acceptability, in principle, of male latex condoms for purchase by United Nations and other agencies (Annex 2)
3. Procedure for assessing the acceptability, in principle, of TCu380A intrauterine devices for purchase by United Nations and other agencies (Annex 3)
4. Guidelines on Active Pharmaceutical Ingredient Master File (APIMF) Procedure (Annex 4)
5. Main principles of INNs for biologicals (Annex 5)

For inclusion in The International Pharmacopoeia

The following monographs were adopted subject to some minor modifications.

- *For antimalarial medicines:*
 - lumefantrine
 - artemether and lumefantrine tablets
- *for antituberculosis medicines:*
 - rifampicin, isoniazid and ethambutol tablets
 - rifampicin and isoniazid dispersible tablets (for paediatric use)
 - rifampicin, isoniazid and pyrazinamide dispersible tablets (for paediatric use)
- *for oral rehydration therapy:*
 - zinc sulfate
 - zinc sulfate oral solution, paediatric
 - zinc sulfate tablets, paediatric
- *other medicines:*
 - magnesium sulfate injection
- *general monographs for:*
 - oral powders
 - liquid preparations for oral use.

The Committee adopted the following new ICRS:

- abacavir sulfate
- anhydrotetracycline hydrochloride
- 4-epianhydrotetracycline hydrochloride
- 4-epitetracycline hydrochloride
- medroxyprogesterone acetate
- nevirapine impurity B
- pyrazinamide.

In addition to the above, the Committee adopted:

- the work plan for future development of monographs for inclusion in *The International Pharmacopoeia*; to be posted on the WHO web site;
- 125 Infrared Reference Spectra for publication on the WHO web site and in the First Supplement to *The International Pharmacopoeia* together with an explanatory text;
- a new general policy for *The International Pharmacopoeia* regarding dissolution testing, allowing a disintegration test as first choice and an alternative for dosage forms containing highly soluble APIs;
- several amendments to recently adopted monographs of *The International Pharmacopoeia*, including a revision of the storage condition for a “cool place” to read “at a temperature not exceeding 15 °C”;

- a revision of the main text of the WHO GMP to include principles of *application of risk management* by adding the following sentence: “*There should be a quality risk management system*”.

In addition, the Committee:

- endorsed, in principle, the suggested approach for prequalification of APIs, and suggested that WHO focus on the prequalification of APIs related to HIV/AIDS, tuberculosis, malaria medicines and reproductive health, in accordance with the priorities of the Prequalification Programme.

The following recommendations were made in the various quality assurance-related areas. Progress on the suggested actions should be reported to the next Expert Committee.

The underlying principle is that the development of specifications and guidelines will be carried out using the established international consultative process.

Organizational

- WHO Secretariat to prepare a standard layout of a document, including points for introduction and action points for use by all presenting WHO staff in order to facilitate the discussion and report writing.

The International Pharmacopoeia

- Continue development of specifications for medicines included in the WHO Model List of Essential Medicines with a special focus on priority diseases and paediatric medicines, including revision of general monographs, the efficacy of antimicrobial preservation, dissolution tests and review of pharmaceutical methods.
- Continue the preparatory work on supplements to *The International Pharmacopoeia*, 4th edition, in printed and in electronic form (CD-ROM and on line).
- Continue collaboration with the International Atomic Energy Agency (IAEA) with a view to replacement of monographs for radio-pharmaceuticals.
- Revise monographs on substances in which alkyl mesilate is present in view of the recent serious safety concerns.

International Reference Standards

- In collaboration with the WHO Expert Committee on Biological Standardization, elaborate a draft policy for cases where a transition from biological to chemical reference preparations may be appropriate in the future. Discuss this topic and related issues in a joint session with the Expert Committee on Biological Standardization.

International Chemical Reference Substances (ICRS)

- Promote use of ICRS through various activities, including a promotional offer to national authorities and improvements to the Collaborating Centre's web site.

External Quality Assurance Assessment Scheme

- Continue the External Quality Assurance Assessment Scheme (EQAAS) for national quality control laboratories.
- Organize further “hands-on” quality control laboratory workshops to enhance the effects of the EQAAS for national quality control laboratories.
- Forge links with capacity building projects in target countries through greater involvement of the WHO regional offices to advise on capacity building for those laboratories from which doubtful or unsatisfactory results have been reported.

Good manufacturing practices (GMP) and manufacture

- Revise WHO GMP for APIs to be revised in line with the principles of ICH Q7.
- Develop *new WHO GMP guidance* texts for:
 - microbiological laboratories.
- Add new section on “utilities” to the *main text of the GMP*.
- Develop a *WHO explanatory document* addressing issues such as corrective and preventive action (CAPA), on how to conduct proper investigations, etc., and consider inclusion of these principles in the WHO GMP.
- Follow up on the revision process for GMP on biological products currently taking place under the aegis of the Expert Committee on Biological Standardization.
- Follow up on development in the area of blood products and their derivatives.
- Assess the need for an update of the WHO Hazard Analysis and Critical Control Point (HACCP) guidelines.

Transfer of technology

- Develop new WHO guidelines on transfer of technology.

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

- Discuss further measures and steps to be taken regarding the WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce in a consultation, taking due account of the comments received during the consultation phase of the discussion paper.

Regulatory guidance

- Review all comments received in a consultation with a view to finalizing the process of revising the WHO guidelines on stability testing.
- Promote discussion on sharing regulatory information between the DRAs to conserve resources in assessment of dossiers and inspection. Further review the evidence on regulatory acceptance currently not being practiced by any national authority.
- Prepare a stand-alone, general WHO guidance text on the use of NIR in pharmaceutical quality assurance, including the methodology, and review existing test methods for later inclusion in the supplementary section of *The International Pharmacopoeia*.

Regulatory burden and inspections

- To reduce the regulatory burden with regard to increasing inspections promote:
 - a risk-based approach to the selection of inspections based on the sharing of information;
 - better cooperation on a regional basis;
 - sharing information on databases where possible;
 - publication of *positive reports*; and
 - exchange of information on negative results among DRAs and inspectorates.

Prequalification procedures

- The Committee adopted, in principle, two sets of guidelines on prequalification of intrauterine devices (IUDs) and of male condoms, unless considerable critical comments were received during the consultation procedure. The Committee also suggested that the topic of prequalification of IUDs and male condoms be included on the agenda for the next ICDRA meeting.

Development of medicines, including “child-size”

- The Committee recommended cooperating with the different departments in WHO working on clinical and quality aspects of paediatric formulations. With respect to advancing the development of paediatric formulations the following steps were proposed:
 - Review literature for information and studies on dosage forms suitable for children.
 - Develop a document explaining the guiding principles for the development of formulations for children’s medicines.
 - Include specifications for *The International Pharmacopoeia* (to continue ongoing work).

- Initiate new WHO guidance on the pharmaceutical development of generics.

WHO databases

- Maintain the consolidated database on terminology used in WHO quality assurance and identify preferred terms when different definitions have been published over time.
- Make pharmacopoeial reference database available to Expert Advisory Panel members, prequalification assessors, those involved in the development of monographs for *The International Pharmacopoeia* and upon request to national quality control laboratories.
- Maintain the INN database.

Prevention of diethylene glycol intoxication

In view of the numerous tragic events caused by diethylene glycol which have seemed to occur persistently over the past 70 years, the Committee made the following recommendations:

- Prepare a general paper with a different target audience:
 - the public; and
 - health professionals working in hospitals (including clinicians).
- Revise the monographs on glycerol and propylene glycol:
 - to include a test for absence of diethylene glycol; if feasible preference should be given to a thin-layer chromatography method.
- Once such a test (see above) is finalized, include it in the External Quality Assurance Assessment Scheme (EQAAS) series.
- Alert DRAs by providing them with a paper including:
 - advice on tools available;
 - advice to assessors to include specifications for absence of diethylene glycol;
 - advise not to allow testing to be skipped, but that strict implementation of rules, also for excipients and especially “risky” ones, is important. Use of excipients in herbal preparations, e.g. cough syrups, also requires special attention.
- Add this topic to the agenda of the next ICDRA meeting in order to review what measures should be taken by Member States to help prevent new incidents involving diethylene glycol poisoning.

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Professor I. Addae-Mensah, University of Ghana, Legon, Ghana; Mrs S. Ahmed Jaffar, Directorate General of Pharmaceutical Affairs and Drugs Control, Ministry of Health, and Office of the WHO Representative, Muscat, Oman; Mr Amaal Al Shaar, RA and Stability Manager, Research and Development Department, Dar Al Dawa, Jordan; Dr R. Andrews, Medicines and Healthcare Products Regulatory Agency, London, England; Professor S.A. Bawazir, Vice-President, Head of Drug Sector, Saudi Food and Drug Authority, Riyadh, Saudi Arabia; Dr L. Bigger, Regulatory and Scientific Affairs, International Federation of Pharmaceutical Manufacturers Associations, Geneva, Switzerland; Professor C.F. Bittencourt, Farmacopéia Brasileira, Universidade Federal de Santa Maria, Santa Maria, RS, Brazil; Dr F.J.

Blanco, Chief, HIV/AIDS and Health Centre, UNICEF Supply Division, Copenhagen, Denmark; Dr M. Bohm, Q/EHS Training/External Standards, Bayer Schering Pharma, Berlin, Germany; Mr P.-A. Bonnet, Scientific Director, Direction des Laboratoires et des Contrôles, Agence française de sécurité sanitaire des produits de santé, Montpellier-Vendargues Site, Vendargues, France; Dr M. Borer, Research Advisor, Eli Lilly and Company, Corporate Reference Standards, Indianapolis, USA; Professor R. Boudet-Dalbin, Faculté de Pharmacie, Laboratoire de Chimie Thérapeutique, Paris, France; Dr J.A. Brittes Funck, Member of International Health Expert Committee, United States Pharmacopeia, Rockville, MD, USA; Mr W. Bukachi, Project Coordinator, International Affairs, United States Pharmacopeia, Rockville, MD, USA; Dr. D. Calam, Wiltshire, England; Mr S. Camplisson, Director of Quality Assurance and Development, Allergan Pharmaceuticals, Dublin, Ireland; Mrs A. Castro, Regulatory Affairs Director, Senior Pharmacist, Roche Servicios S.A., Heredia, Costa Rica; Dr L. Ceron, Adviser, Direccion General de Medicamentos, Insumos y Drogas DIGEMID, Peruvian Ministry of Health, Lima, Peru; Dr B. Chapart, Pharma Review Manager, Global Analytical Development, Sanofi-Aventis Pharma, Anthony, France; Professor Y. Cherrah, Director, Laboratoire National de Contrôle des Médicaments, Rabat, Morocco; Mrs S. Chiroy, Central American Federation of Pharmaceutical Laboratories, Guatemala City, Guatemala; Dr J.C. Craft, Member of International Health Expert Committee, United States Pharmacopeia, Rockville, MD, USA; Dr B. Davani, Senior Scientist, Department of Standards Development, United States Pharmacopeia, Rockville, MD, USA; Professor H. de Jong, International Pharmaceutical Excipients Council, Courbevoie, France; Professor T. Dekker, Research Institute for Industrial Pharmacy, North-West University, Potchefstroom, South Africa; Dr P. Dikshit, Member of International Health Expert Committee, United States Pharmacopeia, Rockville, MD, USA; Professor E. Doelker, Laboratoire de Pharmacie galénique, Faculté des Sciences — Section de Pharmacie, University of Geneva, Geneva, Switzerland; Dr S. Durand-Stamatiadis, World Self-Medication Industry, Ferney-Voltaire, France; Dr R. Fendt, Fine Chemicals Division — Head Regulatory & GMP Compliance Pharma Solutions, Limburgerhof, Germany; Dr P.H.M. Fontilus, Inspector-General of Public Health, Curaçao, Netherlands Antilles; Dr M. Garvin, Senior Director, Scientific and Regulatory Affairs, Pharmaceutical Research and Manufacturers of America, Washington, DC, USA; Dr M. Guazzaroni Jacobs, Director/Team Leader, Regulatory Monitoring, Global Quality Operations, Pfizer Inc., New York, NY, USA; Dr G.T. Gunnarsson, Quality Expert and Junior Assessor, Icelandic Medicines Control Agency, Seltjarnarnes, Iceland; Dr Hakimah Hoseh, Head of Registration Unit, Registration Department, Drug Directorate, Jordan Food and Drug Administration, Amman, Jordan; Mrs M. Hayes Bachmeyer, TRIS Management, Technical Regulatory Affairs, F. Hoffmann-La Roche, Pharmaceuticals Division, Basel, Switzerland; Dr Hua Zhang, GMP Department Head, Center for Certification & Evaluation, Shanghai Food and Drug Administration, Shanghai, People's Republic of China; Dr InKyu Kim, Korean Food and Drug Administration, Seoul, Republic of Korea; Dr M. James, GlaxoSmithKline Services Unlimited, Brentford, Middlesex, England; Professor Jin Shaohong, Executive Deputy Director, National Institute for the Control of Pharmaceutical and Biological Products, Ministry of Public Health, Beijing, People's Republic of China; Dr M. Kaplan, Director, Institute for Standardization and Control of Pharmaceuticals, Jerusalem, Israel; Dr M. Keller, Biologist, Swissmedic, Swiss

Agency for Therapeutic Products, Division Certificates & Licenses, Licensing Sector, Berne, Switzerland; Dr P. Kucera, Warwick, New York, NY, USA; Mr R. Lambour, Central American Federation of Pharmaceutical Laboratories, Guatemala City, Guatemala; Dr R. Luigetti, Scientific Administrator, European Medicines Agency, Inspections Sector, Canary Wharf, London, England; Dr A. Mechkovski, Moscow, Russian Federation; Dr M. Mehmandoust, Quality Assurance and Safety: Medicines, WHO, Geneva, Switzerland; Dr. J.H. Miller, Head, Laboratory Division, European Directorate for the Quality of Medicines and HealthCare, Strasbourg, France; Mr M.G. Moester, Senior Inspector of Health Care, Inspectie voor de Gezondheidszorg, Rijswijk, the Netherlands; Dr K. Morimoto, Office of Review Management, Review Planning Division, Pharmaceuticals and Medical Devices Agency, Tokyo, Japan; Dr O. Morin, Regulatory and Scientific Affairs, International Federation of Pharmaceutical Manufacturers Associations, Geneva, Switzerland; Mr N. Orphanos, Bureau of Policy, Science, and International Programs Division, Therapeutic Products Directorate, Health Products & Food Branch, Health Canada, Ottawa, Canada; Dr C. Pillati, Instituto Nacional de Medicamentos, Administración Nacional de Medicamentos, Alimentos y Tecnología Médica, Buenos Aires, Argentina; Dr J. Pogány, Budapest, Hungary; Dr M. Pokomela, Medicines Evaluation and Research, Department of Health, Pretoria, South Africa; Ms A. Poompanich, Senior Technical Advisor (Efficacy of Medicine), Division of Drug Analysis, Department of Medical Sciences, Ministry of Public Health, Nonthaburi, Thailand; Dr J. Posti, Associate Director, Regulatory Affairs, Pharmaceutical Adviser, Schering Oy, Helsinki, Finland; Mr R. Prabhu, Regulatory Affairs Department, Cipla, Mumbai, India; Dr S. Reddy, Head, Analytical Services Department, Strides Arcolab, Bangalore, India; Dr R. Reh, Quality Control — Microbiology, Bayer HealthCare, Leverkusen, Germany; Dr E.A. Roberts, GlaxoSmithKline, Ware, Hertfordshire, England; Dr S. Rönninger, Global Quality Manager, F. Hoffmann-La Roche, Basel, Switzerland; Dr L.M. Santos, Scientific Liaison — International Health Expert Committee, United States Pharmacopeia, Rockville, MD, USA; Dr P.G. Shrotriya, New Mumbai, India; Dr S. Singh, Department of Pharmaceutical Analysis, National Institute of Pharmaceutical Education and Research, Nagar, Punjab, India; Dr G.N. Singh, Scientific Director, Indian Pharmacopoeia Commission, Government of India, Ministry of Health and Family Welfare, Central Indian Pharmacopoeia Laboratory, Ghaziabad, India; Ms K. Sinivuo, Senior Researcher, National Agency for Medicines, Helsinki, Finland; Ms N. Sittichai, Bureau of Drug and Narcotics, Department of Medical Sciences, Ministry of Public Health, Nonthaburi, Thailand; Dr L. Slamet, Deputy for Therapeutic Product & Narcotic, Psychotropic and Addictive Substance Control, National Agency of Drug and Food Control, Jakarta, Indonesia; Dr S. Stavchansky, Member of International Health Expert Committee, United States Pharmacopeia, Rockville, MD, USA; Dr A. Sulistiowati, Head, Division of Therapeutic Product and Hazardous Substances, National Quality Control Laboratory of Drug and Food, National Agency of Drug and Food Control, Jakarta, Indonesia; Professor M. Sznitowska, Department of Pharmaceutical Technology, Medical University of Gdansk, Gdansk, Poland; Ms E. Taute, Pharmaceutical and Analytical Committee, Medicines Control Council, Pretoria, South Africa; Dr D. Teitz, Bristol-Myers Squibb Company, New Brunswick, NJ, USA; Dr B.B. Thapa, Chief Drug Administrator, Department of Drug Administration, Ministry of Health and Population, Kathmandu, Nepal; Dr P. Travis, Global Compensial Affairs, Merck,

West Point, PA, USA; Ms M. Treebamroong, Senior Pharmacist, Drug Quality & Safety, Department of Medical Sciences, Bureau of Drug and Narcotics, Ministry of Public Health, Nonthaburi, Thailand; Mr P. van der Hoeven, Active Pharmaceutical Ingredients Committee, European Chemical Industry Council, Brussels, Belgium; Dr L. Virgili, Director, Global Testing Standards, Bristol-Myers Squibb Company, New Brunswick, NJ, USA; Dr A. Ward, Regulatory Affairs, Avecia Vaccines, Billingham, England; Dr D.E. Webber, Director-General, World Self-Medication Industry, Ferney-Voltaire, France; Professor W. Wieniawski, Polish Pharmaceutical Society, Warsaw, Poland; Dr J.M. Wiggins, Global Compendial Affairs, Regulatory & Analytical Sciences, Merck, West Point, PA, USA; Professor Yang Zhong-Yuan, Guangzhou Municipal Institute for Drug Control, Guangzhou, People's Republic of China; Dr Yun-Hee Lee, Chemistry and Cardiovascular Drug Team, Korea Food & Drug Administration, Seoul, Republic of Korea; Dr M. Zahn, Keltern, Germany.

Annex 1

List of available International Chemical Reference Substances and International Infrared Reference Spectra

1. International Chemical Reference Substances

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

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

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

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

The stability of the International Chemical Reference Substances kept at the WHO Collaborating Centre for Chemical Reference Substances is monitored by regular re-examination and any material that has deteriorated is replaced by new batches when necessary. Lists giving control numbers for the current batches are issued in the annual reports from the Centre and new lists may also be obtained on request.

Ordering information

Orders for International Chemical Reference Substances should be sent to:

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

The current price for the International Chemical Reference Substances is US\$ 70 per package. An administration charge of US\$ 10 is added to each order to cover costs for handling and dispatch by air mail or air parcel post. If dispatch by air freight is required the freight costs will be about US\$ 200, these costs to be paid by the purchaser. Payment should be made according to the invoice. Kindly direct all payments (e.g. cheques, bills of exchange, banker's drafts, banker's transfers) to:

Nordea Bank Sweden, SE-105 71 Stockholm
(Apoteket AB/APL/ACL/WHO)
Swift: NDEASESS
Account no (PG): 2 98 40-6
IBAN: SE 65 9500 0099 6026 0029 8406

The invoice number must be quoted when payment is made.

If, however, payment in advance is asked for but not allowed according to the regulations of certain countries, **documentary remittance (cash against documents)** may be used. This means that the invoice is paid at the buyer's bank and against that receipt the parcel is collected at the customs office or, when so agreed, at the bank.

The WHO Collaborating Centre cannot accept payment by letter of credit (L/C).

Nor can the WHO Collaborating Centre issue a **Certificate of Origin**, as the bulk material for the International Chemical Reference Substances originates from different parts of the world. Also the Centre cannot assist in any legalization of such or other documents sometimes requested, which has to be respected by the purchaser.

On dispatch by air freight, the freight cost is paid directly to the carrier by the purchaser.

In all cases the payment should be net of charge for the WHO Collaborating Centre.

The administration charge of US\$ 10 covers the cost for **handling and dispatch by air mail** (small parcel or air parcel post). If **registered air mail**

or **express air mail** is required, an extra charge is added. If safe delivery is possible by means of air mail, this is the preferred option as it is much less expensive for all parties.

International Chemical Reference Substances (ICRS) are only supplied in standard packages as indicated in the following list.

Available International Chemical Reference Substances

Catalogue number	Reference substances	Package size	Control number
9931422	abacavir sulfate	100 mg	106238
9930375	<i>p</i> -acetamidobenzalazine	25 mg	290042
9930202	acetazolamide	100 mg	186128
9930204	allopurinol	100 mg	287049
9930206	amidotrizoic acid	100 mg	196205
9930191	2-amino-5-nitrothiazole	25 mg	186131
9930194	3-aminopyrazole-4-carboxamide hemisulfate	100 mg	172050
9930193	3-amino-2,4,6-triiodobenzoic acid	100 mg	196206
9930208	amitriptyline hydrochloride	100 mg	181101
9930209	amodiaquine hydrochloride	200 mg	192160
9930210	amphotericin B	400 mg	191153
9930211	ampicillin (anhydrous)	200 mg	390001
9930212	ampicillin sodium	200 mg	388002
9930213	ampicillin trihydrate	200 mg	274003
9930214	anhydrotetracycline hydrochloride	25 mg	180096
9931408	artemether	100 mg	103225
9931406	artemisinin	100 mg	103222
9931407	artemotil	100 mg	103226
9931410	artemimol	100 mg	103223
9931409	artesunate	100 mg	103224
9930215	atropine sulfate	100 mg	183111
9930216	azathioprine	100 mg	172060
9930218	bacitracin zinc	200 mg	192174
9930219	beclometasone dipropionate	200 mg	192175
9930225	benzylpenicillin potassium	200 mg	180099
9930226	benzylpenicillin sodium	200 mg	280047
9930227	bephenium hydroxynaphthoate	100 mg	183112
9930228	betamethasone	100 mg	183113
9930229	betamethasone sodium phosphate	100 mg	196203

Catalogue number	Reference substances	Package size	Control number
9930230	betamethasone valerate	100 mg	190145
9930233	bupivacaine hydrochloride	100 mg	289054
9930234	caffeine	100 mg	181102
9930236	calcium folinate (leucovorin calcium)	100 mg	194188
9930237	captopril	100 mg	197214
9930238	captopril disulfide	25 mg	198216
9930239	carbamazepine	100 mg	189143
9930240	carbenicillin monosodium	200 mg	383043
9930241	chloramphenicol	200 mg	486004
9930242	chloramphenicol palmitate	1 g	286072
9930243	chloramphenicol palmitate (polymorph A)	200 mg	175073
9930199	5-chloro-2-methylaminobenzophenone	100 mg	172061
9930245	chloroquine sulfate	200 mg	195201
9930190	2-(4-chloro-3-sulfamoylbenzoyl)benzoic acid	50 mg	181106
9930246	chlorphenamine hydrogen maleate	100 mg	182109
9930247	chlorpromazine hydrochloride	100 mg	178080
9930248	chlortalidone	100 mg	183114
9930249	chlortetracycline hydrochloride	200 mg	187138
9930250	cimetidine	100 mg	190150
9930256	ciprofloxacin hydrochloride	400 mg	197210
9930252	ciprofloxacin by-compound A	20 mg	198220
9930253	ciprofloxacin desfluoro-compound	20 mg	198219
9930254	ciprofloxacin ethylenediamine-compound	20 mg	198218
9930258	cisplatin	100 mg	197207
9930259	clomifene citrate	100 mg	187136
	clomifene citrate Z-isomer <i>see</i> zuclomifene		
9930261	cloxacillin sodium	200 mg	274005
9930262	colecalfiferol (vitamin D ₃)	500 mg	190146
9930263	cortisone acetate	100 mg	167006
9930265	dapsone	100 mg	183115
9930266	desoxycortone acetate	100 mg	167007
9930267	dexamethasone	100 mg	388008
9930268	dexamethasone acetate	100 mg	288009
9930269	dexamethasone phosphoric acid	100 mg	192161
9930270	dexamethasone sodium phosphate	100 mg	192158

Catalogue number	Reference substances	Package size	Control number
9930282	diazoxide	100 mg	181103
9930283	dicloxacillin sodium	200 mg	174071
9930285	dicoumarol	100 mg	178077
9931413	didanosine	100 mg	104228
9931414	didanosine for system suitability	10 mg	104230
9930287	diethylcarbamazine dihydrogen citrate	100 mg	181100
9930288	digitoxin	100 mg	277010
9930289	digoxin	100 mg	587011
9930290	dopamine hydrochloride	100 mg	192159
9930292	doxorubicin hydrochloride	100 mg	196202
9930294	emetine hydrochloride	100 mg	187134
9931411	efavirenz	100 mg	104229
9930197	4-epianhydrotetracycline hydrochloride	25 mg	288097
9930198	4-epitetracycline hydrochloride	25 mg	306098
9930295	ergocalciferol (vitamin D ₂)	500 mg	190147
9930296	ergometrine hydrogen maleate	50 mg	277012
9930297	ergotamine tartrate	50 mg	385013
9930298	erythromycin	250 mg	191154
9930299	erythromycin B	100 mg	205186
9930300	erythromycin C	25 mg	194187
9930301	estradiol benzoate	100 mg	167014
9930302	estrone	100 mg	279015
9930304	ethambutol hydrochloride	100 mg	179081
9930305	ethinylestradiol	100 mg	301016
9930306	ethisterone	100 mg	167017
9930307	ethosuximide	100 mg	179088
9930309	flucloxacillin sodium	200 mg	195194
9930310	flucytosine	100 mg	184121
9930311	fludrocortisone acetate	200 mg	195199
9930312	fluorouracil	100 mg	184122
9930313	fluphenazine decanoate dihydrochloride	100 mg	182107
9930314	fluphenazine enantate dihydrochloride	100 mg	182108
9930315	fluphenazine hydrochloride	100 mg	176076
9930316	folic acid	100 mg	388019
9930195	3-formylrifamycin	200 mg	202149

Catalogue number	Reference substances	Package size	Control number
9930355	framycetin sulfate (neomycin B sulfate)	200 mg	193178
9930318	furosemide	100 mg	171044
9930319	gentamicin sulfate	100 mg	205183
9930322	griseofulvin	200 mg	280040
9930323	haloperidol	100 mg	172063
9930324	hydrochlorothiazide	100 mg	179087
9930325	hydrocortisone	100 mg	283020
9930326	hydrocortisone acetate	100 mg	280021
9930327	hydrocortisone sodium succinate	200 mg	194184
9930188	(-)-3-(4-hydroxy-3-methoxyphenyl)-2-hydrazino-2-methylalanine (3- <i>O</i> -methylcarbidopa)	25 mg	193180
9930189	(-)-3-(4-hydroxy-3-methoxyphenyl)-2-methylalanine (3- <i>O</i> -methylmethyldopa)	25 mg	179085
9930328	ibuprofen	100 mg	183117
9930329	imipramine hydrochloride	100 mg	172064
9931415	indinavir	100 mg	105231
9930330	indometacin	100 mg	178078
9930331	isoniazid	100 mg	185124
9930332	kanamycin monosulfate	12 mg	197211
9931416	lamivudine	100 mg	105232
9930333	lanatoside C	100 mg	281022
9930334	levodopa	100 mg	295065
9930335	levonorgestrel	200 mg	194182
9930336	levothyroxine sodium	100 mg	189144
9930337	lidocaine	100 mg	181104
9930338	lidocaine hydrochloride	100 mg	181105
9930339	liothyronine sodium	50 mg	193179
9930340	loperamide hydrochloride	100 mg	194185
9930341	mebendazole	200 mg	195195
9930454	medroxyprogesterone acetate	100 mg	106241
<i>Melting point reference substances</i>			
9930217	azobenzene (69 °C)	1 g	192168

Catalogue number	Reference substances	Package size	Control number
9930438	vanillin (83 °C)	1 g	299169
9930222	benzil (96 °C)	1 g	294170
9930201	acetanilide (116 °C)	1 g	297171
9930380	phenacetin (136 °C)	1 g	297172
9930221	benzanilide (165 °C)	4 g	192173
9930422	sulfanilamide (166 °C)	1 g	192162
9930423	sulfapyridine (193 °C)	4 g	192163
9930286	dicyanodiamide (210 °C)	1 g	192164
9930411	saccharin (229 °C)	1 g	192165
9930235	caffeine (237 °C)	1 g	299166
9930382	phenolphthalein (263 °C)	1 g	299167
9930345	methotrexate 3- <i>o</i> -methylcarbidopa <i>see</i> (-)-3-(4-hydroxy-3-methoxyphenyl)-2-hydrazino-2-methylalanine 3- <i>o</i> -methylmethyldopa <i>see</i> (-)-3-(4-hydroxy-3-methoxyphenyl)-2-methylalanine	100 mg	194193
9930346	methyldopa	100 mg	179084
9930347	methyltestosterone	100 mg	167023
9930348	meticillin sodium	200 mg	274024
9930350	metronidazole	100 mg	183118
9930351	nafcillin sodium	200 mg	272025
9930354	neamine hydrochloride (neomycin a hydrochloride)	0.5 mg	193177
9931417	nelfinavir mesilate neomycin B sulfate <i>see</i> framycetin sulfate	100 mg	105233
9930356	neostigmine metilsulfate	100 mg	187135
9931412	nevirapine anhydrous	100 mg	104227
9931423	nevirapine impurity B	10 mg	106239
9930357	nicotinamide	100 mg	200090
9930358	nicotinic acid	100 mg	179091
9930359	nifurtimox	100 mg	194189
9930360	niridazole	200 mg	186129
9930361	niridazole-chlorethylcarboxamide	25 mg	186130
9930366	norethisterone	100 mg	186132
9930367	norethisterone acetate	100 mg	185123
9930369	nystatin	200 mg	405152

Catalogue number	Reference substances	Package size	Control number
9930371	ouabain	100 mg	283026
9930372	oxacillin sodium	200 mg	382027
9930373	oxytetracycline dihydrate	200 mg	189142
9930374	oxytetracycline hydrochloride	200 mg	189141
9930376	papaverine hydrochloride	100 mg	185127
9930377	paracetamol	100 mg	195198
9930378	paromomycin sulfate	75 mg	195197
9930383	phenoxymethylpenicillin	200 mg	179082
9930384	phenoxymethylpenicillin calcium	200 mg	179083
9930385	phenoxymethylpenicillin potassium	200 mg	176075
9930387	phenytoin	100 mg	179089
9930388	piperazine adipate	100 mg	197212
9930389	piperazine citrate	100 mg	197213
9930390	praziquantel	100 mg	194191
9930391	prednisolone	100 mg	389029
9930392	prednisolone acetate	100 mg	289030
9930393	prednisolone hemisuccinate	200 mg	195196
9930394	prednisolone sodium phosphate	200 mg	194190
9930395	prednisone	100 mg	167031
9930396	prednisone acetate	100 mg	169032
9930397	probenecid	100 mg	192156
9930398	procaine hydrochloride	100 mg	183119
9930399	procarbazine hydrochloride	100 mg	184120
9930400	progesterone	100 mg	167033
9930402	propranolol hydrochloride	100 mg	187139
9930403	propylthiouracil	100 mg	185126
9930404	pyrantel embonate (pyrantel pamoate)	500 mg	192157
9931424	pyrazinamide	100 mg	106240
9930405	pyridostigmine bromide	100 mg	182110
9930406	reserpine	100 mg	186133
9930408	riboflavin	250 mg	382035
9930409	rifampicin	300 mg	203151
9930410	rifampicin quinone	200 mg	202148
9931421	ritonavir	100 mg	105237
9931418	saquinavir mesilate	100 mg	105234

Catalogue number	Reference substances	Package size	Control number
9930412	sodium amidotrizoate	100 mg	198221
9930413	sodium cromoglicate	100 mg	188140
9930415	spectinomycin hydrochloride	200 mg	193176
9931419	stavudine	100 mg	105235
9930416	streptomycin sulfate	100 mg	197215
9930417	sulfacetamide	100 mg	196200
9930419	sulfamethoxazole	100 mg	179092
9930420	sulfamethoxypyridazine	100 mg	178079
9930421	sulfanilamide	100 mg	179094
9930424	sulfasalazine	100 mg	191155
9930425	tamoxifen citrate	100 mg	196208
9930426	tamoxifen <i>E</i> -isomer	10 mg	205209
9930427	testosterone enantate	200 mg	194192
9930428	testosterone propionate	100 mg	167036
9930429	tetracycline hydrochloride	200 mg	205095
9930430	thioacetazone	100 mg	171046
9930196	4,4' - thiodianiline	50 mg	183116
	thyroxine sodium <i>see</i> levothyroxine sodium		
9930431	tolbutamide	100 mg	179086
9930432	tolnaftate	100 mg	176074
9930433	toluene-2-sulfonamide	100 mg	196204
9930434	trimethadione	200 mg	185125
9930435	trimethoprim	100 mg	179093
9930440	vincristine sulfate	9.7 mg/vial	193181
9930439	warfarin	100 mg	168041
9931420	zidovudine	100 mg	105236
9930260	zuclofifene	50 mg	187137

2. **List of available International Infrared Reference Spectra**

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

The current price is US\$ 5 for a single spectrum and US\$ 200 for a set of 50 spectra, including a hardcover binder. The binder can be ordered separately for US\$ 10.

An administrative charge of US\$ 10 is added to each order to cover costs for handling and dispatch by air mail or air parcel post.

Orders should be sent to:

WHO Collaborating Centre for Chemical Reference Substances

Apoteket AB

Produktion & Laboratorier

Farmaci/Centrallaboratoriet (ACL)

Prismavägen 2

SE-141 75 Kungens Kurva, Sweden

Fax: + 46 8 740 60 40

e-mail: who.apl@apoteket.se

web site: <http://www.apl.apoteket.se/who>

Payment should be made according to the invoice. Kindly direct all payments to:

Nordea Bank Sweden, SE-105 71 Stockholm

(Apoteket AB/APL/ACL/WHO)

Swift: NDEASESS

Account no (PG): 2 98 40-6

IBAN: SE 65 9500 0099 6026 0029 8406

The invoice number must be quoted when payment is made.

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

aceclidine salicylate	ibuprofen
acetazolamide	imipramine hydrochloride
allopurinol	indometacin
amiloride hydrochloride	isoniazid
amitriptyline hydrochloride	
ampicillin trihydrate	lidocaine
	lidocaine hydrochloride
beclometasone dipropionate	lindane
benzylpenicillin potassium	
biperiden	metronidazole
biperiden hydrochloride	miconazole nitrate
bupivacaine hydrochloride	
	niclosamide
caffeine (anhydrous)	nicotinamide
calcium folinate	noscapine
carbidopa	
chlorphenamine hydrogen maleate	oxamniquine
clofazimine	
cloxacillin sodium	papaverine hydrochloride
colchicine	phenobarbital
cytarabine	phenoxymethylpenicillin calcium
	phenytoin
dexamethasone	primaquine phosphate
dexamethasone acetate, monohydrate	propylthiouracil
dextromethorphan hydrobromide	protionamide
diazepam	pyrimethamine
dicolinium iodide	
dicoumarol	salbutamol
diethylcarbamazine dihydrogen citrate	salbutamol sulfate
diphenoxylate hydrochloride	sulfadimidine
	sulfadoxine
erythromycin ethylsuccinate	sulfamethoxazole
erythromycin stearate	sulfamethoxy pyridazine
etacrynic acid	
ethionamide	tiabendazole
ethosuximide	trihexyphenidyl hydrochloride
	trimethoprim
furosemide	
	valproic acid
gallamine triethiodide	verapamil hydrochloride
glibenclamide	
haloperidol	
hydrochlorothiazide	

For newly available, additional Infrared Reference Spectra please see section 4.3 in this report.

Annex 2

Procedure for assessing the acceptability, in principle, of male latex condoms for purchase by United Nations agencies

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Appendix

List of standards and specifications

1. Introduction

1.1 Background

The United Nations, through its procurement agencies, supplies medicines and other health products to countries throughout the world, requiring access to a choice of products of acceptable quality, safety and efficacy.

Until 2002, The World Health Organization (WHO) undertook the procurement of condoms, a responsibility which was subsequently transferred to the United Nations Population Fund (UNFPA). However, WHO continued its normative work and together with key partners developed recommended international specifications for condoms and technical and procurement guidelines. The guidelines were published in 2004 as *The male latex condom: specification and guidelines for condom procurement* and include an update of the specifications and recommended procedures for the prequalification, procurement and compliance testing of condoms.

WHO, UNFPA and other key partners developed an evidence-based list of Reproductive Health Essential Medicines (2005), which was subsequently approved by the WHO Expert Committee on the Selection and Use of Essential Medicines. From this list and the recommendations of members of the Reproductive Health Supplies Coalition, it was agreed that WHO would include a core group of reproductive health essential medicines in its Prequalification Programme, implementation of which began in 2006. As part of this activity, it was agreed that UNFPA would take the responsibility for the prequalification of intrauterine devices (IUDs) and male latex condoms and that the scheme would be harmonized with that of the WHO Prequalification Programme.

This document describes the implementation of the scheme for the male latex condom. It is supported by a specific UNFPA management system with detailed standard operating procedures (SOPs).

1.2 Objectives

The overall objective is to implement a scheme to prequalify manufacturers of male latex condoms of assured quality, at specific manufacturing sites, for procurement by United Nations agencies.

Specific objectives are to:

- Promote the procurement of male latex condoms from manufacturing sites that have been assessed as having the capacity to produce quality products.

- Establish a system that promotes the procurement of quality products that conform to the international standard ISO 4074:2002¹ and the WHO specifications for the male latex condom² and retain their effectiveness throughout their stated shelf-life.
- Broaden the supplier base for male latex condoms, which are deemed acceptable, in principle, for procurement by United Nations agencies.
- Maintain and publish a list of prequalified suppliers.

2. The prequalification scheme for male latex condoms

2.1 Eligibility to participate

The prequalification scheme is intended for manufacturers of male latex condoms who undertake the processes of formulation, compounding and dipping, as well as for manufacturers using pre-vulcanized latex, as specified by UNFPA in the call for Expressions of Interest (EOI), as referred to below. An agent may respond to the EOI on behalf of a manufacturer who undertakes the processes described above. The prequalification scheme does not apply to agents, distributors or suppliers engaged only with testing, lubricating and packaging.

2.2 Expression of Interest

2.2.1 *Calls for and submission of Expressions of Interest*

Invitations to interested parties to submit an EOI are published at regular intervals on the United Nations Global Marketplace (UNGM: <http://www.ungm.org>), UNFPA: <http://www.unfpa.org> and WHO web sites (<http://www.who.int/prequal/>).

The invitation is open and transparent and invites manufacturers and/or their agents, as described in Section 2.1 above, to submit an EOI for the products listed in the invitation. The applicants or manufacturers should submit their EOI to the UNFPA focal point with the relevant information requested in the invitation. The applicants or manufacturers will be given a specified period to submit their responses from the time of publication of the advertisement. The information must be submitted in English (see Section 2.10 Language).

UNFPA will receive and record the EOI from each applicant/manufacturer and issue an acknowledgement of receipt.

¹ ISO documents are available from: International Organization for Standardization, ISO Secretariat, 1 rue de Varembé, Case Postale 56, CH-1211 Geneva 20, Switzerland.

² WHO/UNFPA/UNAIDS/FHI *The male latex condom. Specification and guidelines for condom procurement*. Geneva, World Health Organization, 2004.

WHO and UNFPA will provide further guidance on the submission of documentation for prequalification and make such guidance available on the UNFPA and WHO web sites.

In submitting an EOI for product evaluation, the applicant/manufacturer should send to the UNFPA focal point the following:

- a covering letter, expressing interest in participating in the UNFPA prequalification procedure and confirming that the information submitted in the product dossier and site master file summary is complete and correct;
- a product dossier in the format specified in the WHO/UNFPA guidance documents for submitting product data and information;
- product samples, to enable product analysis; and
- a site master file, for each manufacturing site listed in the product dossier, in the requisite format specified in the WHO/UNFPA guidance documents for submitting a site master file.

The information must be accompanied by copies of all current certifications/accreditations, all manufacturing licences and/or registrations held, and a copy of the company registration.

The documentation should be submitted in English and sent by courier or registered mail (see Section 2.10 Language).

2.2.2 *Assessment of documents submitted*

The aim of the assessment of the submitted documentation will be to determine whether the applicant/manufacturer meets the minimum requirements detailed in the relevant ISO standards and WHO specifications in respect of product quality and safety, production and quality management, regulatory approvals and capacity of production.

2.2.2.1 *Initial screening of documentation*

UNFPA will aim to screen the documentation within 30 days of the closing date for receipt of responses to ascertain whether it contains all the required information. If the submission is incomplete, the manufacturer will be informed and requested to complete the dossier within a specified time period. In the event of non-compliance, the dossier may be rejected on the grounds of incompleteness and returned to the applicant. Dossiers that are considered complete following the administrative screening will be retained by UNFPA for evaluation purposes.

UNFPA will exchange letters with the applicant/manufacturer covering provisions of confidentiality and the process of assessment of submitted information and scheduling of possible site inspection.

2.2.2.2 Assessment of the product dossier and the site master file

UNFPA aims to convene a group of experts acting as assessors to complete the assessment of the product dossier and the site master file within a specified time period (90 days) of the closing date for receipt of responses.

The submissions will be evaluated by assessors with documented qualifications and relevant experience. The selection of assessors and the assessment will be carried out in accordance with existing United Nations procedures for the selection of consultants and experts. The team of assessors may include one or more inspectors responsible for subsequent inspections of the manufacturing sites. The assessors must comply with the confidentiality and conflict of interest rules of UNFPA, as laid down in Sections 3 and 4 of this procedure.

The assessment of the submitted documentation will be done in accordance with SOPs established by UNFPA for that purpose. To ensure uniformity in evaluation and timeliness of assessment activities, UNFPA will, if needed, provide training to the assessors.

In making its assessment, UNFPA may take into account information submitted by the applicant during previous applications including results from previous site inspections and laboratory test results on products produced by the manufacturer, which may be in UNFPA's possession.

UNFPA aims to advise the manufacturers of the outcome of the assessment of the documentation within 30 days after completion of the assessment. If applications are found to be in compliance with the requirements of UNFPA, as detailed on the WHO and UNFPA web sites, the manufacturing site will be scheduled for inspection.

2.3 Site inspection

UNFPA will plan and coordinate inspections at the above-mentioned manufacturing sites to assess the manufacturing process and the product and quality management systems for compliance with general and performance requirements of the WHO male latex condom specification and good management practice, including in particular, the following international standards:

- ISO 4074. *Natural latex rubber condoms — requirements and test methods*, 1st ed., 2002. Corrected version, 1 December 2002.
- ISO 16038. *Rubber condoms — guidance on the use of ISO 4074 in the quality management of natural rubber latex condoms*, 1st ed., 1 November 2005.
- ISO 13485. *Medical devices — quality management systems: requirements for regulatory purposes*, 2nd ed., ISO 2003.

- ISO 10993. *Biological evaluation of medical devices. Part 1 Evaluation and Testing*, 3rd ed., ISO 2003.

2.3.1 **Inspection team**

The inspection will be performed by a team of inspectors, consisting of experts appointed by UNFPA who will act as temporary advisers to UNFPA. The inspectors must have documented qualifications; detailed knowledge of male latex condom manufacturing processes; expertise in auditing and quality management systems; and specific experience of inspecting condom manufacturing sites. The inspectors must comply with the confidentiality and conflict of interest rules of UNFPA, as detailed in Sections 3 and 4 of this procedure. If needed, to ensure uniformity in inspection procedures, UNFPA will provide training to these experts.

Where possible UNFPA will appoint at least one inspector able to communicate in and read the local language. Failing this, an interpreter selected by UNFPA will be used. One member of the team will be designated by UNFPA as the “lead inspector” and will be responsible for the coordination of inspection activities. The team may include observers from UNFPA. UNFPA will advise and seek the involvement of the national competent body in the on-site inspection.

UNFPA will advise the manufacturer in advance of the identity of each inspector, composition of the team performing the site inspection, and provide curricula vitae of the inspectors. The manufacturer then has the opportunity to express possible concerns regarding any of the inspectors to UNFPA prior to the visit. If such concerns cannot be resolved in consultation with UNFPA, the manufacturer may object to a team member’s participation in the site visit. Such an objection must be made known to UNFPA by the manufacturer within 10 days of receipt of the proposed team composition. In the event of such an objection, UNFPA may cancel all or part of its agreement with, and the activities to be undertaken by, that inspector.

Each team will perform the inspections and report on its findings to UNFPA in accordance with the SOPs established by UNFPA for that purpose so as to ensure a standardized harmonized approach.

Information submitted in response to the EOI and the assessment report will be made available to the inspectors. All inspectors must comply with the confidentiality and conflict of interest rules of UNFPA as detailed in Sections 3 and 4 of the procedure.

2.3.2 **Scope and scheduling**

The applicant/manufacturer will be informed of the scope of the inspectors’ activities, prior to the inspection. The key components of the inspection are

available on the WHO and UNFPA web sites under the heading *Scope of manufacturing site inspection: male latex condoms*. However, the inspection will not be limited to these components. Manufacturers must be prepared to show the inspectors all aspects of the facility, including records and data that relate to the production of the condoms.

UNFPA aims to advise the applicant of the date of inspection at least 30 days in advance. UNFPA and the inspectors will make reasonable efforts to accommodate any requests by the manufacturers and national regulatory agencies to change the date of inspection.

UNFPA will inform the applicant/manufacturer that the inspectors may request copies of documents presented as evidence during inspection and may request permission to make a photographic record of the inspection, subject always to consideration of confidential information, as referred to in Section 2.5.

2.3.3 **Transparency**

The inspection team is paid by UNFPA to inspect the facilities and the members are reimbursed for their hotel and transport expenses by UNFPA. The manufacturer will not pay for hotel accommodation or make any payments for or to the inspectors and/or UNFPA staff. The manufacturer may be requested to assist in making reservations at an appropriate hotel and for local transportation to and from the airport or station, and to and from their hotel to the facilities.

The inspectors (and UNFPA staff who accompany the inspectors) cannot accept any gifts from the companies they visit. UNFPA requires that applicants or manufacturers do not make any offers of gifts of whatever value to the inspectors and/or UNFPA staff.

By participating in the scheme, the manufacturer agrees to allow full access to any of the facilities which are in any way involved in the production of the product(s) concerned, and to all documentation related to that production. If such access is not provided, the manufacturing site and specific products cannot be prequalified.

Any evidence of fraud or serious omissions by the manufacturer in the initial assessment procedure will lead to termination of the site inspection.

2.4 **Product testing**

Products will be sampled for independent testing prior or subsequent to the inspection by an independent sampler appointed by UNFPA or by the inspectors at an appropriate point during the inspection.

The samples will be packed and sealed by the inspectors or the independent sampler, as may be appropriate. The inspectors may take the samples with

them, or arrange for the manufacturer to have the sealed boxes sent to the selected laboratory by courier at UNFPA's expense.

The sample size is taken in accordance with the current international standard for Male latex condoms ISO 4074:2002 — Annex B. The range of tests to be conducted will be in accordance with the WHO specifications and guidelines for condom procurement. All product testing will be undertaken by independent accredited test laboratories selected by UNFPA. Such test laboratories must possess defined and documented competence and experience as demonstrated by accreditation to the current ISO 17025 standard.

A copy of the test report will be provided to the applicant.

2.5 Reporting and communication of the results of the site inspection

At the conclusion of the inspection, the inspectors will prepare a brief written summary report outlining the key findings and observations discussed with the manufacturer during the site inspection. This report will be provided to UNFPA with a copy to the manufacturer.

In addition, the inspection team will finalize its main report according to the established UNFPA SOP and format, describing the findings, evidence and recommendations. The report will be submitted to UNFPA.

The inspection report will be communicated by UNFPA to the applicant or manufacturer. If any additional information is required, or corrective action has to be taken by the applicants/manufacturer(s), UNFPA will postpone its decision on the acceptability of the respective site(s), until such information has been evaluated, or the corrective action has been taken and found satisfactory in light of the specified standards.

UNFPA reserves the right to terminate the procedure of quality assessment of a specific product if the applicant/manufacturer is either not able to provide the required information or to implement the corrective actions within a specified time period, or if the information supplied is inadequate to complete the quality assessment process.

In the event of any disagreement between an applicant and UNFPA, an SOP established by UNFPA for the handling of appeals and complaints will be followed to discuss and resolve the issue.

The ownership of any of the reports produced in the course of, or as the result of, the assessment of documentation, product testing and inspection of the manufacturing site lies with UNFPA. Thus, UNFPA shall be entitled to use and publish such reports, subject always, however, to the protection of any commercially confidential information of the applicant and/or manufacturer. Confidential information may include:

- confidential intellectual property, “know-how” and trade secrets (including, e.g. formulas, programmes, process or information contained or embodied in a product, unpublished aspects of trademarks, patents); and
- commercial confidences (e.g. structures and development plans of a company).

Provisions of confidentiality will be contained in the exchange of letters, to be concluded before the assessment of the product dossier or inspection of the manufacturing site(s), between UNFPA and each applicant/manufacture.

Notwithstanding the foregoing, UNFPA and WHO reserve the right to share the full evaluation and inspection reports with the relevant authorities of any interested Member State of UNFPA and/or WHO.

2.6 **Decision to prequalify**

It is UNFPA’s responsibility to compile the information submitted in response to the EOI, the assessment report, the inspection report and the test report. A UNFPA staff member with appropriate experience and training will assess the information about each applicant/manufacture and in consultation with the assessors and inspectors will make a final decision about the outcome of the prequalification process.

Based on this assessment UNFPA will either:

- Prequalify male latex condoms manufactured at a specific site without conditions. This will only be the case when there is no evidence that corrective action should be submitted to UNFPA.

Or

- Require the manufacturer, where deemed necessary, to undertake specified corrective action(s). The manufacturer must do this within an agreed time period and provide UNFPA with evidence, where required, showing that the corrective action has been taken. If UNFPA is satisfied with this additional information the manufacturing site will be added to the list of prequalified condom manufacturers.

Or

- Determine that a manufacturing site is ineligible for prequalification (without any requirement for corrective action being offered). This will not, however, preclude the applicant/manufacture from resubmitting an application in response to future invitations for EOIs.

Where the inspectors recommend corrective action requiring a subsequent inspection, the manufacturer must advise UNFPA within an agreed period of time that corrective action has been completed and provide the relevant evidence, if required. The recommendation for corrective action may include

further independent product testing. After review of the evidence, UNFPA will decide whether or not to schedule a further inspection. If a further inspection is deemed necessary the inspection process and assessment will be implemented in accordance with the procedure detailed in Sections 2.3, 2.4, 2.5 and 2.6.

UNFPA reserves the right to terminate the procedure of quality assessment of a specific product if the applicant/manufacturee is not able to provide the required information or implement the corrective actions within a specified time period, or if the information supplied is inadequate to complete the quality assessment process.

The findings of the inspection may include non-mandatory observations aimed at highlighting potential for improved manufacturing and quality management practices.

If evidence supporting mandatory improvement actions or additional information is required, or other corrective actions have to be taken by the manufacturer, UNFPA will postpone its final decision until such information has been evaluated, or the corrective action has been taken and found satisfactory in light of the specified international standards, detailed in the Appendix. If the applicant/manufacturee has not submitted a satisfactory response within 12 months of submission of the report from UNFPA, the application will lapse and the applicant will need to reapply, in response to a future invitation for an EOI.

UNFPA aims to inform the manufacturer formally of the results of the process within 30 days of receipt of all final reports.

2.7 Listing of prequalified male latex condoms and manufacturing sites

Once UNFPA is satisfied that the quality assessment process is complete and where the product dossier and corresponding manufacturing site have been found to meet the above-mentioned prequalification requirements, the product produced at the specified manufacturing site(s) will be listed on the WHO and UNFPA prequalification web sites. The list of prequalified male latex condoms and corresponding manufacturing sites will be compiled and updated in accordance with an SOP established by UNFPA for this purpose.

Each applicant will receive a letter from UNFPA informing them of the outcome of the quality assessment process.

2.8 Maintenance of the prequalification status

Once the product is included in the list of prequalified male latex condoms and corresponding manufacturing sites, the applicant/manufacturee shall be

required to provide UNFPA with prior notification of any intended changes in the manufacturing site and/or manufacturing process.

All manufacturers of prequalified male latex condoms are required to advise UNFPA, within four weeks, of any matter that affects the information on which the approval was based. This includes, but is not limited to:

- change of premises;
- change in production and testing equipment;
- change in senior management;
- product recalls;
- change in certifications or licences held by the manufacturer;
- reports of adverse events;
- change in condom design;
- change in suppliers of latex not previously listed in the site master file;
- change in specification of raw materials;
- change in packaging;
- new information about shelf-life.

It is the applicant's responsibility to provide UNFPA with the appropriate documentation (referring to relevant parts of the dossier) to prove that the implementation of any intended variation will not have an impact on the quality of the product that has been prequalified. UNFPA will undertake an evaluation of variations according to established UNFPA guidelines and SOPs and communicate the outcome to the applicant. Compliance with the requirement to report changes will be checked during the inspections carried out by UNFPA.

At periodic intervals UNFPA may, through an independent sampler, take random samples of male latex condoms produced by listed manufacturers. The sample size will be in accordance with the current international standard for Male latex condoms ISO 4074:2002 — Annex B. The range of tests to be conducted will be in accordance with pre-shipment lot by lot compliance testing as detailed in the WHO specifications and guidelines for procurement. All product testing will be undertaken by an independent test laboratory, selected by UNFPA, of defined and documented accreditation to the current ISO 17025 international standard. In the event of failure to meet the established requirements for testing, UNFPA will investigate the problem and communicate this to the manufacturer and/or applicant if different from the manufacturer.

UNFPA may request reports from consumer or regulatory bodies, or from other procurement agencies, relating to the quality and supply of the prequalified male latex condoms.

Complaints concerning prequalified male latex condoms communicated to UNFPA will be investigated in accordance with an SOP established by

UNFPA for that purpose. After investigation UNFPA will provide a written report of the complaint investigations to the applicant/manufacturee, including recommendations for action. UNFPA will require evidence of effective action taken, where relevant. UNFPA will make the report available to the manufacturer and/or applicant and to the appropriate authorities of the country where the manufacturing site is located, subject always to considerations of commercially confidential information, as referred to in Section 2.5 above.

UNFPA reserves the right to make such reports public, if it considers this to be of public health importance. In addition, UNFPA reserves the right to share the full report and/or recommendations for action with WHO and relevant authorities of interested Member States of WHO.

2.9 Reassessment

UNFPA aims to undertake a reassessment of male latex condoms manufactured at a specific site at intervals of no more than three years. Such reassessments will consist of a comprehensive evaluation of documentation, site inspection and product testing similar to the initial prequalification assessment.

Reassessment may also be required in the following situations:

- If the male latex condoms supplied by the manufacturer are considered by UNFPA, or one or more of the United Nations agencies, not to be in compliance with the agreed WHO specification and pre-shipment compliance testing requirements, detailed in *The male latex condom. Specification and guidelines for condom procurement*. WHO, 2004.
- If a complaint considered serious in nature has been received by UNFPA or one or more of the United Nations agencies or organizations.
- If there is a significant change in the manufacturing process in respect to one or more of the items listed in Section 2.8 above.

All relevant information including the reassessment of submitted documentation and site inspection reports together with monitoring information will be considered by the designated UNFPA official, and a decision will be made to either:

- maintain the male latex condom and its manufacturing site on the list of prequalified products without need for corrective actions;

or

- maintain the prequalification status of the male latex condom and its manufacturing site with a requirement for corrective actions and, where agreed to by UNFPA, a further product testing and/or site inspection;

or

- suspend prequalified status.

UNFPA aims to advise the applicant/manufacturer of the result of the reassessment and make any necessary amendments to the list of prequalified manufacturing sites and products within 30 days of receipt of the data on the basis of which the decision was made. The updated list will be published on the WHO and UNFPA prequalification web sites.

UNFPA will de-list any prequalified product and manufacturing site if the submitted information is subsequently found to be incorrect or fraudulent.

2.10 **Language**

The official language of the programme is English. All documents submitted as part of an application for prequalification will be in English. If the original of any required document is not in English, the manufacturer must submit a copy of the original, plus a certified translation into English. All correspondence between UNFPA and the applicant should be in English. All reports issued by the assessors, inspectors and by UNFPA on the assessment and inspections will be in English.

Inspections will be conducted in English, where necessary with the aid of an interpreter. It is the responsibility of the manufacturer to advise UNFPA and for UNFPA to agree whether an interpreter is required for the inspection.

2.11 **Fees**

At present, UNFPA will cover the expenses of the assessments, inspections and product testing. Manufacturers are responsible for their own costs related to providing the necessary information and help required under the scheme.

Currently the process is conducted by UNFPA free of charge. UNFPA reserves the right, however, to charge a fee on a cost-reimbursement basis.

2.12 **Resolution of disputes**

If there is any disagreement between a manufacturer and UNFPA, an SOP established by UNFPA for the handling of appeals and complaints will be followed to discuss and resolve the issue.

3. **Confidentiality undertaking**

The assessors and inspectors will treat all information to which they will gain access during the evaluations and inspections, or otherwise in connection with the discharge of their responsibilities in regard to the above-mentioned project, as confidential and proprietary to UNFPA or parties collaborating with UNFPA in accordance with the terms set out below.

Assessors and inspectors will take all reasonable measures to ensure:

- that confidential information is not used for any other purpose than the evaluation/inspection activities described in this document; and
- that it is not disclosed or provided to any person who is not bound by similar obligations of confidentiality and non-use as contained herein.

Assessors and inspectors will not, however, be bound by any obligations of confidentiality and non-use to the extent they are clearly able to demonstrate that any part of the confidential information:

- was known to them prior to any disclosure by or on behalf of UNFPA (including by manufacturers); or
- was in the public domain at the time of disclosure by or on behalf of UNFPA (including by manufacturers); or
- has become part of the public domain through no fault of theirs; or
- has become available to them from a third party not in breach of any legal obligations of confidentiality.

4. **Conflict of interest**

Before undertaking the work, each assessor and inspector will also (in addition to the above-mentioned confidentiality undertaking) be required to sign a declaration of interest. If based on this declaration of interest, it is felt that there is no risk of a real or perceived conflict of interest (or it is felt that there is only an insignificant and/or irrelevant conflict of interest), and it is thus deemed appropriate for the evaluator or inspector in question to undertake this work, he/she will discharge his/her functions exclusively as adviser to UNFPA. In this connection, each assessor and inspector is required to confirm that the information disclosed by him/her in the declaration of interest is correct and complete, and that he/she will immediately notify UNFPA of any change in this information.

All inspectors furthermore agree that, at the manufacturer's request, UNFPA will advise the manufacturer, in advance, of the identity of each inspector and composition of the team performing the site inspection, and provide curricula vitae of the inspectors. The manufacturer then has the opportunity to express possible concerns regarding any of the inspectors to UNFPA prior to the visit. If such concerns cannot be resolved in consultation with UNFPA, the manufacturer may object to a team member's participation in the site visit.

Such an objection must be made known to UNFPA by the manufacturer within 10 days of receipt of the proposed team composition from UNFPA. In the event of such an objection, UNFPA reserves the right to cancel all or part of its agreement with, and the activities to be undertaken by, that inspector.

Appendix

List of standards and specifications

WHO/UNAIDS/UNFPA/FHI, *The male latex condom. Specification and guidelines for condom procurement*. Geneva, World Health Organization, 2004.

ISO 4074. *Natural latex rubber condoms — requirements and test methods*, 1st ed., 2002. Corrected version. International Standards Organization, 1 December 2002.

ISO 16038. *Rubber condoms — guidance on the use of ISO 4074 in the quality management of natural rubber latex condoms*, 1st ed. International Standards Organization, 1 November 2005.

ISO 13485. *Medical devices — quality management systems: requirements for regulatory purposes*, 2nd ed., International Standards Organization, 2003.

ISO 10993. *Biological evaluation of medical devices. Part 1 evaluation and testing*, 3rd ed. International Standards Organization, 2003.

Annex 3

Procedure for assessing the acceptability, in principle, of TCU380A intrauterine devices for purchase by United Nations agencies

1. Introduction
 - 1.1 Background
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 - 2.1 Eligibility to participate
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 - 2.3 Site inspection
 - 2.4 Product testing
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 - 2.6 Decision to prequalify
 - 2.7 Listing of prequalified TCU308A intrauterine devices and manufacturing sites
 - 2.8 Maintenance of the prequalification status
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 - 2.10 Language
 - 2.11 Fees
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3. Confidentiality undertaking
4. Conflict of interest

Appendix

List of standards and specifications

1. Introduction

1.1 Background

The United Nations, through its procurement agencies, supplies medicines and other health products to countries throughout the world, requiring access to a choice of products of acceptable quality, safety and efficacy.

The World Health Organization (WHO), the United Nations Population Fund (UNFPA) and other key partners developed an evidence-based list of Reproductive Health Essential Medicines (2005), which was subsequently approved by the WHO Expert Committee on Selection and Use of Essential Medicines. From this list and the recommendations of members of the Reproductive Health Supplies Coalition, it was agreed that WHO would include a core group of reproductive health essential medicines in the Prequalification Programme, implementation of which began in 2006. As part of this activity, it was agreed that UNFPA would take responsibility for the prequalification of copper-bearing intrauterine devices (IUDs) and male latex condoms and that the UNFPA scheme would be harmonized with that of the WHO Prequalification Programme.

WHO continues its normative work and together with key partners, WHO has recently supported the preparation of a Cochrane review¹ on copper-bearing IUDs in order to provide an evidence-base to support the revision of the International Standard for IUDs, ISO 7439: 2002. A Technical Review Committee convened by WHO in September 2006 reviewed the evidence on the safety, efficacy and performance of copper-bearing IUDs and recommended the TCu380A IUD as the most appropriate device for bulk procurement by UNFPA. In addition, a detailed technical review process is currently being undertaken to update the bulk procurement specification for TCu380A IUDs. This will be published by July 2008. The current specification will be used until the revised specification has been published.

This document describes the implementation of the scheme for the TCu380A IUD. It is supported by a specific UNFPA management system with detailed standard operating procedures (SOPs).

1.2 Objectives

The overall objective is to implement a scheme to prequalify manufacturers of TCu380A IUDs of assured quality at specific manufacturing sites for procurement by United Nations agencies.

¹ O'Brien PA et al. Copper containing, framed intra-uterine devices for contraction (Review). *Cochrane Database of Systematic Reviews*, 2006, July 2006, Issue 3, updated August 2007.

Specific objectives are to:

- Promote the procurement of TCu380A IUDs from manufacturing sites that have been assessed as having the capacity to produce quality products.
- Establish a system that promotes the procurement of quality products that conform to the international standard ISO 7439 and the TCu380A IUD specification and retain their effectiveness throughout their stated shelf-life.
- Broaden the supplier base for TCu380A IUDs, which are deemed acceptable, in principle, for procurement by United Nations agencies.
- Maintain and publish a list of prequalified suppliers.

2. **The prequalification scheme for TCu380A intrauterine devices**

2.1 **Eligibility to participate**

The prequalification scheme is intended for manufacturers of TCu380A IUDs that undertake the processes of moulding, assembly, sterilization and packaging, as specified by UNFPA in the call for an Expression of Interest (EOI) referred to below. One or more of these processes may be carried out on a contract basis, but the manufacturer retains overall responsibility for product quality. An agent may respond to the EOI on behalf of a manufacturer who undertakes the process described above. The prequalification scheme does not apply to suppliers/agents engaged only with testing and re-packaging.

2.2 **Expression of Interest**

2.2.1 ***Calls for and submission of Expressions of Interest***

Invitations to interested parties to submit an EOI are published at regular intervals on the United Nations Global Marketplace (UNGM: <http://www.ungm.org>), UNFPA: <http://www.unfpa.org> and WHO web sites (<http://www.who.int/prequal/>).

The invitation is open and transparent and invites manufacturers and/or their agent as described in Section 2.1 above, to submit an EOI for the products listed in the invitation. The applicant/manufacturer should submit their EOI to the UNFPA focal point with the relevant information requested. The applicants/manufacturers will be given a specified period within which to submit their responses from the time of publication of the advertisement. The information must be submitted in English (see Section 2.10 Language).

UNFPA will receive and record the EOI from each applicant/manufacturer and issue an acknowledgement of receipt.

WHO and UNFPA will provide further guidance on the submission of documentation for prequalification and make such guidance available on the WHO and UNFPA web sites.

In submitting an EOI for product evaluation, the applicant/manufacturer should send to the UNFPA focal point the following:

- a covering letter, expressing interest in participating in the UNFPA prequalification procedure and confirming that the information submitted in the product dossier and site master file summary is complete and correct;
- a product dossier, in the format specified in the WHO/UNFPA guidance documents for submitting product data and information;
- product samples for review; and
- a site master file, for each manufacturing site listed in the product dossier, in the requisite format specified in the WHO/UNFPA guidance documents for submitting a site master file.

The information must be accompanied by copies of all current certifications/accreditations, all manufacturing licences/registrations held, and a copy of the company registration.

The documentation should be submitted in English, and be sent by courier or registered mail (see Section 2.10 Language).

2.2.2 Assessment of documents submitted

The aim of the assessment of submitted documentation will be to determine whether the applicant/manufacturer meets the minimum requirements detailed in the relevant ISO standards² and the TCu380A IUD specification³ in respect of product quality and safety, production and quality management, regulatory approvals and capacity of production.

2.2.2.1 Initial screening of documentation

UNFPA will aim to screen the documentation within 30 days of the closing date for receipt of responses, to ascertain whether it contains all the required information. If the submission is incomplete the applicant/manufacturer will be informed and requested to complete the dossier within a specified time period. In the event of non-compliance, the dossier may be rejected on the grounds of incompleteness and returned to the applicant. Dossiers that are considered complete as the result of the administrative screening will be retained by UNFPA for evaluation purposes.

UNFPA will aim to exchange letters with the applicant/manufacturer covering provisions of confidentiality, the process of assessment of submitted information and scheduling of possible site inspection.

² ISO standards are available from: International Organization for Standardization, ISO Secretariat, 1 rue de Varembé, Case Postale 56, CH-1211 Geneva 20, Switzerland.

³ The TCu380A specification is available on the WHO (<http://www.who.int/prequal/>) and UNFPA (<http://www.unfpa.org>) web sites.

2.2.2.2 Assessment of the product dossier and the site master file

UNFPA aims to convene a group of experts acting as assessors to complete the assessment of the product dossier and the site master file within a specified time period (90 days) of the closing date for receipt of responses.

The submissions will be evaluated by assessors with documented qualifications and relevant experience. The selection of assessors and the assessment will be done in accordance with existing United Nations procedures for the selection of consultants and experts. The team of assessors may include one or more inspectors responsible for subsequent inspections of the manufacturing sites. The assessors must comply with the confidentiality and conflict of interest rules of UNFPA, as laid down in Sections 3 and 4 of this procedure.

The assessment of the submitted documentation will be done in accordance with SOPs established by UNFPA for that purpose. To ensure uniformity in evaluation and timeliness of assessment activities, UNFPA will, if needed, provide training to the assessors.

In making its assessment, UNFPA may take into account information submitted by the applicant during previous applications including results from previous site inspections and laboratory test results on products produced by the manufacturer, which may be in UNFPA's possession.

UNFPA aims to advise the applicants/manufacturers of the outcome of the assessment of documentation within 30 days after completion of the assessment. If the application is found to be in compliance with the requirements of UNFPA, as detailed on the WHO and UNFPA web sites, the manufacturing site will be scheduled for site inspection.

2.3 Site inspection

UNFPA will plan and coordinate inspections at the above-mentioned manufacturing sites to assess the manufacturing process and the product and quality management systems for compliance with general and performance requirements of the TCu380A IUD specification and good management practice including, in particular, the following international standards:

- ISO 7439. *Copper-bearing intra-uterine contraceptive devices — requirements, test*, 2nd ed. ISO, 2002.
- ISO 13485. *Medical devices — quality management systems: requirements for regulatory purposes*, 2nd ed. ISO, 2003.
- ISO/IEC 17025. *General requirements for the competence of testing and calibration laboratories*, 2nd ed. ISO, 2005.
- ISO 10993-1. *Biological evaluation of medical devices — Part 1 evaluation and testing*, 3rd ed. ISO, 2003.

- ISO 11135. *Medical devices — validation and routine control of ethylene oxide sterilization*, 1st ed. ISO, 1994.
- ISO 11737-1. *Sterilization of health care products — Radiation — Part 1: requirements for development, validation and routine control of a sterilization process for medical devices*, 1st ed. ISO, 2006.
- ISO 11737-2. *Sterilization of health care products — Radiation — Part 2: establishing the sterilization dose*, 1st ed. ISO, 2006.
- ISO 11607-1. *Packaging for terminally sterilized medical devices — Part 2: requirements for materials, sterile barriers and packaging systems*, 1st ed. ISO, 2006.

2.3.1 **Inspection team**

The inspection will be performed by a team consisting of one or more experts appointed by UNFPA who will act as temporary advisers to UNFPA. The inspectors must have detailed knowledge of the processes for manufacturing IUDs, documented qualifications and experience in auditing and quality management systems; and have specific experience of inspecting IUD manufacturing sites. The inspectors must comply with the confidentiality and conflict of interest rules of UNFPA, as detailed in Sections 3 and 4 of this procedure. If needed, to ensure uniformity in inspection procedures UNFPA will provide training to these experts.

Where possible UNFPA will appoint at least one inspector able to communicate in and read the local language. Failing this an interpreter selected by UNFPA will be used. One member of the team will be designated by UNFPA as the “lead inspector” and will be responsible for the coordination of inspection activities. The team may include observers from UNFPA. UNFPA will advise, and seek the involvement of, the national competent body in the on-site inspection.

UNFPA will advise the manufacturer, in advance, of the identity of each inspector, the composition of the team performing the site inspection, and provide curricula vitae of the inspectors. The manufacturer then has the opportunity to express possible concerns regarding any of the inspectors to UNFPA prior to the visit. If such concerns cannot be resolved in consultation with UNFPA, the manufacturer may object to a team member’s participation in the site visit. Such an objection must be made known to UNFPA by the manufacturer within 10 days of receipt of the proposed team composition. In the event of such an objection, UNFPA may cancel all or part of its agreement with, and the activities to be undertaken by, that inspector.

Each team will perform the inspections and report on its findings to UNFPA in accordance with the SOPs established by UNFPA for that purpose so as to ensure a standardized harmonized approach.

Information submitted in response to the EOI and the assessment report will be made available to the inspectors. All inspectors must comply with the confidentiality and conflict of interest rules of UNFPA as detailed in Sections 3 and 4 of this procedure.

2.3.2 **Scope and scheduling**

The applicant/manufacturee will be informed of the scope of the inspectors' activities, prior to the inspection. The key components of the inspection are available on the WHO and UNFPA web sites under the heading: *Scope of manufacturing site inspection: TCu380A IUDs*. However, the inspection will not be limited to these components. Manufacturees must be prepared to show the inspectors all aspects of the manufacturing process, including sites for compounding, injection moulding and sterilization as well as records and data that relate to the production of the IUDs. Where necessary manufacturees must organize access to the facilities of suppliers. Inspectors may, in consultation with UNFPA, schedule the review of such facilities into their site inspection.

UNFPA aims to advise the applicant/manufacturee of the date of inspection at least 30 days in advance. UNFPA and the inspectors will make reasonable efforts to accommodate any requests made by the manufacturee and/or regulatory agencies to change the date of the inspection.

UNFPA will inform the applicant/manufacturee that the inspectors may request copies of documents presented as evidence during inspection and may request permission to make a photographic record of the inspection, subject always to consideration of confidential information, as referred to in Section 2.5.

2.3.3 **Transparency**

The inspection team is paid by UNFPA to inspect the facilities and the members are reimbursed for their hotel and transport expenses by UNFPA. The manufacturee will not pay for hotel accommodation or make any payments for or to the inspectors and/or UNFPA staff. The manufacturee may be requested to assist in making reservations at an appropriate hotel and for local transportation to and from the airport or station, and to and from their hotel to the facilities.

The inspectors (and UNFPA staff who accompany the inspectors) cannot accept any gifts from the companies they visit. UNFPA requires that applicants/manufacturees do not make any offers of gifts of whatever value to the inspectors and/or UNFPA staff.

By participating in the scheme, the manufacturee agrees to allow full access to any facilities, which are in any way involved in the production of the

product(s) concerned, and to all documentation related to that production. If such access is not provided, the manufacturing site and specific products cannot be prequalified.

Any evidence of fraud or serious omissions by the manufacturer during the initial assessment procedure will lead to termination of the site inspection.

2.4 **Product testing**

Products will be sampled for independent testing, prior to or subsequent to the inspection by an independent sampler appointed by UNFPA or by the inspectors at an appropriate point during the inspection.

The samples will be packed and sealed by the inspectors or the independent sampler, as may be appropriate. The inspectors may take the samples with them, or arrange for the manufacturer to have the sealed boxes sent to the selected laboratory by courier at UNFPA's expense.

The sample size taken and range of tests performed will be in accordance with the current TCu380A specification. All product testing will be undertaken by independent accredited test laboratories selected by UNFPA. Such test laboratories must possess defined and documented competence and experience as demonstrated by accreditation to the current ISO 17025 standard.

A copy of the test report will be provided to the applicant.

2.5 **Report and communication of the results of the site inspection**

At the conclusion of the inspection, the inspectors will provide a brief written summary report outlining the key findings and observations discussed with the manufacturer during the site inspection. This report will be provided to UNFPA with a copy to the manufacturer.

In addition, the inspection team will finalize its main report according to the established UNFPA SOP and format, describing the findings, evidence and recommendations, as described on the WHO and UNFPA web sites under the heading: *Scope of manufacturing site inspection: TCu380A IUDs*. The report will be submitted to UNFPA.

The inspection report will be communicated by UNFPA to the applicant/manufacturer. If any additional information is required, or corrective action has to be taken by the manufacturer, UNFPA will postpone its decision on the acceptability of the site(s), until such information has been evaluated, or the corrective action has been taken and found satisfactory in light of the specified standards.

UNFPA reserves the right to terminate the procedure of quality assessment of a specific product if the applicant/manufacturee is either not able to provide the required information or to implement the corrective actions within a specified time period, or if the information supplied is inadequate to complete the quality assessment process.

In the event of any disagreement between an applicant and UNFPA, an SOP established by UNFPA for the handling of appeals and complaints will be followed to discuss and resolve the issue.

The ownership of any of the reports produced in the course of, or as the result of, the assessment of documentation, product testing and inspection of the manufacturing site lies with UNFPA. Thus, UNFPA will be entitled to use and publish such reports, subject always, however, to the protection of any commercially confidential information of the applicant/manufacturee(s). Confidential information may include:

- confidential intellectual property, “know-how” and trade secrets (including, e.g. formulas, programmes, process or information contained or embodied in a product, unpublished aspects of trademarks and patents); and
- commercial confidences (e.g. structures and development plans of a company).

Provisions of confidentiality will be contained in the exchange of letters, to be concluded before the assessment of the product dossier or inspection of the manufacturing site(s), between UNFPA and each applicant/manufacturee.

Notwithstanding the foregoing, UNFPA and WHO reserve the right to share the full evaluation and inspection reports with the relevant authorities of any interested Member State of UNFPA and/or WHO.

2.6 **Decision to prequalify**

It is UNFPA’s responsibility to compile the information submitted in response to the EOI, the assessment report, the inspection report and the test report. A UNFPA staff member with appropriate experience and training will assess the information about each manufacturee, in consultation with the assessors and inspectors and will make a final decision about the outcome of the prequalification process.

Based on this assessment UNFPA will either:

- Prequalify the TCu380A IUD manufacturing site without conditions. This will only be the case when there is no evidence that corrective action should be submitted to UNFPA.

Or

- Require the manufacturers, where deemed necessary, to undertake specified corrective action(s). The manufacturer must do this within an agreed period of time and provide UNFPA with evidence, where required, showing that the corrective action has been taken. If UNFPA is satisfied with this additional information, the manufacturing site will be added to the list of prequalified TCu380A IUD manufacturing sites.

Or

- Determine that a manufacturing site is ineligible for prequalification (without any requirement for corrective action being offered). This will not, however, preclude the applicant/manufacturer from resubmitting an application in response to future invitations for EOIs.

Where the inspectors recommended corrective action requiring a subsequent inspection, the manufacturer must advise UNFPA within an agreed period of time that corrective action has been completed and provide the relevant evidence, if required. The recommendation for corrective action may include further independent product testing. After review of the evidence, UNFPA will decide whether or not to schedule a further inspection. If a further inspection is deemed necessary, the inspection process and assessment will be implemented in accordance with the procedure detailed in Sections 2.3, 2.4, 2.5 and 2.6.

UNFPA reserves the right to terminate the procedure of quality assessment of a specific product if the applicant/manufacturer is not able to provide the required information or implement the corrective actions within a specified time period, or if the information supplied is inadequate to complete the quality assessment process.

The findings of the inspection may include non-mandatory observations aimed at highlighting potential for improved manufacturing and quality management practices.

If evidence supporting mandatory improvement actions or additional information is required, or other corrective actions have to be taken by the manufacturer, UNFPA will postpone its final decision until such information has been evaluated, or the corrective action has been taken and found satisfactory in light of the specified international standards, detailed in the Appendix. If the applicant/manufacturer has not submitted a satisfactory response within 12 months of submission of the report to UNFPA, the application will lapse and the applicant/manufacturer will need to reapply in response to a future invitation for an EOI.

UNFPA aims to inform the manufacturer of the results of the process within 30 days of receipt of all final reports.

2.7 Listing of prequalified TCU380A intrauterine devices and manufacturing sites

Once UNFPA is satisfied that the quality assessment process is complete, and where the product dossier and corresponding manufacturing site have been found to meet the prequalification requirements, the product as produced at the specified manufacturing site(s) will be listed on the WHO and UNFPA prequalification web sites. The list of prequalified TCU380A IUDs and corresponding manufacturing sites will be compiled and updated in accordance with an SOP established by UNFPA for this purpose.

Each applicant will receive a letter from UNFPA informing them of the outcome of the quality assessment process.

2.8 Maintenance of the prequalification status

Once the product is included in the list of prequalified TCU380A IUDs and corresponding manufacturing sites, the applicant/manufacture will be required to provide UNFPA with prior notification of any intended changes in the manufacturing site and/or the manufacturing process.

All manufacturers of prequalified TCU380A IUDs are required to advise UNFPA, four weeks prior to implementation, of any matter that affects the information on which the approval was based. This includes, but is not limited to:

- change of premises;
- change in production and testing equipment;
- change in senior management;
- product recalls;
- change in certifications or licences held by the manufacturer;
- reports of adverse events;
- change in design;
- change in suppliers of raw materials;
- change in specification of raw materials;
- change in raw material processing;
- change in production;
- change in packaging;
- change in sterilization processes;
- new information about shelf-life.

It is the applicant's responsibility to provide UNFPA with the appropriate documentation (referring to relevant parts of the dossier) to prove that the implementation of any intended variation will not have an impact on the quality of the product that has been prequalified. UNFPA will undertake an evaluation of variations according to established UNFPA guidelines and SOPs and communicate the outcome to the applicant. Compliance with

the requirement to report changes will be checked during the inspections carried out by UNFPA.

At periodic intervals UNFPA may, through an independent sampler, take random samples of TCu380A IUDs produced by listed manufacturers. The sample size taken and range of tests performed will be in accordance with the current TCu380A specification. All product testing will be undertaken by an independent test laboratory, selected by UNFPA, of defined and documented accreditation to the current ISO 17025 international standard. In the event of failure to meet the established requirements for testing, UNFPA will investigate the problem and communicate this to the manufacturer and/or applicant if different from the manufacturer.

UNFPA may request reports from consumer or regulatory bodies, or from other procurement agencies, relating to the quality and supply of the prequalified TCu380A IUD.

Complaints concerning prequalified TCu380A IUDs communicated to UNFPA will be investigated in accordance with an SOP established by UNFPA for that purpose. After investigation UNFPA will provide a written report of the complaint investigations to the applicant/manufacturer, including recommendations for action. UNFPA will require evidence of effective action taken, where relevant. UNFPA will make the report available to the applicant/manufacturer and to the appropriate authorities of the country where the manufacturing site is located, subject always to considerations of commercially confidential information, as referred to in Section 2.5 above.

UNFPA reserves the right to make such reports public, if it considers this to be of public health importance. In addition, UNFPA reserves the right to share the full report and/or recommendations for action with WHO and relevant authorities of interested Member States of WHO.

2.9 **Reassessment**

UNFPA aims to undertake a reassessment of TCu380A IUDs manufactured at a specific site at intervals of no more than three years. Such reassessments will consist of a comprehensive evaluation of documentation, site inspection and product testing similar to the initial prequalification assessment.

Reassessment may also be required in the following situations:

- If the TCu380A IUDs supplied by the manufacturer are considered by UNFPA, or one or more of the United Nations agencies, not to be in compliance with the agreed TCu380A IUD specification.
- If a complaint considered serious in nature has been received by the UNFPA or one or more of the United Nations agencies or organizations.

- If there is a significant change in one or more of the items listed in 2.8 above.

All relevant information including the reassessment of submitted documentation and the site inspection reports together with monitoring information will be considered by the designated UNFPA official and a decision will be made either to:

- maintain the TCu380A IUD and its manufacturing site on the list of prequalified products without need for corrective actions;

or

- maintain the prequalification status of the TCu380A IUD and manufacturing site with a requirement for corrective actions and, where agreed to by UNFPA, a further product testing and/or site inspection;

or

- suspend prequalified status.

UNFPA aims to advise the applicant/manufacture of the result of the reassessment and make any necessary amendments to the list of prequalified manufacturing sites and products within 30 days of receipt of the data on which the decision is based. The updated list will be published on the WHO and UNFPA prequalification web sites.

UNFPA will de-list any prequalified product and manufacturing site if the information submitted is subsequently found to be incorrect or fraudulent.

2.10 Language

The official language of the programme is English. All documents submitted as part of an application for prequalification will be in English. If the original of any required document is not in English, the manufacturer must submit a copy of the original, plus a certified translation into English. All correspondence between UNFPA and the applicant should be in English. All reports issued by the assessors, inspectors and by UNFPA on the assessment and inspections will be in English.

Inspections will be conducted in English, where necessary with the aid of an interpreter. It is the responsibility of the manufacturer to advise UNFPA and for UNFPA to agree whether an interpreter is required for the inspection.

2.11 Fees

At present, UNFPA will cover the expenses of the assessments, inspections and product testing. Manufacturers are responsible for their own costs

related to providing the necessary information and help required under the scheme.

Currently the process is conducted by UNFPA free of charge. UNFPA reserves the right, however, to charge a fee on a cost-reimbursement basis.

2.12 **Resolution of disputes**

If there is any disagreement between a manufacturer and UNFPA, an SOP established by UNFPA for the handling of appeals and complaints will be followed to discuss and resolve the issue.

3. **Confidentiality undertaking**

The assessors and inspectors will treat all information to which they will gain access during the evaluations and inspections, or otherwise in connection with the discharge of their responsibilities in regard to the above-mentioned project, as confidential and proprietary to UNFPA or parties collaborating with UNFPA in accordance with the terms set out below.

Assessors and inspectors will take all reasonable measures to ensure:

- that confidential information is not used for any other purpose than the evaluation/inspection activities described in this document; and
- that it is not disclosed or provided to any person who is not bound by similar obligations of confidentiality and non-use as contained herein.

Assessors and inspectors will not, however, be bound by any obligations of confidentiality and non-use to the extent they are clearly able to demonstrate that any part of the confidential information:

- was known to them prior to any disclosure by or on behalf of UNFPA (including by manufacturers); or
- was in the public domain at the time of disclosure by or on behalf of UNFPA (including by manufacturers); or
- has become part of the public domain through no fault of theirs; or
- has become available to them from a third party not in breach of any legal obligations of confidentiality.

4. **Conflict of interest**

Before undertaking the work, each assessor and inspector will also (in addition to the above-mentioned confidentiality undertaking) be required to sign a declaration of interest. If based on this declaration of interest, it is felt that there is no risk of a real or perceived conflict of interest (or it is felt that there is only an insignificant and/or irrelevant conflict of interest), and it is thus deemed appropriate for the evaluator or inspector in question to

undertake this work, he/she will discharge his/her functions exclusively as adviser to UNFPA. In this connection, each assessor and inspector is required to confirm that the information disclosed by him/her in the declaration of interest is correct and complete, and that he/she will immediately notify UNFPA of any change in this information.

All inspectors furthermore agree that, at the manufacturer's request, UNFPA will advise the manufacturer in advance of the identity of each inspector and composition of the team performing the site inspection, and provide curricula vitae of the inspectors. The manufacturer then has the opportunity to express possible concerns regarding any of the inspectors to UNFPA prior to the visit. If such concerns cannot be resolved in consultation with UNFPA, the manufacturer may object to a team member's participation in the site visit.

Such an objection must be made known to UNFPA by the manufacturer within 10 days of receipt of the proposed team composition from UNFPA. In the event of such an objection, UNFPA reserves the right to cancel all or part of its agreement with, and the activities to be undertaken by, that inspector.

Appendix

List of standards and specifications

World Health Organization. *Draft report of the IUD technical review committee September 2006*. Geneva, World Health Organization, 2007.

O'Brien PA et al. Copper containing, framed intra-uterine devices for contraction (review). *Cochrane Database of Systematic Reviews*, 2006, Issue 3, July 2006, updated August 2007.

ISO 7439. *Copper-bearing intra-uterine contraceptive devices — requirements, test*, 2nd ed. International Standards Organization, 2002.

ISO 13485. *Medical devices — quality management systems: requirements for regulatory purposes*, 2nd ed. International Standards Organization, 2003.

ISO/IEC 17025. *General requirements for the competence of testing and calibration laboratories*, 2nd ed. International Standards Organization, 2005.

ISO 10993-1. *Biological evaluation of medical devices — Part 1 evaluation and testing*, 3rd ed. International Standards Organization, 2003.

ISO 11135. *Medical devices — validation and routine control of ethylene oxide sterilization*, 1st ed. International Standards Organization, 1994.

ISO 11737-1. *Sterilization of health care products — Radiation — Part 1: requirements for development, validation and routine control of a sterilization process for medical devices*, 1st ed. International Standards Organization, 2006.

ISO 11737-2. *Sterilization of health care products — Radiation — Part 2: establishing the sterilization dose*, 1st ed. International Standards Organization, 2006.

ISO 11607-1. *Packaging for terminally sterilized medical devices — Part 2: Requirements for materials, sterile barriers and packaging systems*, 1st ed. International Standards Organization, 2006.

Annex 4

Guidelines on active pharmaceutical ingredient master file procedure^{1,2}

1. Introduction
2. Scope
3. Content of the active pharmaceutical ingredient master file (APIMF)
 - 3.1 Open part of APIMF
 - 3.2 Restricted part of APIMF
4. Use of the APIMF procedure
5. Steps of the APIMF procedure
6. Content of the product dossier when the APIMF procedure is used
7. Changes and updates to the APIMF

Appendix 1

Template letter of access

Appendix 2

Part of covering letter to be submitted by the APIMF holder to WHO

¹ These guidelines are based on the approach described in the *Consultation draft guideline on active substance master file procedure*. London, European Medicines Agency, 2005 (document CPMP/QWP/227/02 Rev 2).

² The APIMF procedure guidelines do not apply to biological APIs.

1. Introduction

The main objective of the Active Pharmaceutical Ingredient Master File (APIMF) procedure is to allow valuable confidential intellectual property or “know-how” of the manufacturer of the active pharmaceutical ingredient (API) to be protected, while at the same time allowing the applicant for prequalification or prequalification variation (from now on named in the text as the applicant) to take full responsibility for the finished pharmaceutical product (FPP) and the quality and quality control of the API. The WHO Prequalification Programme thus has access to all the information necessary for an evaluation of the suitability of the use of the API in the FPP.

The APIMF procedure is a possibility offered to applicants for WHO prequalification of medicinal products and the manufacturers of their APIs. Other means of submission of scientific data on the API include:

- a valid certificate of suitability of pharmacopoeial monographs with which the API complies with all appendices, and adding information which is not covered by the certificate;
- by submitting scientific information on the API to the extent available and organized according to the current guidance documents, available on the WHO Prequalification web site (<http://www.who.int/prequal/>). In this case, the API manufacturer should provide a signed declaration that the synthesis and subsequent purification is conducted in accordance with what is presented in the dossier.

In addition, the WHO pharmaceutical starting materials certification scheme (SMACS) can be used to attest the relevant data as covered in the scheme. (*WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-eighth report. Geneva, World Health Organization, 2004. WHO Technical Report Series, No. 917, Annex 3.*)

2. Scope

These guidelines are intended to assist applicants in the compilation of the information on APIs in their dossiers for prequalification or when submitting a variation to a dossier on a prequalified product (named in the text from now on as product dossier) when the APIMF procedure is used. It is also intended to help APIMF holders in the compilation of their APIMFs.

3. Content of the active pharmaceutical ingredient master file

The APIMF should contain detailed scientific information as indicated in Section 2. Active pharmaceutical ingredient(s) of the “Guideline on

Submission of Documentation for Prequalification of Multi-source (Generic) Finished Pharmaceutical Products (FPPs) Used in the Treatment of HIV/AIDS, Malaria and Tuberculosis”, available on the WHO Prequalification web site at: <http://www.who.int/prequal/>.

The information required should be organized and presented in the structure and format described in these guidelines, which follows that of the Common Technical Document (CTD), agreed in November 2000 within the framework of the International Conference on Harmonisation (ICH, see web site: www.ich.org).

The scientific information in the APIMF should be physically divided into two separate parts, namely the open part (OP) and the restricted part (RP). In addition to the OP and RP, the APIMF should contain a table of contents and a separate quality summary for the OP and the RP. The OP and RP should each have a version number given by the APIMF holder. The structure of the version numbers should be unique and the following structure is suggested:

Name APIMF holder / Name active pharmaceutical ingredient / OP or RP / version number / date in yyyy-mm-dd.

3.1 **Open part of APIMF**

The OP contains the information that the APIMF holder regards as non-confidential to the applicant, whereas the RP contains the information that the APIMF holder regards as confidential. It is emphasized that the OP is still a confidential document that cannot be submitted to third parties without the written consent of the APIMF holder. In all cases the OP should contain sufficient information to enable the applicant to take full responsibility for an evaluation of the suitability of the specifications for the API to control the quality of this API for use in the manufacture of a specified FPP.

For the OP, at least those aspects listed below must be covered by appropriate documentation in the APIMF.

General information

- nomenclature
- structure
- general properties.

Manufacture

- manufacturer(s)/site of manufacture
- description of the manufacturing process and process controls
A flow chart and brief outline of the manufacturing process is regarded as sufficient, if detailed information is presented in the RP. However, full

validation data on the sterilization process may be requested in the OP (in cases where there is no further sterilization of the final product).

- control of critical steps and intermediates
in so far as the information is also relevant for the applicant to prequalification.

Characterization

- elucidation of structure and other characteristics
- impurities.

Control of API

- specification
- analytical procedures
- validation of analytical procedures
- batch analysis
- justification of specification.

Reference standards or materials

Container closure system

Stability

- stability summary and conclusion
- post-approval stability protocol and stability commitment
- stability data.

3.2 Restricted part of APIMF

The RP should contain the remaining information, such as a detailed description of the individual steps of the manufacturing method (reaction operating conditions, data on validation and evaluation of critical steps) and the quality control during the manufacturing method of the API. Information relevant to the applicant such as that on impurities should be discussed in the RP, but it may be also submitted in the OP if considered necessary to enable the applicant to take full responsibility for its product.

For the RP, at least those aspects listed below must be covered by appropriate documentation in the APIMF.

Manufacture

- manufacturer(s)/site of manufacture
- detailed description of the manufacturing process and process controls
- control of materials
- control of critical steps and intermediates

in so far as the information is related to the detailed description of the manufacturing process and in so far as this information is not relevant for the applicant;

- process validation and/or evaluation
- manufacturing process development.

Characterization

- impurities

in so far as the information is related to the detailed description of the manufacturing process and in so far as the APIMF holder sufficiently justifies that there is no need to control these impurities in the final API.

Control of API

- justification of specification

in so far as the information is related to the detailed description of the manufacturing process, control of materials and process validation.

4. Use of the APIMF procedure

An APIMF can only be submitted in support of a product dossier or a variation to a product dossier and is only reviewed in connection with that product dossier. An APIMF is never approved as such, it can be only accepted in relation to an FPP dossier.

The relationship between the quality of the API and its use in the FPP needs to be justified in the relevant product dossier. Although the APIMF procedure is developed to keep the intellectual property relating to the API confidential, it is also permissible to use the procedure when there is no confidentiality issue between the applicant and the API manufacturer, e.g. when the applicant for prequalification manufactures the API itself.

Preferably, the API manufacturer should be the holder of the APIMF. It is, however, permissible for the APIMF to be submitted by another party, considered as the holder. In this case, a formal letter of authorization should be available from the manufacturer of the API.

The APIMF procedure should be used for APIs where a professed standard is declared, i.e. where no monograph exists in *The International Pharmacopoeia*, *European Pharmacopoeia*, *United States Pharmacopoeia* or *Japanese Pharmacopoeia*, or where a monograph exists but a manufacturer's in-house standard is declared. The APIMF procedure can also be used when APIs are described in *The International Pharmacopoeia*, *European Pharmacopoeia*, *United States Pharmacopoeia* or *Japanese Pharmacopoeia*.

A Drug Master File (DMF) of an API (active substance) assessed by a drug regulatory authority in the International Conference on Harmonisation

(ICH)-participating and associated countries can be accepted without further evaluation provided that:

- the complete drug master file is submitted to the WHO Prequalification Programme;

and

- the corresponding assessment report from ICH or the associated authorities is made available through a mechanism of sharing of information;

or

- the manufacturer is able to prove that the API is used in an FPP-approved, in an ICH-participating, or associated country. In this respect, a certificate according to the WHO pharmaceutical starting materials certification scheme (SMACS) issued by a competent regulatory authority can be submitted, if available.

The holder of the DMF should also declare in writing that there have been no changes to the manufacture of batches of API to be supplied for WHO prequalification and to the DMF content since its acceptance by the ICH-participating or associated countries.

5. Steps of the APIMF procedure

The APIMF holder (manufacturer of the API or its authorized representative) should provide the APIMF to WHO only once, independently of the number of applicants and the number of FPP dossiers submitted. The submission of the relevant documentation by the APIMF holder to WHO must be synchronized to arrive at approximately the same time as the first product dossier is received from the FPP manufacturer that refers to the APIMF.

Where the APIMF procedure is used, the applicant for prequalification should submit to WHO the product dossier together with the “letter of access”. The APIMF holder should give permission to WHO, in the form of a “letter of access”, to assess the data in the APIMF in relation to a specific product dossier (see Appendix 1).

The APIMF holder should submit to WHO:

- the APIMF accompanied by a covering letter (see Appendix 2);
- quality summaries on the RP and the OP;
- the letter of access (see Appendix 1).

In addition, the APIMF holder should submit to the relevant FPP applicant(s):

- a copy of the latest version of the OP;

- a copy of the quality summary on the latest version of the OP;
- the letter of access.

WHO requires that any APIMF updates made in relation to one prequalification dossier should apply to all other FPP dossiers referencing that specific APIMF. It is the responsibility of the APIMF holder to notify the applicants and WHO about any changes to the OP and/or RP, so that the applicants can update all affected prequalification dossiers accordingly and file the appropriate variation(s) with WHO as necessary.

6. **Content of the product dossier when the APIMF procedure is used**

The applicant for prequalification is responsible for ensuring that he or she has access to the relevant information concerning the current manufacture of the API.

The specifications used by the applicant to control the quality of the API should be unambiguously laid down in the product dossier. The applicant for prequalification should quote the *OP version number / date in yyyy-mm-dd*, or should include a copy of the OP in the prequalification dossier. The version of the OP in the prequalification dossier should be the most recent and it should be identical to the OP as supplied by the APIMF holder to WHO as part of the APIMF.

The applicant should include all relevant details from the OP in the Quality summary of the product dossier. Aspects of the APIMF that are specifically relevant to the FPP under consideration should be highlighted in this summary.

In the case of a single supplier/manufacturer of the API, and where the APIMF, a valid certificate of suitability of pharmacopoeial monographs or the WHO API prequalification procedure is used, the specifications of the applicant for the API in the product dossier should in principle be identical to those of the APIMF, the certificate of suitability or the prequalified API. The applicant does not, however, need to accept redundant specifications, unnecessarily tight specification limits or outdated analytical methods. In cases where the applicant uses a different analytical method to the one described in the APIMF, both methods should be validated. Technical specifications relevant to the FPP, which are normally not part of the specifications in the APIMF (e.g. particle size), should be part of the API specifications submitted by the applicant for prequalification in its product dossier.

In cases where there is more than one supplier/manufacturer of API using one of the APIMF, certificate of suitability or API prequalification procedures, there should be a core of one single set of specifications for

the API presented by the applicant for prequalification that is identical for each supplier. It is acceptable to lay down in the specification more than one acceptance criterion and/or analytical method for a specific single parameter with the statement “for API from supplier X” (e.g. in the case of residual solvents).

7. **Changes and updates to the APIMF**

As for FPPs, APIMF holders should keep their APIMFs up to date on the actual synthesis or manufacturing process. The quality control methods should be kept in line with the current regulatory and scientific requirements. APIMF holders should not modify the contents of their APIMF (e.g. manufacturing process or specifications) without informing each applicant and WHO when a change introduced requires the filing of a variation to the product dossier. Changes in the RP of an APIMF not requiring filing of a variation, should, however, be notified to WHO. Before implementation, any change to the APIMF should be reported to WHO by every applicant by means of an appropriate variation procedure. A covering letter should be provided. In cases where the contents of the APIMF cannot be changed for a certain period of time, the APIMF holder should still provide the aforementioned data to the applicant and to WHO, making reference to this reason and requesting a later date of implementation.

The covering letter sent by the APIMF holder to WHO should contain the following information:

- a tabular list summarizing the changes carried out since the the APIMF was first compiled;
- an overview comparing the old and new content of the APIMF;
- information as to whether the change has already been accepted, rejected or withdrawn by another drug regulatory authority in the ICH-participating and associated countries;
- the names of the relevant applicants;
- the new OP and/or RP with each new version number;
- an updated Quality summary, if relevant;
- a discussion of the potential impact on the quality of the API as a result of the change(s).

Appendix 1

Template letter of access

Letter of access

Reference number of active pharmaceutical ingredient master file (given by WHO Prequalification, if known):

Manufacturing site: *(name and physical address; specify the unit, block or plot (if applicable))*

Active pharmaceutical ingredient master file holder: *(name and address)*

The aforementioned active pharmaceutical ingredient master file holder hereby authorizes the (WHO relevant staff members and external experts) to refer to and review the above-mentioned active pharmaceutical ingredient master file in support of the following Prequalification application(s) or Variation application(s) submitted by *(name of the applicant)* on *(planned date of submission)*; *(name of FPP product and prequalification code/ reference number, if known)* *(name of applicant)*

The aforementioned active pharmaceutical ingredient master file holder is committed to ensuring batch-to-batch consistency and to informing *(name of the applicant to prequalification)* and WHO of any change in the OP or RP parts of the active pharmaceutical ingredient master file.

Signature for the active pharmaceutical ingredient master file holder *(Date, name and address)*

Appendix 2

Part of covering letter to be submitted by the APIMF holder to WHO

This active pharmaceutical ingredient master file is submitted in relation to the product dossier:

(Name of the FPP in WHO Prequalification Programme for medicinal products)

(Name of applicant for Prequalification for the application concerned)

and describes (changes to) the manufacturing process and specifications of the (or one of the) active pharmaceutical ingredient(s) of this product dossier.

(Name active pharmaceutical ingredient)

The version number *(given by the APIMF holder)* of this active pharmaceutical ingredient master file is:

Open part: version *(version number)*

Restricted part: version *(version number)*

This active pharmaceutical ingredient master file has previously been submitted for assessment in relation to a product dossier for an FPP within the WHO Prequalification Programme.

(Refer to the prequalification code/reference number and name of the FPP and the FPP manufacturer.)

Annex 5

International Nonproprietary Names for biological and biotechnological substances: a review¹

Introduction

1. Pharmacological classification of biological and biotechnological substances
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3. General policies for biological and biotechnological substances
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 - 4.4 Blood coagulation cascade inhibitors
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 - 4.6 Colony-stimulating factors
 - 4.7 Enzymes
 - 4.8 Erythropoietin type blood factors
 - 4.9 Gene therapy products
 - 4.10 Growth factors
 - 4.11 Growth hormone (GH) derivatives
 - 4.12 Growth hormone antagonists

¹ Reference: INN Working Document 05.179 (Update November 2007).

- 4.13 Heparin derivatives including low-molecular mass heparins
- 4.14 Hirudin derivatives
- 4.15 Hormone-release inhibiting peptides
- 4.16 Human papilloma virus
- 4.17 Insulins
- 4.18 Interferons
- 4.19 Interleukin receptor antagonists
- 4.20 Interleukin-type substances
- 4.21 Monoclonal antibodies
- 4.22 Oxytocin derivatives
- 4.23 Peptides and glycopeptides (for special groups of peptides
see -actide, -pressin, -relin, -tocin)
- 4.24 Peptide vaccines/recombinant vaccines
- 4.25 Pituitary/placental glycoprotein hormones
- 4.26 Pituitary hormone-release stimulating peptides
- 4.27 Receptor molecules, native or modified
- 4.28 Synthetic polypeptides with a corticotropin-like action
- 4.29 Thrombomodulins
- 4.30 Toxins
- 4.31 Tumour necrosis factor antagonists
- 4.32 Vasoconstrictors, vasopressin derivatives
- 4.33 Various

5. Current challenges

References

Introduction

More than 50 years ago, WHO established the International Nonproprietary Name (INN) Expert Group/WHO Expert Committee on Specifications for Pharmaceutical Preparations, to assign nonproprietary names to medicinal substances, so that each substance would be recognized globally by a unique name. These INNs do not give proprietary rights, unlike a trademark, and can be used freely as they are public property.

INNs have been assigned to biological products since the early days of the INN Programme. As well as many names for individual substances, animal insulin preparations were given an INN in Recommended list 3 in 1959. In the period up to 1980, names were assigned to antibiotics, synthetic peptides, hormones and other proteins. In names of compounds related by structure and/or function, specific letter groups, called stems, are included to aid recognition by health professionals. The *-actide* synthetic corticotrophin analogues is an example.

In 1982, the name *insulin human* was proposed for the recombinant protein identical to natural human insulin and since then names have been assigned to a growing number of recombinant products. Within the INN Programme, names have not been assigned to natural human blood products or vaccines. For those groups of biological products the WHO Expert Committee on Biological Standardization (ECBS) has been adopting the scientific names of the biological products within the definitions of respective requirements.

Since the time that *insulin human* became the first recommended INN (rINN) for a recombinant product, the range of biological/biotechnological products has increased in size and complexity. For example, new stems have been introduced for tissue plasminogen activators (*-plase*) among other groups. Analogues of recombinant glycosylated proteins produced in different cell systems have been classified using Greek letters as indicators in the sequence of product introduction: erythropoietin (*epoetin alfa, beta* and so on) and glycoprotein hormones (*follitropin*) are examples. In the 1990s, a systematic scheme for naming monoclonal antibodies was implemented, based on the stem *-mab*, which indicates the origin (mouse, human, etc.) of the antibody and its intended use: tumour, immunomodulator and so on.

As a result of the scientific and technical developments currently taking place, new products of biotechnology and other biological products are being introduced and more products can be expected for the treatment or prevention of disease. Examples of such new products include recombinant blood products, transgenic products (human proteins expressed in animals or plants), products for gene therapy and novel vaccines.

As this area is becoming more and more complex and challenging, the INN Expert Group has requested the WHO–INN Secretariat to prepare

a document intended to summarize and review the past and present INN situation in this field.

This annex presents an inventory of the policy decisions taken by the INN Expert Group during all these years of change, and of the names assigned to biological and biotechnological substances. Considering the potential for further developments in the field of biologicals, this review is intended to be a *living document* which will be regularly updated to include new policies, and future INNs assigned. Please see the INN web page: <http://www.who.int/medicines/services/inn/en/index.html>.

Comments and suggestions from all interested parties are most welcome and will be presented to the INN Expert Group for its consideration and for possible incorporation in future updates of this review.

1. **Pharmacological classification of biological and biotechnological substances (1)**

Alimentary tract and metabolism

insulins (see item 4.17).

Anti-infectives

antimicrobial, bactericidal permeability increasing polypeptides (see item 4.1)

human papilloma virus (see item 4.16).

Antineoplastics

peptide vaccines/recombinant vaccines (see item 4.24)

toxins (see item 4.30).

Blood and agents acting on the haemopoietic system

antithrombins (see item 4.3)

blood coagulation cascade inhibitors (see item 4.4)

blood coagulation factors (see item 4.5)

erythropoietin type blood factors (see item 4.8)

heparin derivatives including low-molecular mass heparins (see item 4.13)

hirudin derivatives (see item 4.14)

thrombomodulins (see item 4.29).

Immunomodulators and immunostimulants

- colony-stimulating factors (see item 4.6)
- interferons (see item 4.18)
- interleukin receptor antagonists (see item 4.19)
- interleukin type substances (see item 4.20)
- monoclonal antibodies (see item 4.21)
- receptor molecules, native or modified (see item 4.27)
- tumour necrosis factor antagonists (see item 4.31).

Hormones, hormone antagonists, hormone-release stimulating peptides or hormone-release inhibiting peptides (excluding insulins)

- growth hormone (GH) derivatives (see item 4.11)
- growth hormone antagonists (see item 4.12)
- oxytocin derivatives (see item 4.22)
- pituitary/placental glycoprotein hormones (see item 4.25)
- pituitary hormone-release stimulating peptides (see item 4.26)
- synthetic polypeptides with a corticotropin-like action (see item 4.28)
- vasoconstrictors, vasopressin derivatives (see item 4.32).

Various

- antisense oligonucleotides (see item 4.2)
- enzymes (see item 4.7)
- gene therapy products (see item 4.9)
- growth factors (see item 4.10)
- peptides and glycopeptides (for special groups of peptides see
 - actide (see item 4.28), -pressin (see item 4.32), -relin (see item 4.26),
 - tocin (see item 4.22)) (see item 4.23).

2. Current status of existing stems or systems for biological and biotechnological substances (1–8)

2.1 Groups with respective stems

Name of the group	Stem
antisense oligonucleotides	<i>-rsen</i>
blood coagulation cascade inhibitors	<i>-cogin</i>
blood coagulation factors	<i>-cog</i>
colony stimulating factors	<i>-stim</i>
enzymes	<i>-ase</i>
erythropoietin type blood factors	<i>-poetin</i>
growth factors	<i>-ermin</i>
growth hormone derivatives	<i>som-</i>
heparin derivatives including low molecular mass heparins	<i>-parin</i>
hirudin derivatives	<i>-irudin</i>
hormone-release inhibiting peptides	<i>-relix</i>
interleukin receptor antagonists	<i>-kinra</i>
interleukin type substances	<i>-kin</i>
monoclonal antibodies	<i>-mab</i>
oxytocin derivatives	<i>-tocin</i>
peptides and glycopeptides (for special groups of peptides see <i>-actide</i> , <i>-pressin</i> , <i>-relin</i> , <i>-tocin</i>)	<i>-tide</i>
pituitary hormone-release stimulating peptides	<i>-relin</i>
receptor molecules, native or modified (a preceding infix should designate the target)	<i>-cept</i>
synthetic polypeptides with a corticotropin-like action	<i>-actide</i>
tumour necrosis factor antagonists	<i>-nercept</i>
vasoconstrictors, vasopressin derivatives	<i>-pressin</i>

2.2 Groups with respective pre-stems

Name of the group	Pre-stem
antimicrobial, bactericidal permeability increasing polypeptides	<i>-ganan</i>

2.3 Groups with INN schemes

Name of the group
antithrombins
gene therapy products
insulins
interferons
pituitary/placental glycoprotein hormones

2.4 Groups without respective stems/pre-stems and without INN schemes

Name of the group
growth hormone antagonists
human papilloma virus
peptide vaccines/recombinant vaccines
thrombomodulins
toxins

3. General policies for biological and biotechnological substances

3.1 General policies for blood products (5)

- INNs have not been assigned to natural human blood products.
- Many natural blood products have well-established names, so the recombinant version should have a distinctive name reflecting as much as possible the established name used in the field.
- It is essential to add “activated” to the name of the blood product when this is presented for therapeutic use in its activated form.

3.2 General policies for fusion proteins (5)

- INNs have been assigned to some fusion proteins. If a stem exists for one or the other part of the fusion protein, this stem should be brought into the name. This allows the constant part of a fusion protein to be recognized in the name.
- At present it is considered unnecessary to indicate that the product is a fusion product within the name, but this position may need to be reviewed in the future.

3.3 General policies for gene therapy products (2)

In 2005, the Nomenclature Scheme for Gene Therapy Products was formally adopted. The scheme is shown in Table 1.

Table 1

Two-word scheme

	Prefix	Infix	Suffix
Word 1 (gene component)	to contribute to the distinctive name e.g. <i>al-</i> ; <i>bet-</i> ; <i>val-</i>	to identify the gene using, when available, existing infixes for biological products or using similar infix as for the protein for which the gene codes. e.g. <i>-ermin-</i> : growth factor <i>-kin-</i> : interleukin <i>-lim-</i> : immunomodulator <i>-mul-</i> : multiple gene <i>-tusu-</i> : tumour suppression	<i>-(a vowel)gene</i> e.g. <i>-(o)gene</i>
Word 2 (vector component)	to contribute to the distinctive name	e.g. <i>-adeno-</i> : adenovirus <i>-cana-</i> : canarypox virus <i>-herpa-</i> : herpes virus <i>-lenti-</i> : lentivirus <i>-morbilli-</i> : paramyxoviridae morbillivirus <i>-parvo-</i> : adeno-associated virus (parvoviridae dependovirus) <i>-retro-</i> : (other retrovirus) <i>-vari-</i> : (vaccinia virus)	<i>-vec</i> (non-replicating viral vector) <i>-repvec</i> (replicating viral vector)
			<i>-plasmid</i> (plasmid vector)

In the case of naked DNA, there is no need for a second word in the name.

3.4 General policies for glycosylated compounds (9)

For glycoproteins/glycopeptides

- Identification of the group with a stem, e.g. for erythropoietin: *-poetin*; indication of differences in the amino acid chain by using a random prefix and indication of differences in the glycosylation pattern by another designator, expressed by a Greek letter spelt in full and added as a second word to the name (e.g. *epoetin alfa (66)*)¹. The Greek letters are used in the Greek alphabetical order.
- Identification of the group with a word, e.g. interferon. Subgroups are identified by a Greek letter spelt in full and added as a second word to the name; differences in the composition of the amino acid sequence are indicated by using an Arabic figure; different compounds, including different glycosylation pattern, are indicated by a small letter (e.g. *interferon beta (73)*, *peginterferon alfa-2a (84)*).

¹ The number in parentheses indicates the proposed list number.

3.5 General policies for immunoglobulins (10, 11)

Not to select an INN for each of immunoglobulins.

The “systematic” or descriptive name is essential since the prescriber must know all the information conveyed by this name and there is no benefit in assigning an INN from which it will not be readily apparent.

3.6 General policies for monoclonal antibodies (1, 3)

- The common stem for monoclonal antibodies is *-mab*.
- Sub-stems for source of product are shown in Table 2.

Table 2

Sub-stems for source of product

<i>a</i>	rat
<i>axo</i> (<i>pre-sub-stem</i>)	rat-murine hybrid
<i>e</i>	hamster
<i>i</i>	primate
<i>o</i>	mouse
<i>u</i>	human
<i>xi</i>	chimeric
<i>zu</i>	humanized

The distinction between chimeric and humanized antibodies is as follows:

A *chimeric* antibody is one that contains contiguous foreign-derived amino acids comprising the entire variable region of both heavy and light chains linked to heavy and light constant regions of human origin.

A *humanized* antibody has segments of foreign-derived amino acids interspersed among variable region segments of human-derived amino acid residues and the humanized heavy-variable and light-variable regions are linked to heavy and light constant regions of human origin.

- Sub-stems for disease or target class are shown in Table 3.

Table 3

Sub-stems for disease or target class

<i>-ba(c)-</i>	bacterial
<i>-ci(r)-</i>	cardiovascular
<i>-fung-</i>	fungal
<i>-ki(n)-</i> (<i>pre-sub-stem</i>)	interleukin
<i>-le(s)-</i>	inflammatory lesions
<i>-li(m)-</i>	immunomodulator
<i>-os-</i>	bone
<i>-vi(r)-</i>	viral

Tumours

-co(l)-	colon
-go(t)-	testis
-go(v)-	ovary
-ma(r)-	mammary
-me(l)-	melanoma
-pr(o)-	prostate
-tu(m)-	miscellaneous

Whenever there is a problem with pronunciation, the final letter of the sub-stems for diseases or targets may be deleted, e.g. -vi(r)-, -ba(c)-, -li(m)-, -co(l)-, etc.

Prefix

The prefix should be random, i.e. the only requirement is to contribute to a euphonious and distinctive name.

Second word

If the product is radiolabelled or conjugated to another chemical, such as toxin, identification of this conjugate is accomplished by use of a separate, second word or acceptable chemical designation.

If the monoclonal antibody is used as a carrier for a radioisotope, the latter will be listed first in the INN, e.g. *technetium (^{99m}Tc) pintumomab (86)*.

-toxa- infix

For monoclonals conjugated to a toxin, the infix -toxa- can be inserted either into the first (main) name or included in the second word.

3.7 General policies for non-glycosylated compounds (9)

For proteins/peptides:

- Identification of the group with a stem, e.g. for hirudin analogues: -irudin, and indication of differences in the amino acid chain by using a random prefix (e.g. bivalirudin (72)).
- Identification of the group with a word, e.g. insulin, and indication of differences in the composition of the amino acid chain as a second element of the name (e.g. *insulin argine (58)*).

3.8 General policies for skin substitutes (5)

The products within this system are made of cells within a matrix, and skin substitutes can be considered to be engineered tissue and thus fall outside the scope of the INN system.

3.9 General policies for transgenic products (5)

- If an INN already exists, the same name should be used for the transgenic product, qualified in some way to identify that this product is transgenic.
- A similar system to that used for glycosylated recombinant products is suggested to differentiate new or additional sources of the same substance, and the source of the substance should be included in the definition of the INN.

3.10 General policies for vaccines (5–8)

- At present, vaccines are not included within the INN system, but names are assigned through recommendations of the Expert Committee on Biological Standardization and through the pharmacopoeial monograph.
- During the INN Consultation in 1993, it was agreed that the prerequisite for an INN application for a recombinant vaccine would be fulfilled if the manufacturer was able to provide all information outlined in the guidelines entitled *Definition of INNs for substances prepared by biotechnology* (12).
- During the Consultation in 1998, following discussion on recombinant viruses, the experts agreed not to attempt to name live viruses.
- Another approach in vaccine technology seems to be the development of peptide vaccines¹ (epitopes involved in immune response formation): since these peptides are chemically well-defined, their naming will be less problematic.

4. Summary of INN assigned to biological and biotechnological substances (1, 3, 4, 8, 9, 13, 14–21)

4.1 Antimicrobial, bactericidal permeability-increasing polypeptides

The pre-stem for antimicrobial, bactericidal permeability-increasing polypeptides is *-ganan*.

iseganan (85), *omiganan* (89), *pexiganan* (78).

4.2 Antisense oligonucleotides

The common stem for antisense oligonucleotides is *-rsen*.

afovirsen (97), *alicaforsen* (97), *aprinocarsen* (97), *cenersen* (97), *fomivirsen* (97), *oblimersen* (97), *trabedersen* (97), *trecovirsen* (97).

¹ The definition of peptide vaccines is given in item 4.24.

4.3 **Antithrombins**

antithrombin III (60), *antithrombin alfa (93)* (Rec. Glycoprotein (432aa) from transgenic goats).

4.4 **Blood coagulation cascade inhibitors**

The common stem for blood coagulation cascade inhibitors is *-cogin*.
drotrecogin alfa (activated) (86), *taneptacogin alfa (90)*, *tifacogin (78)*.

4.5 **Blood coagulation factors**

The common stem for blood coagulation factors is *-cog*.

The sub-stems *-eptacog*, *-octocog* and *-nonacog*, have been selected to date for recombinant blood coagulation factors.

A prefix will be necessary if the amino acid sequence does not match that of the naturally occurring material.

In accordance with the general policy, *alfa*, *beta*, etc., will be added for the glycoproteins (see item 3.4 — general policies for naming glycoproteins).

When the additional statement “activated” is needed, e.g. for the blood coagulation factor VIIa, it should be spelt out in full and added in parentheses after the name.

blood coagulation VII: *-eptacog*
eptacog alfa (activated) (77), *vatreptacog alfa (activated) (97)*

blood factor VIII: *-octocog*
beroctocog alfa (95), *morooctocog alfa (72)*, *octocog alfa (73)*

blood factor IX: *-nonacog*
nonacog alfa (77).

4.6 **Colony-stimulating factors**

The common stem for colony-stimulating factors is *-stim*.

ancestim (79) (cell growth factor), *garnocestim (86)* (immunomodulator), *pegacaristim (80)* (megakaryocyte growth factor), *romiplostim (97)* (platelet stimulating factor (through Mpl receptor))

combination of two different types of colony-stimulating factors: *-distim*
leridistim (80), *milodistim (75)*

granulocyte colony-stimulating factor (G-CSF) type substances: *-grastim*
filgrastim (64), *lenograstim (64)*, *nartograstim (66)*, *pegfilgrastim (86)*, *pegnartograstim (80)*

granulocyte macrophage colony-stimulating factor (GM-CSF) types substances: *-gramostim*

ecogramostim (62), molgramostim (64), regramostim (65), sargramostim (66)

macrophage-stimulating factors (M-CSF) type substances: *-mostim*

cilmostim (71), lanimostim (91), mirimostim (65)

interleukin-3 analogues and derivatives: *-plestim*

daniplestim (76), muplestim (74).

4.7 Enzymes

The common stem for enzymes, in general, is *-ase*.

Sub-stems refer to the activity of the substances.

proteinase:

with *-ase* suffix:

brinase (22), kallidinogenase (22), ocrase (28), pegaspargase (64), promelase (47), rasburicase (82), serrapeptase (31), sfericase (40), streptokinase (6), urokinase (48), urokinase alfa (77)

without *-ase* suffix:

batroxobin(29), bromelains(18), chymopapain(26), chymotrypsin (10), defibrotide (44), fibrinolysin (human) (10), sutilains (18)

-lipase: bucelipase alfa (95), rizolipase (22)

enzymes with superoxide dismutase activity: *-dismase*

- *ledismase (70), sudismase (58)*
- isomerase: *orgotein (31), pegorgotein (72)*

plasminogen activator combined with another enzyme: *-diplase*

amediplase (79)

tissue-type-plasminogen activators: *-teplase*

alteplase (73), anistreplase (59), desmoteplase (80), duteplase (62), lanoteplase (76), monteplase (72), nateplase (73), pamiteplase (78), reteplase (69), silteplase (65), tenecteplase (79)

urokinase-type-plasminogen activators: *-uplase*

nasaruplase (76), nasaruplase beta (86), saruplase (76)

others:

agalsidase alfa (84), agalsidase beta (84), alfimeprase (85), alglucerase (68), alglucosidase alfa (91), dornase alfa (70), epafipase (85), eufauserase (84), galsulfase (92), glucarpidase (92), hyalosidase (50), hyaluronidase (1), idursulfase (90), imiglucerase (72),

laronidase (86), pegademase (63), penicillinase (10), ranpirnase (81), streptodornase (6), tilactase (50).

4.8 Erythropoietin type blood factors

The common stem for erythropoietin type blood factors is *-poetin*.

In the case of erythropoietins, it was decided to select epoetin together with a Greek letter to differentiate between compounds of the same amino acid sequence as human erythropoietin which vary in the glycosylation pattern (see item 3.4 — general policies for glycosylated compounds).

Substances with different amino acid sequences will be named using the *-poetin* stem and a random prefix.

darbepoetin alfa (85), epoetin alfa (66), epoetin beta (62), epoetin gamma (67), epoetin delta (85), epoetin epsilon (72), epoetin zeta (95), epoetin theta (95), epoetin kappa (97), epoetin omega (73).

4.9 Gene therapy products

alferminogene tadenovec (95), amolimogene bepiplasmid (selected during the 42nd Consultation), beperminogene perplasmid (95), contusugene ladenovec (97), sitimagene ceradenovec (97), velimogene aliplasmid (97).

4.10 Growth factors

The common stem for growth factors is *-ermin*.

Sub-stems allow distinction between the various types of growth factors.

INNs for tumour necrosis factors (TNF) are also classified under the stem *-ermin*.

vascular endothelial growth factors: *-bermin*
telbermin (85)

epidermal growth factors: *-dermin*
murodermin (63), nepidermin (97)

fibroblast growth factors: *-fermin*
ersofermin (66), palifermin (88), repifermin (82), trafermin (74), velafermin (94)

leukaemia-inhibiting factors: *-filermin*
emfilermin (82)

tumour necrosis factors: *-nermin*
ardenermin (88), plusonermin (73), sonermin (68), tasonermin (78)

platelet-derived growth factors: *-plermin*

becaplermin (74)

insulin-like growth factors: *-sermin*

mecasermin (66), mecasermin rinfabate (92)

transforming growth factors: *-termin*

cetermin (74), liatermin (81)

bone morphogenetic proteins: *-otermin*

avotermin (77), dibotermin alfa (89), eptotermin alfa (92), adotermin (92)

others:

dapiclermin (93) (modified ciliary neurotrophic factor (CNTF)).

4.11 Growth hormone (GH) derivatives

The common stem for growth hormone derivatives is *som-*.

human growth hormone derivatives:

somatrem (54), somatropin (74)

For substances other than human, suffixes are added to indicate the species specificity of the structure.

bovine-type substances: *-bove*

somagrebove (63), somavubove (63), sometribove (74), somidobove (58)

porcine-type substances: *-por*

somalapor (62), somenopor (62), somfasepor (66), sometripor (75)

salmon-type substances: *-salm*

somatosalm (69)

others (growth hormone related peptides):

somatorelin (57) (growth hormone release-stimulating peptides, see item 4.26), *somatostatin (46)* (growth hormone release inhibitor).

4.12 Growth hormone antagonists

pegvisomant (82).

4.13 Heparin derivatives including low-molecular mass heparins

The common stem for heparin derivatives including low-molecular mass heparins is *-parin*.

ardeparin sodium (68), bemiparin sodium (75), certoparin sodium (70), dalteparin sodium (77), deligoparin sodium (89), enoxaparin sodium (77),

heparin sodium (54), livaraparin calcium (86), minolteparin sodium (74), nadroparin calcium (78), parnaparin sodium (77), reviparin sodium (78), tinzaparin sodium (77).

4.14 Hirudin derivatives

The common stem for hirudin derivatives is *-irudin*.

bivalirudin (72), desirudin (76), lepirudin (76), pegmusirudin (77).

4.15 Hormone-release inhibiting peptides

The common stem for hormone-release inhibiting peptides is *-relix*.

abarelix (78), cetrotorelix (66), degarelix (86), detirelix (56), ganirelix (65), iturelix (79), ozarelix (94), prazarelix (81), ramorelix (69), teverelix (78).

4.16 Human papilloma virus

verpasep caltespen (95) (heat-shock protein HSP 65 (*Mycobacterium bovis* strain BCG) **fusion protein** with transcription factor E7 (human papillomavirus 16)).

The suffix *-tespen* is the indicator of heat shock protein.

4.17 Insulins

Up to now, the insulin derivatives have been named using the two-word approach. The compounds named represent a structure with an additional amino acid, such as insulin argine, or represent modifications of the amino acid sequence, i.e. *insulin aspart (76)*.

biphasic insulin injection (16), compound insulin zinc suspension (06), dalanated insulin (14), globin zinc insulin injection (06), insulin argine (58), insulin aspart (76), insulin defalan (37), insulin detemir (80), insulin glargine (76), insulin glulisine (84), insulin human (48), insulin lispro (72), insulin zinc suspension (amorphous) (04), insulin zinc suspension (crystalline) (04), isophane insulin (04), neutral insulin injection (15), protamine zinc insulin injection (06).

4.18 Interferons

Interferon was published as an INN in 1962 with a general definition based on the origin and activity, e.g. “a protein formed by the interaction of animal cells with viruses capable of conferring on animal cells resistance to virus infection”.

The name was revised in the 1980s when human interferon and its variations *alfa, beta* and *gamma* were produced by recombinant biotechnology. The

INN Expert Group would have preferred to replace the old INN interferon by **alfaferon**, **betaferon** and **gammaferon**; however, this approach was barred as these names had already been registered as trademarks. The system adopted was thus to take interferon alfa, interferon beta and interferon gamma, and to provide, when necessary, for further distinction by additional numbers, or in the case of mixtures, by additional codes.

albinterferon alfa-2b (97), interferon alfa (73), interferon alfacon-1 (77), interferon beta (73), interferon gamma (73), peginterferon alfa-2a (84), peginterferon alfa-2b (84).

4.19 Interleukin receptor antagonists

The common stem for interleukin receptor antagonists is **-kinra**.

interleukin-1 (IL-1) receptor antagonists: *-nakinra*
anakinra (72)

interleukin-4 (IL-4) receptor antagonists: *-trakinra*
pitracinra (87).

4.20 Interleukin-type substances

The common stem for interleukin-type substances is **-kin**.

In accordance with general policy for naming glycosylated proteins (see item 3.4), it was agreed to publish the INNs for glycosylated interleukins with alfa, beta.

interleukin-1 (IL-1) analogues and derivatives: *-nakin*

interleukin-1 α analogues and derivatives: *-onakin*
pifonakin (77)

interleukin-1 β analogues and derivatives: *-benakin*
mobenakin (72)

interleukin-2 (IL-2) analogues and derivatives: *-leukin*
adargileukin alfa (89), aldesleukin (63), celmoleukin (65), denileukin difitox (78), pegaldesleukin (74), teceleukin (67), tucotuzumab celmoleukin (95)

interleukin-3 (IL-3) analogues and derivatives: *-plestim*
daniplestim (76), muplestim (74)

interleukin-4 (IL-4) analogues and derivatives: *-trakin*
binetrakin (82)

interleukin-6 (IL-6) analogues and derivatives: *-exakin*
atexakin alfa (72)

interleukin-8 (IL-8) analogues and derivatives: *-octakin*
emoctakin (74)

interleukin-10 (IL-10) analogues and derivatives: *-decakin*
ilodecakin (81)

interleukin-11 (IL-11) analogues and derivatives: *-elvekin*
oprelvekin (76)

interleukin-12 (IL-12) analogues and derivatives: *-dodekin*
edodekin alfa (79)

interleukin-13 (IL-13) analogues and derivatives: *-tredekin*
cintredekin besudotox (92)

a recombinant human interleukin-18 (IL-18) with 157 amino acids:
iboctadekin (92)

neurotrophins (interleukin-78, brain derived neurotropic factor): *-neurin*
(pre-stem)
abrineurin (84)

4.21 **Monoclonal antibodies**

The common stem for monoclonal antibodies is *-mab*.

INNs for monoclonal antibodies alphabetically by origin:

***-axomab* (pre-sub-stem, rat-murine hybrid)**

catumaxomab (93), *ertumaxomab* (93)

***-omab* (mouse origin)**

abagovomab (95), *afelimomab* (80), *altumomab* (80), *anatumomab*
mafenatox (86), *arcitumomab* (74), *bectumomab* (81), *besilesomab* (92),
biciromab (66), *capromab* (80), *detumomab* (80), *dorlimomab aritox* (66),
edobacomab (80), *edrecolomab* (74), *elsilimomab* (89), *enlimomab* (80),
enlimomab pegol (77), *epitumomab* (97), *epitumomab cituxetan* (89),
faralimomab (81), *gavilimomab* (84), *ibritumomab tiuxetan* (86), *igovomab*
(86), *imciromab* (66), *inolimomab* (80), *lemalesomab* (86), *maslimomab*
(66), *minretumomab* (80), *mitumomab* (82), *nacolumab tafenatox* (80),
naptumomab estafenatox (96), *nerelimomab* (81), *odulimomab* (81),
oregovomab (86), *satumomab* (81), *sulesomab* (86), *taplitumomab paptox*
(84), *technetium (^{99m}Tc)fanolesomab* (86), *technetium (^{99m}Tc)nofetumomab*
merpentan (81), *technetium (^{99m}Tc) pintumomab* (86), *telimomab aritox*
(66), *tositumomab* (80), *vepalimomab* (80), *zolimomab aritox* (80).

***-umab* (human origin)**

adalimumab (85), adecatumumab (90), atorolimumab (80), belimumab (89), bertilimumab (88), canakinumab (97), denosumab (94), efungumab(95), exbivirumab (91), gantenerumab (97), golimumab (91), ipilimumab (94), iratumumab (94), lerdelimumab (86), lexatumumab (95), libivirumab (91), mapatumumab (93), metelimumab (88), morolimumab (79), nebacumab # (66), ofatumumab (93), panitumumab (96), primumab (89), raxibacumab (92), regavirumab (80), sevirumab (66), stamulumab (95), tremelimumab (97), tuvirumab (66), votumumab (80), zalutumumab (93), zanolimumab (92), ziralimumab (84).

-ximab (chimeric origin)

abciximab (80), basiliximab (81), bavituximab (95), cetuximab (82), clenoliximab (77), ecromeximab (87), galiximab (89), infliximab (77), keliximab (81), lumiliximab (90), pagibaximab (93), priliximab (80), rituximab (77), teneliximab (87), vapaliximab (87), volociximab (93).

-zumab (humanized origin)

alemtuzumab (83), apolizumab (87), aselizumab (88), bapineuzumab (93), bevacizumab (86), bivatumab (86), cantuzumab mertansine (89), cedelizumab (81), certolizumab pegol (97), daclizumab (78), eculizumab (87), efalizumab (85), epratuzumab (82), erlizumab (84), felvizumab (77), fontolizumab (87), gemtuzumab (83), ibalizumab (97), inotuzumab ozogamicin (92), labetuzumab (85), lintuzumab (86), matuzumab (88), mepolizumab (81), motavizumab (95), natalizumab (79), nimotuzumab (94), ocrelizumab (95), omalizumab (84), palivizumab (79), pascolizumab (87), pertuzumab (89), pexelizumab (86), ranibizumab (90), reslizumab (85), rovelizumab (81), ruplizumab (83), sibrotuzumab (86), siplizumab (87), sontuzumab (94), tadocizumab (94), talizumab (89), tefibazumab (92), teplizumab (97), tocilizumab (90), toralizumab (87), trastuzumab (78), tucotuzumab celmoleukin (95), urtoxazumab (90), visilizumab (84), yttrium ⁹⁰Y tacatuzumab tetraxetan (93).

4.22 Oxytocin derivatives

The common stem for oxytocin derivatives is *-tocin*.

argiprestocin (13), aspartocin (11), carbetocin (45), cargutocin (35), demoxytocin (22), nacartocin (51), oxytocin (13).

4.23 Peptides and glycopeptides (for special groups of peptides see

***-actide* (see item 4.28), *-pressin* (see item 4.32), *-relin* (see item 4.26), *-tocin* (see item 4.22))**

The common stem for peptides and glycopeptides is *-tide*.

analgesic: *leconotide* (86), *ziconotide* (78)

angiogenesis inhibitor: *cilengitide* (81)

angiotensin converting-enzyme inhibitor: *teprotide* (36)

anti-inflammatory: *icrocaptide* (89)

antiarrhythmic: *rotigaptide* (94)

antidepressant: *nemifitide* (87)

antidiabetic: *albiglutide* (97), *amlintide* (76), *exenatide* (89), *liraglutide* (87),
pramlintide (74), *seglitide* (57)

antidiarrhoeal: *lagatide* (75)

antiobesity drug: *obinepitide* (96)

antithrombotic: *eptifibatide* (78)

antiviral: *enfuvirtide* (85), *tifuvirtide* (91)

atrial natriuretic factor type substance: *anaritide* (57), *neseritide* (80),
ularitide (69)

cardiac stimulant: *carperitide* (65)

diagnostic: *betiatide* (58), *bibapcitide* (78), *ceruletide* (34), *depreotide* (80),
mertiatile (60), *pendetide* (70), *technetium (^{99m}Tc) apcitide* (86),
teriparatide (50)

gastrointestinal bleeding/antineoplastic: *edotreotide* (84), *ilatretotide* (68),
lanretotide (64), *octretotide* (52),
pentetreotide (66), *vapretotide* (62)

gastrointestinal functions normalizing agent: *teduglutide* (90), *linaclotide* (97)

growth stimulant-veterinary: *nosiheptide* (35)

gut motility increasing: *ociltide* (52)

hormone analogue: *semparatide* (80)

immunological agents — antineoplastics: *almurtide* (74), *delmitide* (92),
disomotide (94), *edratide* (89),
goralatile (72), *mifamurtide* (95),
murabutide (49), *ovemotide* (94),
pentigetide (60), *pimelautide* (53),
prezatide copper acetate (67),
rolipoltide (94), *romurtide* (61),
tabilautide (60), *temurtide* (60),
tigapotide (95), *tiplimotide* (82)

inhibition of growth hormone release: *pasireotide* (90)
kallikrein inhibitor: *ecallantide* (93)
melanocortin receptor agonist: *bremelanotide* (95)
neuromodulator: *ebiratide* (56)
peptic ulcer: *sulglicotide* (29), *triletide* (50)
pulmonary surfactant: *lusupultide* (80), *sinapultide* (78)
sedative: *emideltide* (70)
treatment of Parkinson's disease: *doreptide* (59), *pareptide* (38)
wound healing agent: *rusalotide* (96)
other: *defibrotide* (44) (nucleotide).

4.24 Peptide vaccines/recombinant vaccines

Definition of peptide vaccines: vaccine in which antigens are produced from synthetic peptides and transported through the bloodstream by an adjuvant, in order to stimulate an immune response.

Definition of recombinant vaccines: vaccine produced from a cloned gene.

Description of recombinant vaccines: there are certain antigens on viruses and bacteria which are better at stimulating an antibody response by the animal than others. The genes for these antigens can be isolated, and made to produce large quantities of the antigens they code for. A recombinant vaccine contains these antigens, not the whole organism. Compare with “modified live vaccine” and “killed vaccine”.

The following substances are peptide vaccines:

disomotide (94), *ovemotide* (94).

4.25 Pituitary/placental glycoprotein hormones

The names selected by the International Union of Pure and Applied Chemistry–International Union of Biochemistry (IUPAC-IUB) have, to date, been chosen for compounds with an amino acid sequence identical to that of naturally occurring human hormones. Addition of a Greek letter as the second part of the name will allow differentiation of different glycosylation patterns for compounds produced by biotechnology (see item 3.4 — general policies for naming glycoproteins).

follicle stimulating hormones: ending in (-)*follitropin*

corifollitropin alfa (80), *follitropin alfa* (71), *follitropin beta* (75), *urofollitropin* (57)

gonadotropin: ending in *-gonadotropin*

choriogonadotropin alfa (76), *chorionic gonadotrophin (01)*: chorionic gonadotropins, obtained from human serum and urine during pregnancy and has both lutropin and follitropin activity

serum gonadotrophin (01): used for the follicle stimulating hormone (FSH, follitropin) from serum of pregnant mares

luteinizing hormones: ending in *(-)lutropin*

lutropin alfa (71).

4.26 Pituitary hormone-release stimulating peptides

The common stem for pituitary hormone-release stimulating peptides is *-relin*.

LHRH-release-stimulating peptides:

avorelin (74), *buserelin (36)*, *deslorelin (61)*, *fertirelin (42)*, *gonadorelin (32)*, *goserelin (55)*, *histrelin (53)*, *leuprorelin (47)*, *lutrelin (51)*, *nafarelin (50)*, *peforelin (93)*, *triptorelin (58)*

growth hormone release-stimulating peptides: *-morelin*

anamorelin (97), *capromorelin (83)*, *dumorelin (59)*, *examorelin (72)*, *ipamorelin (78)*, *pralmorelin (77)*, *rismorelin (74)*, *sermorelin (56)*, *tabimorelin (86)*, *tesamorelin (96)*

other: *somatorelin (57)*

thyrotropin releasing hormone analogues: *-tirelin*

azetirelin (60), *montirelin (58)*, *orotirelin (58)*, *posatirelin (60)*, *protirelin (31)*, *taltirelin (75)*

thyrotropin alfa (78) (thyrotropin releasing hormone (TRH) analogue)

other: *corticorelin (66)* (diagnostic agent).

4.27 Receptor molecules, native or modified

The stem for receptor molecules, native or modified is *-cept*.

A preceding infix should designate the target.

vascular endothelial growth factor receptors: *-ber-*
aflibercept (96)

complement receptors: *-co-*
mirococept (91)

subgroup of interferon receptors: *-far-*
bifarcept (86)

lymphocyte function-associated antigen 3 receptors: *-lefa-*
alefacept (84)

interleukin-1 receptors: *-na-*
rilonacept (95)

cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) receptors: *-ta-*
abatacept (91), *belatacept* (93)

antiviral receptors: *-vir-*
alvircept sudotox (69)

other: atacicept (95) (**fusion protein**)

see item 4.31 *-nercept*.

4.28 **Synthetic polypeptides with a corticotropin-like action**

The common stem for synthetic polypeptides with a corticotropin-like action is *-actide*.

alsactide (45), *codactide* (24), *giractide* (29), *norleusactide* (18),
seractide (31), *tetracosactide* (18), *tosactide* (24), *tricosactide* (44),
tridecactide (97).

4.29 **Thrombomodulins**

thrombomodulin alfa (94).

4.30 **Toxins**

toxin ML-1 (mistletoe lectin I) (*Viscum album*): *aviscumine* (86).

4.31 **Tumour necrosis factor antagonists**

The common stem for tumour necrosis factor antagonists is *-nercept*.

etanercept (81), *lenercept* (72), *onercept* (86), *pegsunercept* (95).

4.32 **Vasoconstrictors, vasopressin derivatives**

The common stem for vasoconstrictors, vasopressin derivatives is *-pressin*.

argipressin (13), *desmopressin* (33), *felypressin* (13), *lypressin* (13),
ornipressin (22), *terlipressin* (46), *vasopressin injection* (16).

4.33 **Various**

- *angiotensin II* (65): 5-L-isoleucineangiotensin II (the source of the material should be indicated)

- *angiotensinamide (12)*: N-{1-{N-{N-[N-(N²-asparaginyllarginyl)valyl]tyrosyl}valyl}histidyl}prolyl}-3-phenylalanine
- *calcitonin (80)*: a polypeptide hormone that lowers the calcium concentration in blood (the species specificity should be indicated in brackets behind the name)
- *epelestat (92)*: human recombinant neutrophil elastase inhibitor, bovine pancreatic trypsin inhibitor (BPTI) homologue
- *edifoligide (89)*: oligonucleotide
- *hemoglobin glutamer (80)*: the species specificity should be indicated in brackets behind the name “(bovine)”; the average mass of the polymer is given as e.g. haemoglobin glutamer-250 for 250 kD
- *hemoglobin crosumaril (76)*: hemoglobin A₀ (human $\alpha_2\beta_2$ tetrameric subunit), α -chain 99,99'-diamide with fumaric acid
- *hemoglobin raffimer (89)*
- *iropact (74)*: N-L-methionyl blood platelet factor 4 (human subunit)
- *ismomultin alfa (91)*: 47-261-Glycoprotein gp 39 (human clone CDM8-gp39 reduced)
- *litenimod (96)*: (3'-5')d(P-thio)(T-A-A-A-C-G-T-T-A-T-A-A-C-G-T-T-A-T-G-A-C-G-T-C-A-T)
- *macrosalb (¹³¹I) (33)*: macroaggregated iodinated (¹³¹I) human albumin
- *macrosalb (^{99m}Tc)(33)*: technetium (^{99m}Tc) labelled macroaggregated human serum albumin
- *metenkefalin (97)*: L-tyrosylglycylglycyl-L-phenylalanyl-L-methionine β -endorphin human-(1-5)-peptide
- *metreleptin (82)*: N-methionylleptin (human)
- *mirostipen (85)*: [23-methionine] human myeloid progenitor inhibitory factor 1-(23-99)-peptide
- *muromonab-CD3 (59)*: a biochemically purified IgG_{2 α} immunoglobulin consisting of a heavy chain of approx. 50 000 daltons and a light chain of approx. 25 000 daltons. It is manufactured by a process involving the fusion of mouse myeloma cells to lymphocytes from immunized animals to produce a hybridoma which secretes antigen-specific antibodies to the T3 antigen of human T-lymphocytes.
- *nagrestipen (76)*: 26-L-alaninelymphokine MIP 1 α (human clone pAT464 macrophage inflammatory)
- *opebacan (83)*: 132-L-alanine-1-193-bactericidal/permeability-increasing protein (human)
- *orgotein (31)*: a group of soluble metalloproteins isolated from liver, red blood cells and other mammalian tissues
- *parathyroid hormone (90)*: non-glycosylated human parathyroid hormone; the origin should be indicated in parentheses after the INN, for example (r. *E. coli*) for recombinant produced by *Escherichia coli*

- *pegaptanib* (88): 5'-ester of (2'-deoxy-2'-fluoro)C-Gm-Gm-A-A-(2'-deoxy-2'-fluoro)U-(2'-deoxy-2'-fluoro)C-Am-Gm-(2'-deoxy-2'-fluoro)U-Gm-Am-Am-(2'-deoxy-2'-fluoro)U-Gm-(2'-deoxy-2'-fluoro)C-(2'-deoxy-2'-fluoro)U-(2'-deoxy-2'-fluoro)U-Am-(2'-deoxy-2'-fluoro)U-Am-(2'-deoxy-2'-fluoro)C-Am-(2'-deoxy-2'-fluoro)U-(2'-deoxy-2'-fluoro)C-(2'-deoxy-2'-fluoro)C-Gm-(3'→3')-dT with α, α' -[[[(1*S*)-1-[[[5-(phosphonoxy)pentyl]carbamoyl]pentane-1,5-diy]bis(iminocarbonyl)]bis[ω -methoxypoly(oxyethane-1,2-diy)]]
- *secretin* (01): hormone of the duodenal mucosa which activates the pancreatic secretion and lowers the blood-sugar level
- *talactoferrin alfa* (93): recombinant human lactoferrin
- *tadekinig alfa* (90): interleukin-18 binding protein (human gene IL 18BP isoform a precursor)
- *thrombin alfa* (97): human thrombin (recombinant, glycoform α)
- *torapsel* (91): 42-89-glycoprotein (human clone PMT21:PL85 P-selectin glycoprotein ligand 1) **fusion protein** with immunoglobulin (human constant region)
- *tremacamra* (78): 1-453-glycoprotein ICAM-I (human reduced)
- *votucalis* (96): methionyl[145-leucine]FS-HBP2 (*Rhipicephalus appendiculatus* (Brown ear tick) female-specific histamine-binding protein 2).

5. Current challenges

- The INN Expert Group, when selecting names for recombinant proteins, has to deal not with substances with well-defined structures, but with products of highly complex composition or even with mixtures of such products.
- It is not only modified proteins that might differ from their naturally occurring counterparts; products derived by expression of the natural gene in foreign host cells may also differ structurally, biologically or immunologically from the natural protein.
- Glycoproteins particularly may occur in forms that differ in the structure of one or more of their carbohydrate units, a phenomenon known as microheterogeneity, which results in a heterogeneous population of molecules. Such differences may affect both the size and the charge of individual glycoproteins.
- A variety of novel biotechnology-derived products are under development, all of which will require specific policies on how to deal with such products.
- Clearly, INN nomenclature of biological medicinal products is an area of increasing complexity.

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¹ These documents are available on the INN Programme web site at: <http://www.who.int/medicines/services/inn/en/>.

