RECOMMENDED INN LIST 44
INTERNATIONAL NONPROPRIETARY NAMES FOR PHARMACEUTICAL SUBSTANCES

WORLD HEALTH ORGANIZATION • GENEVA
General Policy Issues

International harmonization of regulatory activities: future options

The World Health Organization (WHO) has traditionally supported the process of international harmonization by directing and coordinating health work and in encouraging technical cooperation. The Organization has been involved in a number of important harmonization activities having a major impact on the development, production and regulatory control of pharmaceutical products. Among these, the preparation of specifications and guidelines for the quality assurance, safety and efficacy of pharmaceutical substances has been carried out in close collaboration and consultation with Member States.

New regional and interregional harmonization activities related to drug regulation are now under way in many parts of the world and, as this situation unfolds, it is clear that the establishment of international standards needs more than ever to be focused on interests of public health. Possible options for the continued involvement of WHO in the international harmonization of drug regulatory activities were recently evaluated in a report developed by a WHO independent review team*.

The report highlights the urgent need for WHO to sustain regional and international harmonization efforts through greater participation in activities under development.

The report discusses two main areas of harmonization. The first concerns regional harmonization currently in progress throughout the world. The second, which is summarized below, addresses the respective roles of WHO and the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) involving the harmonization efforts of regulatory requirements of pharmaceuticals in the European Union, Japan and the United States of America. The report proposes options for the future role of WHO.

Global harmonization and the ICH

Harmonization of various elements of drug regulatory activities has taken place in the last decade and has involved intergovernmental initiatives at regional and interregional levels. The driving force behind the harmonization effort is the need to improve availability of pharmaceutical products and respond to the forces of international trade with adequate standardized technical regulations on safety, quality and efficacy. By reducing unnecessary duplication of regulatory requirements, it is proposed that therapeutic advances will be made more rapidly and at a lower developmental cost.

A prerequisite to any harmonized approach to international drug regulation is the existence in each of the participating countries of a functional drug regulatory system. This is understood as full drug registration processes, pharmaceutical inspection services and certified compliance with good manufacturing practice.

The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) was established in 1990 by the drug regulatory authorities and research-based pharmaceutical industries of the European Union, Japan and USA to focus on new drug development requirements. ICH is a tripartite venture of 17 high-income countries. To date, ICH has produced over 45 guidelines describing technical requirements related to specific components of the drug registration process drawn up by groups of specialists from drug regulatory authorities and the

*The report of the WHO independent review team is available from Quality Assurance and Safety: Medicines, Department of Essential Drugs and Medicines, World Health Organization, Geneva. The Team comprised: Dr Susan Alder, Australia, Professor Ali Haggag, Egypt, Dr Helen Rees, South Africa, and Professor Witold Wieniawski, Poland (Team Leader). The final draft of the report has been extensively circulated for comment, including the Expert Committee on Specifications for Pharmaceutical Preparations.
pharmaceutical industry of the ICH countries. The scientific level of each guideline is high and reflects state-of-the-art technology. The cost related to full implementation of the guidelines may in some cases be considerable but, it is argued, this is offset by more rapid registration of new drugs in the ICH countries.

The ICH initiative was established to harmonize the documentation needed for drug development and subsequent regulatory evaluation of products containing new chemical entities or products obtained by biotechnology. WHO is accorded observer status within the ICH Steering Committee, but is not directly involved in the process of drafting or developing ICH guidelines and has no control over their approval.

History of ICH
The International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH) was established in 1990 as a tripartite regulatory/research-based industry venture. The major aim of the ICH is to provide a forum for constructive discussion on the real and perceived differences in technical requirements for the registration of new chemical entities. Other objectives are to achieve greater harmonization in the interpretation and application of technical guidelines for the registration of new chemical entities or products obtained by biotechnology by its members, to improve the efficiency of global drug development, and to reduce redundant studies.

The co-sponsors of ICH comprise the European Commission and the European Federation of Pharmaceutical Industries and Associations (EFPIA); the Japanese Ministry of Health and Welfare (JMHW) and the Japanese Pharmaceutical Manufacturers Association (JPMA); and the US Food and Drug Administration (FDA) and the Pharmaceutical Research and Manufacturers of America (PhRMA). These six co-sponsors represent the voting members of the ICH Steering Committee.

The ICH thus represents 17 countries comprising 15% of the world’s population and accounting for 90% of the US $200 billion annual sales made by the multinational research-based pharmaceutical industry. ICH regulatory authorities are among the first to evaluate new chemical entities and new products obtained from biotechnology. The Secretariat is provided by the International Federation of Pharmaceutical Manufacturers Associations (IFPMA).

WHO, Health Canada and the European Free Trade Association (EFTA) hold observer status in the ICH Steering Committee.

Expanded ICH initiatives
Following the completion of the majority of harmonized ICH objectives in 1997, it was agreed that a further phase of harmonization activities should be continued. The terms of reference of ICH were amended to include provisions for updating existing guidelines and global harmonization. The revised terms of reference are:

- To maintain a forum for constructive dialogue between regulatory authorities and the pharmaceutical industry on the real and perceived differences in the technical requirements for product registration in the European Union, USA and Japan in order to ensure a more timely introduction of new medicinal products, and their availability to patients.
- To monitor and update harmonized technical requirements leading to a greater mutual acceptance of research and development data.
- To avoid divergent future requirements through harmonization of selected topics needed as a result of therapeutic advances and the development of new technologies for the production of medicinal products.
- To facilitate the adoption of new or improved technical research and development approaches which update or replace current practices, where these permit a more economical use of human, animal or material resources, without compromising safety.
- To facilitate the dissemination and communication of information on harmonized guidelines and their use to encourage the implementation and integration of common standards.

As part of the expanded phase of ICH activities, the ICH Steering Committee has established a Global Cooperation Group. Its stated purpose is to “make information available on ICH, ICH activities and ICH guidelines to any country or company that requests the information.” The principles and terms of reference for this group were finalized recently and a formal approach has been made to WHO to join the Group. The aim of the Global Cooperation
Group is to disseminate finalized ICH guidelines with an anticipated goal of acceptance and adoption of ICH guidelines in non-ICH countries.

The implications of the establishment of the Global Cooperation Group are discussed below.

**Globalization of ICH guidelines**

Although countries excluded from the ICH process are free to attend some ICH meetings and conferences, they do not make up part of the decision-making process. It is therefore estimated that the interests of approximately 85% of the world’s population are not directly represented within the ICH process.

While laudable in its support of ICH members, some countries and nongovernmental organizations excluded from the process have become vocal about perceived shortcomings of the ICH. The composition of the ICH has been a cause for concern from a range of interested parties, including patients and consumer groups. For example, the ICH has produced Guidelines on Good Clinical Practice which include reference to ethics committees and to informed consent. Some consumer groups have argued that while these are central to consumer protection, there has been little consultation with patient or consumer groups in the development of these guidelines. It has also been pointed out that while many clinical trials are conducted in developing countries, there has been no consultation between ICH and key officials from these countries.

While it is fair to assume that the partners within ICH are satisfied with the infrastructure and process, commentators outside have questioned the appropriateness of having the IFPMA coordinate the process and provide the Secretariat. Some critics have stated that this structure has led to an industry driven agenda, with the regulators tending to accept this as the status quo. Similar comments have been made about perceived lack of sufficient consultation with academics, scientists and the medical profession. While these concerns may be theoretical, specific examples given below tend to support this view.

Over the years, ICH has grown to rely more on advanced pharmaceutical technology in its standard setting on the assumption that this technology will lead to increased safety of new drugs. An example is the ICH Guidelines for Impurities in New Drug Substances (Q3A). The additional safety benefits from these rigorous standards have not yet been demonstrated but the costs incurred by manufacturers in meeting these requirements are significant. Setting such norms allows only the well-resourced pharmaceutical companies to achieve the necessary standards. This will become a concern if the guidelines are intended for global application. Smaller pharmaceutical companies, generic companies and many larger companies responsible for essential drug production in developing countries may be effectively squeezed out of the drug manufacturing picture if ICH guidelines start to be interpreted as the only global standard. For example, the application of the ICH Guideline on Impurities – Residual Solvents (Q3C) was developed for new products but is being extended to cover all products registered in the European Union. Another example is the ICH Guideline on Stability Testing (Q1) which covers only stability requirements in Climatic Zones I and II (temperate climates), and does not yet cover Climatic Zones III and IV (stability requirements for hot/dry and hot/humid climates).

The public health implications of the application of these guidelines in developing countries may be far reaching. In many countries, essential drugs required for the prevention and treatment of locally endemic conditions are not supplied by the major multinationals, but by local industry or by generic manufacturers. If they are unable to meet what may be unsubstantiated quality standards, the adverse impact of the withdrawal of these drugs on the health of the population would be far more dramatic than that of any hypothetical risk posed by failing to achieve the ICH standards.

Another element of some ICH guidelines is that they describe high safety requirements as appropriate for drugs which are marketed in the high-income countries but many of these products are intended to improve the quality of life of the population. Since the ICH guidelines do not address specific requirements for any category of products, they do not cover neglected diseases, including debilitating tropical diseases.

It might be argued that the above scenarios are irrelevant, since the initial aims of the ICH were not to set global standards for drug development and evaluation. Further, ICH has no legal mandate from the international community on which to base such an assumption. However, recent developments concerning the ICH Global Cooperation Group would suggest that ICH activities are set to gain
wider international acceptance. During the initial phase of ICH activities, it was made clear that the intentions of the ICH had relevance only to the co-sponsors, to the extent that approaches from other individual countries seeking membership were refused by the Steering Committee as unnecessary and a potential cause of confusion. It should, however, be stressed that ICH advocacy seminars have already been held in different regions of the world, and participating countries look on the ICH guidelines as the international "norm".

This interpretation of the ICH process is a particular challenge for WHO as reflected in the recommendations of the Ninth International Conference of Drug Regulatory Authorities (ICDRA) held in Berlin in 1999 which requests WHO to take into account the full implications for non-ICH countries when participating as an observer in the ICH process.

**Benefits of the ICH process**

The establishment of ICH ten years ago reflected a need felt by the research-based industry and certain governments to streamline the approval process for the registration of new drugs. The tendency of many countries to regard ICH guidelines as international standards further supports the argument that there was a need for such a process. The widespread reference to ICH guidelines by countries attests to the quality of their technical content. Indeed, many of the scientists involved in the ICH working groups responsible for developing the different guidelines have contributed to the high calibre of technical and scientific content in the recommendations. They argue that while recognizing serious omissions in some of the guidelines, this should not detract from the quality of the content of those already approved.

While the structure of the ICH was clearly exclusive from the outset, this position continues to be defended by its supporters as an appropriate partnership to achieve ICH aims and objectives. The omission of other participants, such as the generics industry, was not seen as a barrier to ICH work, as the original aim was not to harmonize the approval of generic drugs. Similarly, the ICH partners would argue that before countries implement the guidelines, regulatory authorities are able to involve consumer groups who can give comments. Additionally, in all the countries represented within ICH, there are appropriate mechanisms which allow public comment on the guidelines before they are finally adopted.

One of the most important criticisms of the ICH process is that its guidelines have been increasingly perceived as the 'gold standard' for international harmonization. The ICH has never claimed to have formal international authority to produce global standards and it further indicates that it is in no position to compel national drug regulatory authorities to adopt these standards. Nevertheless, many countries consider adoption of the guidelines as a necessary move. ICH proponents argue further that the intention of involving WHO as an observer in ICH was to ensure that international concerns about the protection of public health interests are met.

**Challenges for WHO**

Recommendations about the future role of WHO with respect to ICH must take into account both the current high status achieved by ICH internationally, the applicability of ICH products in non-ICH countries, and valid criticisms of the ICH process. WHO is the only international organization that has a legal international mandate from 191 Member States to set global standards for the promotion and protection of public health. The ICH, in contrast, has been established to harmonize standards for components of specific drug regulatory activities from 17 countries that are economically developed and where multinational research-based pharmaceutical companies involved in new drug development are situated.

Conversely, there is no proof that ICH guidelines will produce additional public safety benefits. Indeed, in replacing existing standards, there may be an impact on the availability of essential drugs in developing countries. This could also disrupt the generics industry and pharmaceutical manufacturers from countries outside the ICH tripartite, particularly with regard to increased costs as a result of implementation of ICH guidelines.

Currently, WHO attends ICH Steering Committee meetings as an observer and WHO has also been asked to become an observer to the work of the Global Cooperation Group. While the Group expresses the desire for the globalization process to be consultative and open, this initiative could give rise to concern for WHO and countries outside the ICH process since WHO, although not a full partner in the decision-making process of ICH, would be looked on as endorsing the globalization of ICH guidelines. Although the terms of reference of ICH are expanding into a wider international arena, there are no indications that ICH intends to broaden
its membership base or change its process of guideline development to reflect these new global ambitions.

A concern commonly voiced in this complex debate, is that the setting of different standards for the process of drug regulatory harmonization by ICH and by WHO will effectively produce a dual standard — a higher one for the more affluent countries and a lower one for poorer countries. This concern is untested. However, the raising of standards to such a level that essential drugs cannot be produced would be of tremendous concern. Furthermore, the rationale for introducing new expensive technologies to increase safety in drug production has yet to be proven in many situations.

Present developments in the international harmonization of drug regulation should be seen as a challenge to WHO to revisit the standards and guidelines that it has already set. In the opinion of the Review Team the setting of international standards should rightly remain within the domain of WHO and should be protected from interests beyond those of public health.

The fact that ICH guidelines have increasingly been perceived within countries as a global standard should seriously concern WHO. Before any discussion of global recognition, it is imperative that guidelines should be subjected to an international review for their global applicability. The consultative processes utilized by WHO are necessary in order to promote the public health interests of populations in all countries. In some instances, this may also result in a need for WHO to develop standards for the quality, safety and efficacy of generic products to ensure that supplies of essential drugs are not squeezed off the market by standards that are unrealistic for the settings in which generic and essential drugs are produced and traded.

**Recommendations to WHO**

The ICH has made clear that it is committed to maintaining the status quo to achieve full effectiveness of the ICH process. However, other groups have influenced the ICH to change some of its procedures. Although it is considered unlikely that the ICH would accept a significant change in either the membership of its Steering Committee or current guideline modification or development, WHO should be encouraged to find ways to work more closely with ICH to engage and seek input from other countries.

The following recommendations are proposed for implementation by WHO. They are dependent on resources being made available for implementation.

- WHO continues to play an observer role within the ICH Steering Committee.
- The review team proposes that observer status takes on a more critical role within ICH. This could take the form of proposals of topics for guideline development and opinions on the potential public health implications of some of the guidelines proposed.
- WHO accepts observer status within the ICH Global Cooperation Group. However, measures should be taken for this not to be considered as an endorsement of ICH guidelines or procedures by WHO Member States.
- WHO establishes a mechanism to review, modify and/or adopt ICH guidelines as WHO international guidelines for drug regulatory activities, as relevant.

Within this mechanism, a series of consultations and meetings should be convened to review the existing ICH guidelines. These meetings should include national representatives, selected experts and academics other than those involved in ICH, as well as senior policy staff and scientific advisors from ICH and non-ICH countries encompassing all levels of regulatory activity.

As part of the process, endorsement could be achieved through WHO governing bodies or similar mechanisms.

- WHO should include the recommendations of the review group as topics for discussion at the Tenth ICDRA which will be held in Hong Kong in November 2001.

The review team also considered that a more active involvement of WHO as a full partner to the ICH process would be beneficial in allowing development of guidelines which would take public health issues fully into account. However, this would represent a significant structural change for the ICH.
**International Conference on Harmonization (ICH) Guidelines**

ICH **guideline development**
A total of 45 guidelines were produced during the first phase of ICH under quality, safety, efficacy and multidisciplinary topics. It soon became clear that updating of the guidelines is an ongoing activity. A selected listing of the guidelines is set out on the following pages and complete copies are available from [http://www.ifpma.org](http://www.ifpma.org).

Harmonization initiatives that are undertaken under the auspices of ICH are guided and overseen by the ICH Steering Committee, which is composed of representatives of the six co-sponsors and observers. The Committee meets on average 2-3 times a year.

ICH Expert Working Groups (EWGs) are responsible for the drafting of individual guidelines. EWGs are made up of representatives from the six co-sponsors, according to the topic under discussion. Participation has also been extended recently to observers, the pharmacopoeial authorities, generic industry associations and representatives of the non-prescription pharmaceutical industry.

Each ICH guideline proceeds through the following stages:

**Step 1:** The development of a consensus among scientists working in industry and regulatory agencies who discuss the topic in Expert Working Group meetings and exchange views on successive draft documents. The drafting process is conducted by a Rapporteur.

**Step 2:** Is reached when the Steering Committee accepts the consensus draft and it is transmitted to the three regional regulatory agencies for formal consultation in accordance with normal internal and external procedures.

**Step 3:** The draft guideline leaves the ICH process and is treated in the three ICH regions as a regulatory draft for consultation. In the European Union it is circulated as a CPMP draft guideline, in Japan it is translated and circulated internally and externally for consultation, and in the USA it is published as a consultation document in the Federal Register. Comments are collected by the regulatory agencies in the three regions and are consolidated by a Regulatory Rapporteur in order that a single, harmonized text can be adopted for implementation.

**Step 4:** Is reached when the final consolidated draft is accepted by the Steering Committee and “signed off” by the six co-sponsors.

**Step 5:** Is reached when the guideline has been adopted by the three regulatory authorities and incorporated into their appropriate administrative procedures. Simultaneous public announcements are made by regulatory authorities.

**ICH documents currently available**

The following summaries describe ICH Guidelines produced so far and are provided as information. An update of those Guidelines discussed during the recent International Conference on Harmonization held in November 2000 follows on page 159.

**Efficacy testing guidelines**
To date, the ICH has produced 11 guidelines addressing the efficacy assessment of new chemical and biological entities.

**E1A The Extent of Population Exposure to Assess Clinical Safety (Adopted at Step 4 - 1994)**
This is a brief guideline which establishes the number of patients to be treated and minimum duration of
treatment periods for the safety evaluation of drugs intended for the long-term treatment of non-life threatening diseases.

**E2A Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (Adopted at Step 4 - 1994)**

Definitions for adverse event (or experience) terms and adverse reactions. The guideline also gives the recommended timeframe for reporting to regulatory agencies adverse drug reactions which occur during clinical development. Attachment 1 sets out the Key Data Elements for inclusion in expedited reports of serious adverse drug reactions.

**E2B Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports (Adopted at Step 4 - 1997)**

This guideline extends E2A to give details of the data elements required for reporting individual cases of safety events (adverse drug reactions or adverse drug events) for both pre and post approval periods. The guideline covers reporting of adverse drug reactions and events from all sources and to any destinations, including reporting from authorities to the WHO Collaborating Centre for International Drug Monitoring.

**E2C Periodic Safety Update Reports for Marketed Drugs (Adopted at Step 4 - 1996)**

This guideline sets out the format and content for comprehensive periodic safety updates of marketed drugs for reporting to regulatory authorities. The PSUR presents the worldwide safety experience of a medicinal product at defined times (6-monthly or in multiples of 6-monthly reports) after the date of the first marketing authorization for the product granted to any company in any country in the world (international birthdate). The guideline also provides a sample model for a periodic safety update report.

**E3 Structure and Content of Clinical Study Reports (Adopted at Step 4 - 1995)**

This guideline sets out the structure and content of a report to allow for the compilation of a single integrated full report of any clinical study which will be acceptable to all regulatory authorities of the ICH. The report consists of the clinical and statistical description, presentations, and analysis integrated into a single report text and with appendices containing the protocol, sample case report forms, investigator related information, information related to the test drugs/investigational products including active control/comparators, technical statistical documentation, related publications, patent data listings and technical statistical details such as deviations, computations, analysis and computer output, etc. Appendices are intended to be additional information required by only some regulatory authorities and may be requested as needed.

**E4 Dose Response Information to Support Drug Registration (Adopted at Step 4 - 1994)**

This guideline sets out the purpose, principles and study design for the determination of the relationship among dose, drug-concentration in blood, and clinical response (effectiveness and undesirable effects).

**E5 Ethnic Factors in the Acceptability of Foreign Clinical Data (Adopted Step 4 - 1998)**

This guideline recommends a framework for evaluating the impact of ethnic factors upon a medicine’s effect (its efficacy and safety at a particular dosage and dose regimen) in order to facilitate the registration of medicines among the ICH regions. Ethnic factors are defined as those factors relating to the genetic and physiological (intrinsic) and the cultural and environmental (extrinsic) characteristics of a population. The guideline also provides an outline of the properties of a compound which makes it more or less likely to be sensitive to ethnic factors. It also defines the circumstances when additional data (called bridging studies) may be needed in order to allow extrapolation of the foreign data to a new region.

**E6 Good Clinical Practice: Consolidated Guideline (Adopted at Step 4 - 1996)**

This guideline sets out the principles and procedures to be followed when designing, conducting, recording and reporting clinical trial data that are intended to be submitted to regulatory authorities. It also provides details on the information which should be included in the Investigator’s Brochure, the clinical trial protocol and the essential documentation to be collected during the course of a clinical trial.
**E7 Studies in Support of Special Populations: Geriatrics (Adopted at Step 4 - 1993)**

This guideline sets out the principles required for the development of new drugs, new formulations and new combinations of established medicinal products which are likely to have significant use in the elderly, either because the disease intended to be treated is characteristically a disease of ageing or because the population to be treated is known to include substantial numbers of geriatric patients. The guideline defines the geriatric population and details the pharmacokinetic, pharmacodynamic (dose/response studies) and drug interaction studies which should be undertaken.

**E8 General Considerations for Clinical Trials (Adopted at Step 4 — 1997)**

This guideline provides an overview of the principles and practices in undertaking clinical trials for the development of new medicinal products. It illustrates the relationship between the phases of clinical development and types of study by objective and the general principles of design, conduct and analysis of trials.

**E9 Statistical Principles for Clinical Trials (Adopted at Step 4 — 1998)**

This guideline sets out the principles of statistical methodology to be applied to clinical trials for medicinal products being developed for marketing applications in the ICH regions.

**E10 Choice of Control Group and Related Issues in Clinical Trials (Adopted at Step 4 – 2000)**

The purpose of this guideline is to describe the general principles involved in choosing a control group for clinical trials intended to demonstrate the efficacy of a treatment and to discuss related trial design and conduct issues. This guideline does not address the regulatory requirements in any region, but describes what trials using each design can demonstrate.


The goal of this guideline is to encourage and facilitate timely paediatric medicinal product development internationally. The guideline provides an outline of critical issues in paediatric drug development and approaches to the safe, efficient, and ethical study of medicinal products in the paediatric population.

**Quality testing guidelines**

**Q1A Stability Testing of New Drug Substances and Products (Adopted at Step 4 — 1993)**

The scope of the guideline is confined to new molecular entities and associated drug products. Well-established active substances and associated products (generics) are not included.

**Stability testing conditions**

Long-term testing: for both drug substances and drug products: 25°C ± 2°C / 60% RH ± 5% for 12 months. Accelerated testing: for both drug substances and drug products: 40°C ± 2°C /75% RH ± 5% for 6 months. The long-term testing is continued for a sufficient period of time beyond 12 months to cover all appropriate re-test periods for drug substances. Where “significant change” occurs during 6 months storage under conditions accelerated testing, additional testing at intermediate conditions of 30°C ± 2°C /60% RH ± 5% is carried out. “Significant change” at 40°C/75%RH or 30°C/60%RH is defined as failure to meet the specifications. Mutual acceptability of information generated on stability in any one of the areas has been established, provided it meets the appropriate requirements of the guideline and the labelling is in accordance with national/regional requirements.

The ICH Harmonized Tripartite Guideline on stability testing of new drug substances and products (Q1A) notes that light testing should be an integral part of stress testing.

(Note: The WHO Stability Guideline covers the four climatic zones, whereas the ICH guideline covers only two climatic zones.)
Furthermore, the WHO guidelines cover multisource products, whereas the ICH Guideline is confined to new molecular entities and associated drug products.

**Q1B Photostability Testing of New Drug Substances and Products (adopted at Step 4 - 1996)**

The Guideline on Photostability Testing Q1B is an annex to guideline Q1A. The Q1B guideline addresses the generation of photostability information for submission of Registration Applications for New Molecular Entities and associated drug products. The guideline does not cover photostability of drugs after administration (i.e. under conditions of use).

A systematic approach to photostability testing is recommended in the guideline covering studies such as: (i) Tests on the drug substance; (ii) Tests on the exposed drug product outside the immediate pack; (iii) Tests on the drug product in the immediate pack (if necessary); and (iv) Tests on the drug product in the marketing pack (if necessary). A detailed Decision Flow Chart is established which describes how the extent of drug product testing can be established by assessing the change that has occurred at the end of the light exposure testing. Acceptable change is change within limits justified by the applicant. The guideline gives detailed information on light sources, procedure, presentation of samples, analysis of samples and judgement of results.

**Q1C Stability Testing: Requirements for New Dosage Forms (adopted at Step 4 - 1996)**

This guideline is an annex to guideline Q1A. The Q1C guideline addresses the recommendations on what should be submitted regarding stability of new dosage forms by the owner of the original application after the original submission of new drug substances and products. Stability protocols for new dosage forms should follow the Q1A guideline in principle. However, a reduced stability data base at submission time (e.g. 6 months accelerated and 6 months long-term data from ongoing studies) may be acceptable in certain cases.

**Q2A Text on Validation of Analytical Procedures (adopted at Step 4 -- 1994)**

The guideline discusses the characteristics to be considered during the validation of analytical procedures included in the Registration Application submitted to drug regulatory authorities (DRA) in the EU, Japan and USA. The guideline contains a collection of terms and their definitions with the object of bridging the differences that often exist between various compendia and DRAs in the EU, Japan and USA. The types of analytical procedures to be validated are included in the guideline besides a tabular summation of the characteristics applicable to these different types: identification tests, control of impurities (i.e. quantitative tests for impurities content, limit tests for the control of impurities) as well as assay procedures (i.e. quantitative tests of the active moiety in samples of drug substance or drug product, or other selected components of the drug product). The validation characteristics of an analytical procedure (Accuracy, Precision, Repeatability, Intermediate Precision, Specificity, Detection Limit, Quantitation Limit, Linearity and Range) are defined in a glossary at the end of the guideline. Although robustness is not included in the table of typical validation characteristics, it's stated that it should be considered at an appropriate stage in the development of the analytical procedure. Revalidation should be carried out in case of changes in the synthesis of drug substance, in the composition of the finished product or in the analytical procedure.

**Q2B Validation of Analytical Procedure — Methodology (adopted at Step 4 - 1996)**

The guideline is complementary to the parent guideline Q2A on Validation of Analytical Procedures. The purpose of the guideline is to provide some guidance and recommendations on how to consider various validation characteristics for each analytical procedure. The guideline states that different approaches may be applicable for the validation, provided that they demonstrate that the procedure is suitable for its intended use. Also analytical procedures for biological and biotechnological products may be approached differently. The guideline considers the various validation characteristics in distinct sections: Specificity (identification and assay as well as impurity tests), Linearity, Range, Accuracy (assay, quantitation of impurities), Precision (repeatability, intermediate precision, reproducibility), Detection limit (based on visual evaluation, based on signal-to-noise, based on standard deviation of the response and the slope), Quantitation limit (based on visual evaluation, based on signal-to-noise, based on standard deviation of the response and the slope), Robustness, System suitability testing.
Q3A Impurities in New Drug Substances (Adopted at Step 4 - 1995)

The guideline provides guidance for Registration Applications on the content and qualification of impurities in new drug substances produced by chemical synthesis. It is not intended to apply to new drug substances used in clinical trials. It does not cover biological/biotechnological peptides, oligonucleotides, radiopharmaceuticals, fermentation products, herbal products, and crude products of animal or plant origin. The guideline addresses chemistry aspects and safety aspects of impurities which are classified into the three following categories: organic impurities, inorganic impurities, residual solvents. Regarding organic impurities, the new drug substance specifications should include, where applicable, limits for: (i) Each Specified Identified Impurity; (ii) Each Specified Unidentified Impurity at or above 0.1%; (iii) Any Unspecified Impurity, with a limit of not more than 0.1%; and (iv) Total Impurities. Significant emphasis is placed on the qualification of impurities, i.e. establishing the safety of impurities at the levels specified. The applicant should provide a rationale for selecting impurity limits based on safety considerations. Qualification threshold is 0.05% in case the maximum daily dose exceeds 2g/day. The guideline includes a glossary and a decision tree for safety studies.

Q3B Impurities in New Drug Products (Adopted at Step 4 - 1996)

The guideline provides guidance recommendations for registration or marketing applications on the content and qualification of impurities in new drug products produced from chemically synthesized new drug substances. The guideline is an annex to the guideline on Impurities in New Drug Substances (Q3A). The scope of the guideline is confined to degradation products of the active ingredients or reaction products of the active ingredients with an excipient and/or immediate container/closure system. The guideline does not apply during clinical research stages of development. Biological/biotechnological products, peptides, oligonucleotides, radiopharmaceuticals, fermentation products and semisynthetic products, herbal products, and crude products of animal or plant origin are not covered. The guideline does not apply to impurities arising from excipients present in the drug product. The guideline describes two options for describing limits of class 2 solvents. Also concentration limits for solvents to be avoided are given. The guideline includes a glossary, thresholds for reporting, thresholds for identification and thresholds for qualification of degradation products in New Drug Products. A decision tree for safety studies is included.

Q3C Impurities: Guideline for Residual Solvents (Adopted at Step 4 - 1997)

The guideline recommends acceptable amounts for residual solvents in pharmaceuticals for the safety of the patient. The solvents are classified in the guideline into three classes: Class 1: solvents to be avoided; Class 2: solvents to be limited; Class 3: solvents with low toxic potential. The guideline describes two options for describing limits of class 2 solvents. Also concentration limits for solvents to be avoided are given. The guideline includes a glossary and an appendix listing solvents included in the guideline in addition to a second appendix giving additional background and a third appendix describing methods for establishing exposure limits.

Q4 Pharmacopoeial Harmonization

Already at the start of the ICH process, it was realized that the harmonization of drug quality requirements and test methods presented in pharmacopoeia monographs would not be possible through elaboration of specific guidelines, but should be treated differently, because harmonization has to affect separately each method and each individual substance. For that reason, a Pharmacopoeia Discussion Group (PDG) was established by representatives of three pharmacopoeias from the ICH group of countries: the European Pharmacopoeia, the Japanese Pharmacopoeia and the United States Pharmacopeia. The activity of PDG has proceeded in parallel to the work of ICH and in close involvement with its harmonization efforts. In the period 1992 - 1999 the efforts of the PDG were directed toward harmonization of a number of general methods of drug analysis, including methods used for the analysis of biotechnology products, and towards harmonization of quality requirements contained in pharmacopoeia monographs for a...
considerable number of excipients and several products obtained by biotechnology. In the process of harmonization, the PDG has established a list of 45 excipients that were most widely used in preparation of dosage forms or were considered critical for their quality. By mid-1999 the PDG has achieved harmonization of some 70% of the relevant monographs between the 3 pharmacopoeias. Considerable progress has also been achieved towards harmonization of important general methods and apparatus used in quality testing of dosage forms. Further efforts in this area are continuing in connection with the work on Q6A guideline where a number of pharmacopoeial test methods which previously differed between the 3 pharmacopoeias has been now harmonized. The harmonization of pharmacopoeial requirements through the PDG activities results in practice in the elevation of quality standards through the use of more sophisticated test methods but this requires the use of highly special apparatus and costly reagents. Also the requirement to use in the tests of only official reference materials of high unit cost, which is now quite frequent in the case of testing drug impurities, tends to increase further the expenses for the testing of drug quality according to harmonized methods.

Q5A Viral Safety Evaluation of Biotechnology Products (Adopted at Step 4 - 1997)
The guideline is concerned with testing and evaluation of the viral safety of biotechnology products derived from characterized cell lines of human or animal origin (i.e. mammalian, avian, insect). The term virus in this guideline excludes non-conventional transmissible agents such as those associated with Bovine Spongiform Encephalopathy (BSE) and scrapie. The scope of the guideline covers products derived from cell cultures initiated from characterized cell banks. It covers products derived from in-vitro cell culture, such as interferons, monoclonal antibodies and recombinant DNA-derived products including recombinant subunit vaccines, and also includes products derived from hybridoma cells grown in vivo as ascites. Excluded from the scope of this guideline are inactivated vaccines, all live vaccines containing self-replicating agents, and genetically engineered live vectors.

The guideline describes potential sources of virus contamination. It states that viral contamination of biotechnology products may arise from the original source of the cell line or from adventitious introduction of viruses during production processes. The guideline describes cell line qualification: Testing for viruses; Tests for Master Cell Bank (MCB), for Working Cell Bank (WCB), and cells at the limit of in vitro cell age used for production and recommended viral detection and identification assays such as: tests for retroviruses, in-vitro assays, in-vivo assays, antibody production tests. The guideline describes the acceptability of cell lines used for the manufacture of product on a risk-benefit basis. Also testing for viruses in unprocessed bulk is described. Inactivating or removing viruses is described in the guideline on the basis of viral clearance studies. The guideline includes specific precautions to be observed as well as a glossary. In summary, the guideline suggests approaches for the evaluation of the risk of viral contamination and for the removal of virus from the product, thus contributing to the production of safe biotechnology products derived from animal or human cell lines.

Q5B Quality of Biotechnological Products: Analysis of the Expression Construct in Cells Used for Production of rDNA derived protein products (Adopted at Step 4 - 1995)
The guideline presents guidance for the characterization of the expression construct for the production of recombinant DNA derived protein products in eukaryotic and prokaryotic cells. This is important to ensure the consistent production of a recombinant DNA derived product. Nucleic acid analysis data and the evaluation of the final purified protein serve to ensure the quality of a recombinant protein product.

Q5C Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products (Adopted at Step 4 - 1995)
The guideline is considered an annex to the parent guideline Q1A, “Stability Testing of New Drug Substances and Products” (1993), whose content applies to biotechnological/biological products. However, because of the distinguishing characteristics of the biotechnological/biological products, these should be given special consideration in stability testing. Being proteins and/or polypeptides, maintenance of molecular conformation is dependent on covalent and non-covalent forces. They are particularly sensitive to temperature change, oxidation, light, ionic contents and shear. Stringent storage
conditions are usually necessary to ensure maintenance of biological activity. For stability studies complex analytical methodologies may be necessary. Assays for biological activity, where applicable, should be part of the stability studies. Biochemical, physicochemical and immunochemical methods for the analysis of the molecular entity and the quantitative detection of degradation products should be part of the stability studies. The scope of the guideline covers products such as cytokines (interferons, interleukins, colony stimulating factors, tumour necrosis factors), erythropoietins, plasminogen activators, blood plasma factors, growth hormones and growth factors, insulin, monoclonal antibodies and vaccines consisting of well-characterized proteins or polypeptides, i.e. well-characterized proteins and polypeptides, their derivatives and products of which they are components, and which are isolated from tissues, body fluids, cell cultures or produced using rDNA technology. The guideline does not cover antibiotics, allergenic extracts, heparins, vitamins, whole blood, or cellular components. The guideline handles selection of batches of bulk materials, intermediates and final container products as well as sample selection. Validated methods should be used to assess potency, purity and molecular characteristics. The guideline describes further storage conditions, testing frequency, specification and labelling of biotechnology products. A glossary is included.

Q5D Quality of Biotechnological Products: Derivation and Characterization of Cell Substrates used for Production of Biotechnological/Biological Products (Adopted at Step 4 - 1997)
The guideline provides broad guidance on standards for the derivation of human and animal cells and microbial cells to be used to prepare biotechnological/biological products and for the preparation and characterization of cell banks to be used for production. The guideline covers cell substrates having a cell banking system, i.e. microbial cells or cell lines derived from human or animal sources that possess the full potential for the generation of the desired biotechnological/biological products for human in vivo or ex vivo use. Reagents for in vitro diagnostic use are outside the scope of this guideline. Animal sources of cell lines include all those of metazoan origin. Microbial sources include bacteria, fungi, yeast, and other unicellular life forms. Biotechnological/biological products in the guideline are any products prepared from cells cultivated from cell banks with the exception of microbial metabolites, such as antibiotics, amino acids, carbohydrates, and other low molecular weight substances. Included in the guideline are cell banks used to prepare gene therapy products or vaccines. Also certain viral vaccines are prepared in primary cell cultures derived directly from animal tissues or organs. Primary cells are not banked and therefore not addressed by this guideline. However, other considerations which may apply to primary cells are discussed further in the Appendix. The guideline handles generation of cell substrates, origin, sources and history of cells, cell banking, cell banking procedures as well as principles of characterization and testing of cell banks, such as tests of identity, tests of purity for both microbial and metazoan cells. The guideline describes further how cell substrate stability is tested. Also tests for karyology and tumourigenicity are used for characterization. A glossary is included.

Q6A Specifications for New Drug Substances and New Drug Products: Chemical Substances (Adopted at Step 4 - 1999)
The guideline is intended to assist in the establishment of a single set of global specifications for new drug substances and new drug products. It provides guidance on the setting and justification of acceptance criteria and the selection of test procedures for new drug substances of synthetic chemical origin and new drug products produced from them. The guideline addresses specifications, i.e. those tests, procedures and acceptance criteria used to assure the quality of the new drug substance and new drug product at release and during shelf-life. Specifications are an important component of quality assurance, but are not its only component. Other components are design, development, in-process controls, GMP controls, and process validation. Guidance is provided with regard to universal acceptance criteria, which should be established for all new substances and drug products and those which are considered specific to individual drug substances and/or dosage forms. The guideline gives a definition for general concepts which are important in setting harmonized specifications. These concepts are not universal, but can be considered in particular circumstances. They include: periodic/skip testing, release vs. shelf-life acceptance criteria, in-process tests, design and development considerations, limited data available at filing, parametric release, alternative procedures, pharmacopoeial tests and acceptance criteria, evolving technologies, impact of drug substance on drug product specifications, reference standards.
The guideline does not address drug substances or drug products during clinical research stages of drug development. Biological/biotechnological products, high molecular weight peptides, oligonucleotides, fermentation products, radiopharmaceuticals, herbal products, and crude products of animal or plant origin are not covered by the guideline. The full utility of this guideline is dependent on the successful completion of harmonization of pharmacopoeial procedures for several attributes commonly considered in the specifications for new drug substances or new drug products.

**Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products (Adopted at Step 4 – 1999)**

The guideline contains the requirements for the testing of products obtained by biotechnology. The guideline provides general principles on the setting and justification of a uniform set of international specifications for biotechnological and biological products to support marketing applications. The scope of the guideline covers proteins and polypeptides, their derivatives, and products of which they are components, e.g. conjugates. These proteins and polypeptides are produced from recombinant or nonrecombinant cell-culture expression systems and can be highly purified and characterised using an appropriate set of analytical procedures. The principles outlined in this guideline apply also to proteins and polypeptides isolated from tissues and body fluids. The following are not covered: antibiotics, synthetic peptides and polypeptides, heparins, vitamins, cell metabolites, DNA products, allergenic extracts, conventional vaccines, cells, whole blood and cellular blood components. The principles to be considered in setting specifications are described in detail as: • characterization (physicochemical properties, biological activity, immunochemical properties, purity, quantity) • analytical considerations; (reference standards and reference materials, validation of analytical procedures) • process control (process-related considerations, in-process acceptance criteria and action limits, raw materials and excipient specifications) • pharmacopoeial specifications • release limits versus shelf-life limits • statistical concepts. A justification of the specifications is handled in detail. A glossary is included in the guideline.

**Safety testing guidelines**

**S1A Guideline on the Need for Carcinogenicity Studies of Pharmaceuticals (Adopted Step 4 - 1995)**

This guideline sets out the definitions of the circumstances under which it is necessary to undertake carcinogenicity studies on new drugs, taking account of known risk factors and the intended indications and duration of exposure.

**S1B Testing for Carcinogenicity of Pharmaceuticals (Adopted Step 4 - 1997)**

This guideline outlines the scientific approach to testing pharmaceuticals for carcinogenicity in both mice and rats, and provides guidance on alternative testing procedures which may be applied without jeopardizing safety.

**S1C Dose Selection for Carcinogenicity Studies of Pharmaceuticals (Adopted Step 4 - 1995)**

This guideline sets out the criteria for the selection of the high dose to be used in carcinogenicity studies for new therapeutic agents.

**S2A Genotoxicity: Guidance on Specific Aspects of Regulatory Genotoxicity Tests for Pharmaceuticals (Adopted Step 4 - 1995)**

This guideline gives specific guidance and recommendations for in vitro and in vivo tests and on the evaluation of test results. It also includes a glossary of terms related to genotoxicity tests.

**S2B Genotoxicity - A Standard Battery for Standard Genotoxicity Testing of Pharmaceuticals (Adopted Step 4 - 1997)**

This guideline sets out a standard set of assays to be conducted for registration of new medicinal products and the extent of confirmatory experimentation in any particular genotoxicity assay in the standard battery.
S3A Note for Guidance on Toxicokinetics: the Assessment of Systemic Exposure in Toxicity Studies ( Adopted Step 4 - 1994)
This guideline gives guidance on developing test strategies in toxicokinetics and the need to integrate pharmacokinetics into toxicity tests in order to aid in the interpretation of the toxicity findings and promote rational study design development.

S3B Pharmacokinetics: Guidance for Repeated Dose Tissue Distribution Studies (Adopted Step 4 - 1994)
This guideline gives guidance on the circumstances when repeated dose tissue distribution studies should be considered (i.e. when appropriate data cannot be derived from other sources). It also gives recommendations on the conduct of such studies.

S4 Single Dose Toxicity Tests (Adopted at ICH-1, 1991)
Agreement was made in 1991 that the LD\textsubscript{50} determination should be abandoned on pharmaceuticals.

S4 Duration of Chronic Toxicity Testing in Animals (Rodent and Non-Rodent Toxicity Testing) (Adopted Step 4 - 1998)
Sets out guidance for repeated dose toxicity tests.

S5A Detection of Toxicity to Reproduction for Medicinal Products (Adopted Step 4 - 1993)
This guideline gives guidance on the tests required for reproductive toxicity, in which animals are treated during defined stages of reproduction, in order to better reflect human exposure to medicinal products and allow more specific identification of stages of risk.

S5B Reproductive Toxicology: Male Fertility Studies (an Addendum to S5A) (Adopted Step 4 - 1995)
This guideline is an Addendum to S5A to provide a better description of the testing concept and recommendations for male fertility studies, especially those addressing flexibility, pre-mating treatment duration and observations.

S6 Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals (Adopted at Step 4 - 1997)
This guideline gives guidance on the preclinical safety testing requirements for biotechnology products. It covers the use of animal models of disease, determination of when genotoxicity assays and carcinogenicity studies should be performed and the impact of antibody formation on the duration of toxicology studies.

Multidisciplinary guidelines
In this group of guidelines only guideline M3 has reached the implementation stage although M1, M2 and M3, discussed on page 159, are nearing implementation.

M3 Non-Clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals (Adopted at Step 4 - 1997)
The guideline addresses the principles of developing pre-clinical strategies on the timing of toxicity studies in relation to the conduct of clinical trials. It covers the timing of single dose and repeated dose toxicity studies, reproduction toxicity studies, genotoxicity studies, local tolerance studies and carcinogenicity studies as well as studies for safety pharmacology and pharmacokinetic studies in relation to different phases of human clinical trials.

ICH documents currently under discussion (2000)
The main ICH documents that are at present at the development stage include the M4 guideline on Common Technical Document and the Q7A guideline on GMP for Active Pharmaceutical Ingredients. Other guidelines that are still under development include guidelines in the drug efficacy and drug safety
areas as well as a revision of several quality guidelines. At the International Conference on Harmonization held in November 2000 further progress in preparation of the guidelines was achieved and several other guidelines proposed for development.

**Efficacy Guidelines**
Guidelines that are under development include:
- E2B(M) – Data Elements for Transmission of Individual Case Safety Reports.
- E12A – Principles for Clinical Evaluation of New Antihypertensive Drugs. It is intended that this guideline should serve as an example for a whole series of guidelines on clinical trials of specific groups of drugs.

**Quality guidelines**
Several important guidelines related to this area are still at various stages of development including:
- Q1Ar – Guideline on Stability Testing of New Drug Substances and Products.
- Q3Ar – Guideline on Impurities in New Drug Substances.
- Q3Br – Guideline on Impurities in New Drug Products.
- Q3C(M) – Impurities: Residual Solvents – (PDE for tetrahydrofuran) (PDE for N-methylpyrrolidone).
- Q7A – Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients. The guideline is intended to produce a common text for good practices in the manufacture of pharmaceutical substances used as active ingredients. It will describe all elements of control required in process during production of active pharmaceutical ingredients, as well as requirements for all wholesalers (agents, brokers, distributors, etc.) trading in these products.

**Safety Guidelines**
- S7 – Safety Pharmacology Studies for Human Pharmaceuticals. The guideline will describe the core battery of safety pharmacology studies, the necessity of such studies and the application of Good Laboratory Practices to safety pharmacology.

**Multidisciplinary Guidelines**
- **M1 Medical Terminology**
The guideline will describe a single medical terminology for drug regulatory purposes, including adverse drug reaction reporting. After discussing medical terminologies that currently exist and are in extensive use it was decided to select the MEDDRA terminology developed by the Medicines Control Agency in UK as suitable for the needs of the electronic transfer of data. The MEDDRA dictionary has taken into consideration the terms of several widely used terminologies, including WHOART (WHO Adverse Reaction Terminology), COSTART (used by US FDA) and ICD 9. Future modifications may include additional terms, such as those in the ICD 10.

- **M2 Electronic Standards for the Transfer of Information and Data**
The guideline will define electronic communication standards for direct communication of applications for drug registration, and drug safety data in a way that ensures the integrity of information. It should facilitate the exchange of data between pharmaceutical companies and drug regulatory authorities.

- **M4 Common Technical Document**
The Common technical document should serve as a standard document for submission of applications to drug regulatory authorities for registration of a new product. The document would consist of a general part (M4) and 3 specialized parts for sub-topics M4Q, M4S and M4E. The latter deal with the elements related to quality, safety and efficacy issues. Various parts of the document have now been completed and it was finalized during the International Conference on Harmonization in November 2000.
Current Topics

Declaration of Helsinki

The World Medical Association (WMA) General Assembly has recently revised the Declaration of Helsinki, the most widely accepted guideline on medical research involving human subjects. This set of principles forms the basis for the CIOMS International Guidelines for Biomedical Research Involving Human Subjects, and the ethical components of both the WHO and the ICH Good Clinical Practice Guidelines.

The Declaration sets out the obligations and responsibilities of doctors and physicians to subjects taking part in medical research and makes clear that research is justified only if the populations to be studied stand to benefit from the intervention. Individuals enrolled in trials must be given full information before consenting and the benefits, risks, burdens and effectiveness of any new trial method should be tested against those of the best current treatment, whenever this exists, rather than placebo. The same ethical rules need to be applied wherever research is being conducted and developing countries should not be targeted for clinical trial research because it is cheaper or because laws are not enforced to the same extent as developed countries.

Ethical Principles for Medical Research Involving Human Subjects

A. Introduction

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.

2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.

6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.

7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.

8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protec-
tion. The particular needs of the economically and medically disadvantaged must be recognized.

Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.

9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. Basic principles for all medical research

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.

11. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.

12. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.

15. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.

16. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.

17. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.

18. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.

19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.

20. The subjects must be volunteers and informed participants in the research project.

21. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient’s information and to minimize the impact of the study on the subject’s physical and mental integrity and on the personality of the subject.

22. In any research on human beings, each potential subject must be adequately informed of the
aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.

23. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.

24. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.

25. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.

26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.

27. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. Additional principles for medical research combined with medical care

28. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.

29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.

30. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.

31. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.

32. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.
Regulatory and Safety Matters

Misoprostol and pregnancy: reminder of dangers

A letter has been circulated by the manufacturer of misoprostol (Cytotec®) to remind health care providers that misoprostol administration by any route is contraindicated in women who are pregnant because it can cause abortion.

Misoprostol is indicated for the prevention of gastric ulcers induced by use of nonsteroidal anti-inflammatory drugs (NSAIDs) in patients at high risk of complications from gastric ulcer.

The uterotonie effect of misoprostol is an inherent property of prostaglandin E₂, of which misoprostol is a stable, orally active, synthetic analogue. Serious adverse events reported following off-label use in pregnant women include maternal or foetal death, uterine hyperstimulation, rupture or perforation requiring uterine surgical repair, hysterectomy or salpingo-oophorectomy, amniotic fluid embolism, severe vaginal bleeding, retained placenta, shock, foetal bradycardia and pelvic pain.


Southern hemisphere influenza vaccine composition

World Health Organization — The composition for the southern hemisphere influenza season (2001) has been decided and communicated to vaccine manufacturers. It is recommended that the influenza vaccine will contain the following three components:

- An A/Moscow/10/99 (H3N2)-like virus (A/Panama/20007/99 is this kind of virus).
- An A/New Caledonia/20/99 (H1N1)-like virus.

WHO strongly recommends the use of vaccine as an effective preventive measure against this potentially fatal disease. About 50–80% of vaccine recipients will be protected against the disease when there is a good match between the vaccine and strains of circulating influenza virus. However, in those cases where the vaccine does not fully protect against influenza, severity of illness and frequency of complications are reduced.

Most populations have been previously exposed to influenza A(H3N2), influenza A(H1N1) and B viruses and are known to have some degree of residual immunity. One dose of influenza vaccine should therefore be sufficient for all ages except young children. Previously unimmunized children should receive two doses of vaccine at an interval of at least four weeks.

The specific vaccine viruses used in each country should be approved by the national control authorities who are responsible for making recommendations on their use.


Zafirlukast: labelling changes

With increased use over the past three years, additional events have been reported for zafirlukast (Accolate®), a leukotriene receptor antagonist indicated for the prophylaxis and chronic treatment of asthma in adults and children 7 years of age and older. As a result, the precautions and adverse reactions sections of the package insert have been updated.

Based on reports of liver dysfunction, more specific recommendations are made for patient management, as follows. Hepatic events have occurred predominantly in females.

- If liver dysfunction is suspected based upon clinical signs, zafirlukast should be discontinued.
- If liver function tests are consistent with hepatic dysfunction, zafirlukast therapy should not be resumed and patients should not be re-exposed if no other attributable cause is identified.

In addition to the above changes, the adverse reactions section now also includes the information
that reports have been received of patients experiencing arthralgia and myalgia in association with zafirlukast therapy.


**Thioridazine: major labelling modifications**

Important labelling changes have been made for all dosage forms of thioridazine hydrochloride (Mellaril®) by the manufacturer.

A boxed warning has been added to prominently advise clinicians that thioridazine has been shown to prolong the QTc interval in a dose-related manner and drugs with this potential have been associated with torsade de pointes-type arrhythmias and sudden death. Mesoridazine is the major active metabolite of thioridazine and appears to have the capacity to prolong the QTc interval.

Thioridazine hydrochloride is now indicated only for schizophrenic patients who fail to show an acceptable response to adequate courses of treatment with other antipsychotic drugs. It is contraindicated with certain other drugs, including fluvoxamine, propranolol, pindolol, any drug that inhibits P450 2D6 isozyme, e.g. fluoxetine and paroxetine, and agents known to prolong the QTc interval such as disopyramide, procainamide and quinidine. Thioridazine hydrochloride is also contraindicated in patients who have reduced levels of the P450 2D6 isozyme as well as in patients with congenital long QT syndrome or a history of cardiac arrhythmias.

Before being considered for treatment, patients should have a baseline electrocardiogram (ECG) performed and serum potassium levels measured. Periodic ECGs and serum potassium levels may be useful. Thioridazine should be discontinued in patients who are found to have a QTc interval over 500 m/sec.

Patients currently being treated with thioridazine hydrochloride should be fully informed of this information. Switching to a different antipsychotic agent should be considered and continuation of thioridazine hydrochloride treatments should be based on a careful assessment of the potential benefits and risks.


**Mesoridazine besylate: new warning**

The manufacturer of mesoridazine besylate (Serentil®) has advised doctors and pharmacists of important prescribing information changes to the 25 mg and 50 mg tablets. Mesoridazine besylate has been shown to prolong the QTc interval in a dose-related manner and drugs with this potential have been associated with torsade de pointes and sudden death. The following major modifications should be implemented immediately:

- Mesoridazine besylate is now indicated only for schizophrenic patients who fail to show an acceptable response to other antipsychotic drugs. Efficacy of mesoridazine besylate in treatment refractory schizophrenic patients is unknown.
- Mesoridazine besylate is contraindicated with other drugs known to prolong the QTc interval, in patients with congenital long QT syndrome or a history of cardiac arrhythmias.
- Patients considered for treatment with mesoridazine besylate should have a baseline ECG performed and serum potassium levels measured.
- Patients currently being treated with mesoridazine besylate should be fully informed of these information changes and switching to a different antipsychotic agent should be considered. Thioridazine, a metabolic precursor of mesoridazine also appears to have the capacity to prolong the QTc interval.


**Lopinavir and ritonavir for HIV infection**

United States of America — An accelerated approval has been issued for Kaletra®, a combination of the protease inhibitors lopinavir and ritonavir for HIV infection in adults and children over 6 months of age. Lopinavir's antiviral properties are combined with a low dose of ritonavir that inhibits
lopinavir's metabolism. This results in blood levels of lopinavir that enhance effectiveness.

Side effects associated with Kaletra® are diarrhoea, fatigue, headache, and nausea. It also produces increases in blood lipid levels which in some patients may be large enough to require treatment. Infrequent cases of pancreatitis have been observed among patients receiving antiretroviral regimens that included Kaletra® and, as observed with other protease inhibitors, may also be associated with adverse events including increase in blood glucose, redistribution of body fat, and potentially serious drug interactions.


Arsenic trioxide for leukaemia

United States of America — The Food and Drug Administration has approved arsenic trioxide (Trisenox®) for the treatment of patients with acute promyelocytic leukaemia who have not responded to first-line therapy with transretinoic acid and anthracycline-based chemotherapy.

Acute promyelocytic leukaemia is a cancer of the white blood cells characterized by a rapid accumulation of abnormal white blood cells in the bone marrow and blood resulting in anaemia, susceptibility to infections, bleeding and haemorrhage.

Arsenic-containing preparations have been in medical use for more than 2000 years and interest in arsenic-based therapy was revived by reports of anti-leukaemia activity of some traditional Chinese preparations.

Arsenic trioxide can cause an increase in the QT interval and lead to arrhythmia. Other adverse effects include abdominal discomfort, nausea, vomiting, headache, fatigue, skin changes, and fluid accumulation. These were considered mild and resolved after therapy was completed.


International plasma trafficking

World Health Organization — Several newspaper articles have reported on international trafficking of contaminated human plasma emanating from southern Africa.

The articles refer to investigations under way since 1996 when the Austrian authorities seized a consignment of illegally imported plasma. The trial of plasma brokers involved in this trafficking is due to take place soon in Austria. The Austrian health authorities as well as the Swiss authorities, who have been investigating the same issue, have confirmed that countries identified during the investigation as having received potentially dangerous blood products have been notified (1).

Exchange of information between national control authorities is essential. In line with Regulation and Licensing of Biological Products in Countries with Newly-developing Regulatory Authorities (2), the national control authority is able to request information on the quality of products from the authority in the exporting country.

References


Cardiac failure and pioglitazone hydrochloride

Japan — Pioglitazone hydrochloride (Actos®) was approved for marketing in 1999 for the treatment of diabetes and is considered to improve resistance to insulin. The Ministry of Health and Welfare in Japan has received five case reports of cardiac failure, four out of five serious, associated with the use of the drug, and instructed the manufacturer to revise the labelling and to issue a letter to health professionals to draw their attention to cardiac failure during treatment.

Case reports show that oedema and rapid weight gain — potentially due to plasma volume expansion — have occurred in patients during the use of pioglitazone and this has triggered cardiac failure.

As reflected in the revised labelling, pioglitazone is now contraindicated in patients with cardiac failure or a medical history of cardiac failure. Special attention should be paid to oedema and rapid weight gain during the treatment of patients and patients should consult their physician immediately in the event of any symptoms occurring.
New dosing for didanosine

The manufacturer of the nucleoside analogue reverse transcriptase inhibitor, didanosine (Videx®), has advised health care providers of a change in prescribing information. The results of a recent clinical trial have demonstrated that the treatment response rate of once-daily didanosine was significantly lower than in the comparator arm. Although once daily dosing is available, it should only be considered for adult patients whose management requires this administration.

It is therefore recommended that the more effective dosing frequency of didanosine is twice-daily.

Reference: Letter from Bristol-Myers Squibb Company, USA, dated 1 August 2000.

Alosetron: guide and labelling improve risk detection

United States of America — The Food and Drug Administration (FDA) has developed a Medication Guide for distribution by pharmacists to help ensure that patients using the prescription drug alosetron hydrochloride (Lotronex®) for treatment of the diarrhoea-predominant form of irritable bowel syndrome will understand the rare but serious risks and how they can take action. Risks include complications from constipation and the risk of ischemic colitis, caused by reduced blood flow to the intestines.

Irritable bowel syndrome is a functional abnormality of the gastrointestinal tract that is estimated to affect up to 15% of the US population. People with this condition experience chronic or recurrent abdominal pain and irregular bowel movements. This condition is two to three times more common in women than men.

Prescribing information has also been updated. This states that treatment should not be started when women are constipated and it informs prescribers that alosetron hydrochloride is now contraindicated in women with:

- A history of intestinal obstruction, stricture, toxic megacolon, gastrointestinal perforations, and/or adhesions or ischemic colitis;
- Active diverticulitis; or
- Current Crohn's Disease or ulcerative colitis, or a history of such a disease.


Meningitis C vaccines

United Kingdom — In November 1999, a mass national immunization campaign to vaccinate all children under 18 years of age with the new meningococcal group C conjugate vaccine commenced. Two vaccines were used (Meningotec® and Menjugate®). Before licensing, the vaccines were tested in approximately 8000 children and adolescents in the United Kingdom and over 20 000 children and adults in other countries. To date over 15 million doses have been distributed in the United Kingdom.

Recent press reports of death following Meningitis C vaccination are based on misinterpretation of data which have not been linked to fatal outcomes. By 1 June 2000 the Committee on Safety of Medicines had received 4764 reports of patients experiencing adverse reactions to the vaccine. This corresponds to a reporting rate of 1 per 2875 doses distributed. The adverse reactions reported most frequently include dizziness, pyrexia, headache, nausea, vomiting and fainting. Patients normally recover rapidly.

After reviewing the data, the Committee on Safety of Medicines has recommended that the following adverse reactions should be added to the product information: nausea, vomiting, rash, malaise, lymphadenopathy, headache, myalgia and allergic reactions, including anaphylactic reactions which were reported once in 500 000 doses distributed. The Committee considers that the risk/benefit ratio is overwhelmingly favourable and there is no suggestion that the vaccine has led to any deaths.

References

2. Message from the Chairman of the Committee on Safety of Medicines, 30 August 2000.
Mifepristone approval linked to stringent conditions

**United States of America** — The Food and Drug Administration has approved mifepristone (Mifeprix®) for the termination of early pregnancy, defined as 49 days or less from the beginning of the last menstrual period.

Under the approved treatment regimen, 600 mg of mifepristone is followed two days later with 400 micrograms of misoprostol, a prostaglandin. A follow-up visit should be scheduled 14 days after administration to determine whether pregnancy has been terminated.

A medication guide will be provided to each woman receiving mifepristone explaining how to take the drug, when to avoid taking it and possible side effects.

Mifepristone should not be used on women with the following conditions:

- Confirmed or suspected ectopic pregnancy.
- Intrauterine device (IUD) in place.
- Chronic failure of the adrenal glands.
- History of allergy to mifepristone, misoprostol or other prostaglandins.
- Bleeding disorders or current anticoagulant therapy.

Physicians allowed to administer mifepristone must be part of a national registry and must be qualified to perform surgical intervention in cases of incomplete abortion or severe bleeding, or they must have made plans in advance to provide such care through others.

Mifepristone was first approved for use in France in 1988. Since then 620 000 European women have taken mifepristone in combination with a prostaglandin to terminate pregnancy.


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Proposed withdrawal of enrofloxacin in poultry

**United States of America** — The Food and Drug Administration has proposed to withdraw use of the fluoroquinolone antimicrobial enrofloxacin for use in poultry on the grounds that it has not be shown to be safe. This action is put forward by the Center for Veterinary Medicine in consideration that:

- Use of fluoroquinolones in poultry causes the development of fluoroquinolone-resistant Campylobacter.
- Campylobacter is transferred to humans and is a significant cause of fluoroquinolone-resistant Campylobacter infections in humans; and
- Such infections are a hazard to human health.

Fluoroquinolones are considered to be one of the most valuable antimicrobial drug classes available for human infections because of their spectrum of activity, safety and ease of administration. They are used both in the treatment and prophylaxis of bacterial infections in hospitals and for the treatment of foodborne diseases.

Data from the National Antimicrobial Resistance Monitoring surveillance programme were used to determine that poultry carrying fluoroquinolone-resistant Campylobacter are the predominant source of campylobacteriosis in humans.

Fluoroquinolones have been available for human use since 1986, yet resistance did not increase among Campylobacter until 1997, soon after the approval and use of these drugs in poultry. Fluoroquinolone-resistant Campylobacter infections in humans had risen in the USA to 17.6% by 1999.

Consultative Document

Operational issues in the procurement of essential drugs and medical supplies

Medical supply is a complex and competitive area. A buyer is not only expected to obtain the right goods at the right price but to be aware of the many other key factors impacting on the procurement process. It is therefore important to acquire as much information as possible on basic requirements and to consider these in relation to other operational issues affecting the purchase of medical goods and pharmaceuticals. The following text has been prepared by Dr Bonface Fundafunda at ECHO International Health Services Limited in the United Kingdom and does not yet represent the views of WHO nor reflect current WHO terms and definitions. It sets out to provide an aide memoire of the procedures to be followed and standards which can be expected of suppliers of pharmaceuticals and medical devices.

The importance of procurement procedures

Procurement staff are typically given little training or technical support to help them evaluate the products they are buying or verify the sources of those products adequately. More often than not, the decision to buy is based on cost alone, with assumptions about quality necessarily being left to trust rather than evidence. Given the distances that separate most procurement activities from the end user of the products, feedback mechanisms are often unavailable when problems occur.

To be effective, any health care project will depend on a whole series of procedures concerned with planning, evaluation, management and implementation. Most health care providers place a great deal of emphasis on quality when considering their interventions yet they appear not to give the same degree of attention to their procedures when purchasing pharmaceuticals and medical supplies.

When considering the use of a medical supplier, buyers should always make sure that they are satisfied with the information being provided with the products including the measures being taken to ensure the quality of the products. A basic overview of the major issues is presented on the following pages and suggestions are made for some reasonable demands which can be made in order to confirm the quality and appropriateness of the medical products being purchased.

There are over 100,000 different pharmaceutical preparations available on the world market. Composition, presentation and quality control, as well as price, can vary enormously between manufacturers and countries, with implications for product performance, appropriateness and potential harm to human health. Even when regulations are in place to govern manufacturing practices and the manufacturing chain, there can be considerable differences in the application of such standards.

Terms and definitions

A number of regulations exist to ensure that products supplied are fit for intended use. The following terms are used in procurement practice.

**Brand-name product:** refers to a novel product with patent protection. Other terms commonly used are proprietary or ethical product.

**Generic product:** in pharmaceutical supply terms the word generic implies that the product is free of patent restrictions. The pharmaceutical manufacturer will use a generic or International Nonpropri-
One objective served by the essential drugs list is to ensure that planning and expenditure for pharmaceuticals is transparent. When purchasing products for use in a country, first ensure that the products are on the national essential drugs list. If the products are not listed, they may not be made available in the public sector.

**National regulatory requirements**

The following are some of the general regulations affecting pharmaceutical supply which will need to be addressed before undertaking pharmaceutical procurement.

**License to procure, hold and supply medicinal products:** This requirement applies to any institution outside a Ministry of Health structure. If you are a nongovernmental organization (NGO), a charity, or agency working in health care, you will need to apply for a licence to the authority responsible for drug regulation.

**License to import medicinal products:** Your organization will need to receive an import licence if it is supporting the health authority in health care provision. Therefore, before importing drugs, ensure that licenses have been granted.

**Responsible person:** In many cases, the regulatory authority will require that you have the necessary qualified staff and a health professional on your team who will serve as the responsible person for procurement, stock control, use and advice as well as the supervision and monitoring of medicinal product supply. Depending on the country regulations, this is normally a qualified and registered pharmacist. Alternatively, the authorities may appoint another health professional (e.g. pharmacy technician, nurse, doctor or medical assistant) to take on this role. The responsibility of this person is to ensure that all legal aspects of the practice, including procurement, storage, dispensing, use, professional advice to other health care staff and patients is not compromised.

**National drug formulary:** The national health authorities may have developed a guideline on recommended indications and therapeutic uses of the medicinal products listed according to its essential drugs list. One of the objectives served by the drug formulary is to provide common information for all health care providers in the country. When purchasing, it is preferable to buy products which are included in the formulary since treatment information will be readily available to prescribers.
**National product registration:** The national health authorities will maintain a register of all pharmaceutical products on the market in the approved dosage form in order to ensure safety, efficacy and quality.

The product licence holder is legally responsible for an application to register its products in a recipient country. The process of registration opens up that market to the product licence holder. Given the costs associated with this process, the product licence holder has to assess the viability of that market before proceeding to register itself and its products. This process can be done through a representative office (an agent) resident in the recipient country, or through another authorized body (such as a wholesaler or distributor). It is important to stress that wholesale distributors cannot register products unless they have authority from the product licence holder.

Always ensure that the products you are purchasing are registered in the recipient country.

**Manufacturer registration:** As a further step to ensure the control of pharmaceutical products in circulation, drug regulators also license manufacturers and providers of medicinal products. There are many pharmaceutical manufacturers making generic products. Given the highly competitive nature of the generic market, care should be taken that manufacturers have followed WHO guidelines for good manufacturing practice (GMP).

Manufacturers are inspected by national inspectors or inspectors approved by other internationally recognized bodies or accredited commercial firms. The main focus of inspection is to ensure that a manufacturer is producing pharmaceutical products manufactured to quality standards and in accordance with GMP. When purchasing, ensure that products are from manufacturers registered in the country and inspected to GMP standards.

**Secondary manufacture:** Business opportunities, economies of scale, and cutting operational costs are all elements and realities of business. The result of such strategies may be that some manufacturers subcontract or outsource production of registered products to another manufacturer (secondary manufacture). The secondary manufacturer may or may not be a marketing establishment or it may concentrate only on contract manufacture.

While national regulators want to know who is the actual manufacturer, it is important to note that it is not illegal for a primary manufacturer to have its products manufactured elsewhere. The primary manufacturer will have declared this part of the business under its Manufacturing Licence. However, it is the primary manufacturer’s responsibility to demonstrate that secondary manufacture is carried out under identical production conditions as at the primary manufacturing premises.

**Wholesaler registration:** As with manufacturers, wholesalers fall under the same degree of regulatory control to ensure that they abide by principles of good storage and distribution practice and follow requirements for the handling of pharmaceutical products. Since distribution involves less capital investment, it has attracted a large number of entrepreneurs who may not necessarily have sufficient knowledge or show enough responsibility towards the quality handling and safety of pharmaceutical products.

However, among these are the so-called ‘suitcase merchants’, who operate by seeking out those countries where regulation and enforcement is weak or nonexistent. They offer a source of cheap goods, but cannot guarantee the quality of supplies.

When buying from wholesalers, ensure that they are reliable, are known by the regulatory body, and that they can guarantee the required quality of products. Many international wholesalers conduct extensive evaluation and inspection of manufacturers, which reduces the need for inspection by the buyer. Request documentary evidence from the wholesaler which demonstrates inspection by a competent body. You may also request references from other sources such as bank institutions, the Chamber of Commerce, or fellow overseas buyers.

**Public tender:** Buyers announcing their requirements by public tender often attract suppliers who recognize that many buyers tend to focus on price alone rather than the quality of the product. One way of avoiding this problem is to develop long-term relationships with known wholesalers and manufacturers. By doing this, the buyer can also benefit from significant price discounts or price freezing, which may reduce the costs of annual tendering.

**National quality control laboratory:** Most countries will have an appointed institution such as a national quality control laboratory that is responsi-
ble for testing the claimed quality of the product. The role of this institution is to ensure that all pharmaceutical products for use in both the public and private sectors and in animal health care (veterinary products), as well as the agricultural sector (agrochemicals), are fit for intended use. All importers and suppliers of these products must be aware of the regulations and samples of product batches must be supplied for analysis.

**Inspection of manufacturers**: Most national health authorities require that the original source of medicinal products including drugs, chemicals, diagnostic agents and sterile disposable items is inspected before approval for use. The objective of these inspections is to ensure that the manufacturer abides by and complies with all licensing, GMP, quality control, and good distribution practices (GDP) requirements as stated in the business profile (drug master file). Further, these inspections aim to ensure that the products they intend to market conform to the stated standards. One of the key elements of inspection is the demonstration by the manufacturer that in-house or independent validation of all processes affecting the manufacture of their licensed products is conducted.

For a manufacturer, the main objective of an inspection is the demonstration of manufacturing legitimacy and ability to meet relevant national and/ or WHO GMP. The first step for the manufacturer, therefore, is to call for inspection of its premises, processes, procedures and management. The national regulatory authorities responsible for the quality of medicinal products for use in human and animal health conduct such GMP inspections.

Where the manufacturer seeks to market its products on the international market, it will call for inspection by an internationally recognized inspectorate. The results of these inspections are made available to authorities responsible for registering products from that source. The number of times an inspection is conducted will vary depending on national legal requirements, observations and recommendations from previous inspections, etc. Inspections tend to be performed once a year, or once every two years.

It is important to note that inspections can be very expensive and most countries, organizations and agencies cannot afford to conduct full inspections. However, these inspections are required to be performed routinely and a manufacturer must show that the product is inspected independently. Consequently, manufacturer evaluation may be performed at two levels. The first will ensure that the manufacturer can provide minimum requirements for manufacture and product quality assurance. Preliminary informed and professional judgement on whether or not to proceed in accepting that manufacturer can then be made. The second level is to institute independent inspection of the manufacturer either fully (total infrastructure inspection), or limited to processes leading to the manufacture and supply of the product of interest.

Inspection of manufacturers’ premises is a legal requirement, and not an imposition on the manufacturer and a buyer may request a copy of the inspection report. Additionally, a buyer may undertake an independent inspection at his own cost. Such reports tend to be the confidential and private property of the buyer and cannot be used by others without their permission. In view of the costs of these inspections, mutual recognition of inspections — whereby two or more purchasers perform one inspection — may be acceptable to the regulatory authorities.

A buyer should purchase from selected manufacturers that are inspected routinely by the national authority or, if you buy from a wholesaler, you must ensure that you provide the wholesaler with information on how products are regulated in the country of import.

**Checking quality**

With regard to quality assurance, all factors relating to the manufacture and supply of finished products should be in place and functioning according to required quality standards. Efforts should be made to ensure that products in the supply system are safe, and will not need to be replaced due to failure in quality.

**A. About the manufacturer**

**Good manufacturing practice (GMP) certificate**: Applies to manufacturers of all medicinal products (drugs and medical devices). This certificate ensures that products are consistently manufactured and controlled to quality standards necessary for intended use, and as established by the ‘country of origin’ regulatory authority. The certificate is issued following inspection of the premises, manufacturing equipment, personnel, product and marketing documentation, in-house quality control, in-house process validation, etc. and is valid for a certain period of time. Its usefulness in assessing quality is
debatable, largely due to the differing rigour with which assessments are carried out in different countries. None the less, lack of a GMP certificate from a manufacturer should be a cause for concern.

ISO Standards: These are standards of general quality assurance issued by the International Organization for Standardization (ISO), a nongovernmental organization. The standards are not official standards and may be seen as voluntary, unless a government adopts them as part of regulatory legislation. ISO standards apply to manufacturing systems, or the creation and provision of a service, with a view to assuring customer satisfaction.

The following is information relating to the supply of pharmaceutical products that must be requested from the manufacturer or the wholesaler:

Country of origin: Regulatory authorities in the end-user’s country may have a list of countries (as well as of manufacturers) whose regulatory and licensing procedures are not approved because the quality and safety of the products cannot be guaranteed. Products from these countries will not be authorized for importation.

Manufacturer’s name: Information will need to be provided on whether the name of the manufacturer appearing on the product is that of the actual manufacturer, whether the product is made by a subcontractor, and what the implications for product quality, safety and efficacy are.

Current manufacturing licence: Shows that the manufacturer is legally licensed to produce the listed pharmaceutical products.

Good distribution practice (GDP) certificate: This measure ensures that the quality of products is maintained during internal and external transport and distribution of goods.

Certificate of a pharmaceutical product (CPP): This certificate is part of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce. The regulatory authority in the country of manufacture (exporting country) issues this certificate to the regulatory authority of the importing country. The certificate contains all the relevant information on a stated product (its manufacture, quality, etc.) that would be required by regulatory authorities in the importing country. A CPP can contain a list of products to be supplied with individual information for each product.

A CPP relating to one product cannot be taken as acceptable evidence of licensing for another product not mentioned in the document. As well as indicating that a manufacturer has been licensed to produce a particular pharmaceutical substance, the CPP also states whether the product is for export only, or if it is authorized for use in the country of manufacture (issuing country). Finally, it gives an indication of whether the manufacturer is routinely inspected by the relevant authority.

Free sale certificate: The regulatory authorities may wish to know whether the products being offered for sale by the manufacturer or wholesaler are in fact registered for use in the country of manufacture. This certificate is supported by a product licence (PL) issued by regulatory authorities in the manufacturing country; the PL is issued for the purpose of marketing and free distribution. However, the WHO certificate of a pharmaceutical product (CPP) is increasingly supersedes this document, since many manufacturers tend to produce for export.

Certificate of analysis (COA): This document applies to a specific batch of product being offered for sale. It shows whether the product in question has been manufactured according to a stated international standard by comparing actual chemical analysis of a sample from the batch in question with the minimum requirements set out by the standard chosen. A buyer will generally look for equivalence of British Pharmacopoeia (BP), European Pharmacopoeia (EP) or US Pharmacopeia (USP) standards.

It should be noted that in the absence of other supporting evidence these documents alone do not constitute guarantees of product quality. However, the inability of a manufacturer or supplier to provide such basic information should alert you as a buyer.

B. About the wholesaler

While manufacturers will supply directly to the larger customers, such as a government central medical stores, they tend not to supply to low value buyers.

The wholesaler is not a manufacturer, but offers the flexibility to deal with a large number of customers, and has the expertise to source from a wide geographical area and offer goods at affordable cost. Due to low overheads, the wholesaler is also able to entertain a variation in order sizes, unlike a manufacturer. And this is the advantage wholesalers offer.
As a buyer, you may request the wholesaler to provide any information normally available from a manufacturer. In addition, a Letter of authorization to supply can be requested which ensures that the wholesaler is legitimately offering products which he has the authority to sell.

C. About the agent or representative
Many manufacturers and some wholesalers will not have offices in the recipient country for business reasons. In order to effectively market their goods, they normally appoint an agent or representative to look after their business interests. Increasingly, one finds that there is a regulatory obligation for an overseas supplier (manufacturer or wholesaler) to have such representation in the recipient country. The advantage is that the regulatory authorities and potential clients have someone to whom they can address their concerns and needs. If such an agent is not exclusively representing one supplier, he or she may be a source of valuable product-related information (e.g., cost, alternatives, product literature, research papers, brochure, etc.). There are disadvantages, however. For example, the cost of the goods procured through the agent will include commission. Further, and more worrying, in places where laws and regulations affecting the supply of medicinal products are weak, one finds that anyone with capital can work as an agent. In this case, professionalism or a concern for safety and quality of the product may be lacking.

D. About the product
Original manufacturer: As mentioned above, it may be important to know who is the original manufacturer of the product. Many manufacturers are now able to subcontract production of licensed products to other local or international manufacturers. This is acceptable practice which is necessary for economies of scale to be achieved in production. In this case, the original manufacturer is considered to be the contractor. However, the subcontractor’s identity must appear on the documents relating to the product. Further, the subcontractor must be inspected with the same rigour as for the contractor.

Manufacturing date: This date must appear on the label and all documents relating to the product.

Expected shelf life upon sight or receipt by the buyer: You may set a standard requirement that all pharmaceutical and other date-related products such as consumable items and sterile items must have a minimum life span once opened. In some cases, the national regulatory authority will have set this limit, which you must follow.

The supplier must state these dates, or state that they will supply goods according to your requirements, demonstrating that you will receive products that meet the shelf life requirements. Note that this becomes a contractual obligation on the part of the supplier.

Label requirements: Clear, informative labels on medical products are part of regulatory requirements. Pharmaceutical product labels should state:

• The International Nonproprietary Name (INN) or generic name of the active ingredients and formulation in addition to the brand-name.
• Pharmacopoeial standard of the formulation (e.g. BP/EP/USP).
• Dosage form (e.g. tablets, capsules, syrup, injection).
• Quantity of active ingredient(s) in the dosage form.
• Appropriate cautionary advice (use, warnings and precautions),
• Number of units per package.
• Batch number.
• Date of manufacture.
• Expiry date of the product.
• Storage or handling instructions.
• Manufacturer’s name and contact details.

If the product carries the wholesaler’s logo, the label must also contain the manufacturers name and all other details listed above.

Quality of packaging (both inner and outer): Packaging is also an important issue, particularly as it can have a substantial impact on damage in transit/storage and on potential degeneration of products. Do not be afraid to ask your supplier what kind of packaging you can expect to receive as part of the price. Inadequate packaging can cause very significant hidden costs to purchasers.
E. Heat-sensitive products

Cold storage items refer to those medical products that are heat sensitive; that is, their efficacy is dependent on the surrounding temperature. Effectiveness may be reduced by a decrease or increase in the surrounding temperature. It is important to note that most terms apply to temperate climates and in many cases may not apply to the tropics or other climatic zones.

Generally speaking, substances that appear in the pharmacopoeias are formulated to be stable at a specific temperature, or within a range of temperatures. One of the tests performed to this end is the accelerated stability test, where a batch undergoes a series of temperatures for a defined period of time, to assess product viability and therefore effectiveness. Depending on the product, temperatures may range from freezing to simulated temperatures found in extreme conditions. The marketing licence will be related to these and other factors.

If a product is reformulated to be stable at non-standard temperatures, it ceases to be a standard product (i.e., it cannot be referred to BP or USP). Be aware that products developed to be stable at temperatures prevailing in tropical areas will need a new monograph and may require specific stability, safety and bioequivalence tests and further clinical trials. This is a very expensive process.

Store frozen: This refers to some products such as vaccines which need to be transported within a cold chain and stored at -20 °C.

Store at 2-8 °C: This is for very heat sensitive products. Products must not be frozen. Traditionally they are kept in the first and second part of the refrigerator (never the freezer compartment).

Keep cool: This will mean storage between 8-15 °C. Traditionally, the bottom part of a refrigerator.

Store at room temperature: This is generally assumed to mean storage at 15-25 °C.

Store at ambient temperature: This means storage at the surrounding temperature. Not a widely used term, due to significant variation in ambient temperatures. It must be assumed to mean ‘room temperature’ as above.

Storage: This means keeping in one place, and can be short-term (such as the period of waiting to be sent to consumer), medium-term (as when waiting at freight forwarders) or long-term (long term storage at the consumer’s premises).

Storage temperature: Advice from the manufacturer applies to long-term storage at the supplier’s premises, at the freight forwarder’s premises and at the consumer’s premises. The supplier will hold such items in stock at the specified temperature. The freight forwarder is expected to keep the item at this specified temperature if the length of time it will take to actually ship the item is longer than the recommended period.

Transit: refers to the period in which a product is being shipped from one place to another.

Transit time: This is the time a product is in the state of moving from one point of storage (for example, the wholesaler’s warehouse or the freight forwarder’s warehouse) to another point, the latter being a point of medium- to long-term storage. Manufacturers will recommend a time-scale in which a ‘keep cool’ item can remain outside its storage temperature.

Transit temperature: Where a product requires shipment at a specific storage temperature, the manufacturer will recommended the appropriate temperature.

F. Medical equipment and medical devices

This is one of the rather complex areas of procurement and supply. There is no essential list of commonly used medical equipment and devices. While it may be considered ‘generic’ to use the description ‘X-ray machine’ or ‘ultrasound machine’, this does not suggest that these machines are available in generic form. They remain heavily patent bound and available to buyers in brand form. This situation applies equally to surgical instruments which tend to be known by a combination of the descriptive and name function e.g. Lange Hohmann elevator, for reducing fractures; Kocher intestinal clamp, for occlusion of a section of intestine, rather than some generic functional name. This also applies most famously to suturing materials, where the manufacturer and brand name Ethicon is accepted as an alternative name for ‘suture’. Users of equipment tend to be the ones who decide on the machine to buy for their facility or practice.
As users change, new staff will also request the purchase of different machines or products, reflecting their own experiences of those machines, and not other makes. Consequently, there is no universally agreed minimum requirement with respect to specifications or quality. The cost of procuring new and discarding other makes of machines can account for a great proportion of public health expenditure. There is therefore a serious need to standardize equipment at all levels of health care services. This not only saves money, but it also helps in training. It is advisable to use a source with an appropriate level of technical knowledge of the products, who can advise and give support where necessary.

Owing to the absence of clear guidelines, variations exist in the quality and specifications of products available in the market place. When it comes to larger capital items, either new or reconditioned, issues such as reliability, technological appropriateness, mains supply (voltage and frequency), warranties, spare parts/technical support and consistency with what is already available in a country are all factors which should be borne in mind.

Ready-made kits: In certain situations, particularly in the initial response phase of a rapid onset emergency or when building up a specialty or primary facility from scratch, ready-made kits offered by a number of suppliers can sometimes be a very practical way forward. However, buyers should be aware that even where kit contents are supposedly standardized, such as with the WHO New Emergency Health Kit 1998, variations in product quality and specifications between suppliers could be enormous. Quality assurance considerations which are applicable to pharmaceuticals, consumables and equipment generally should also be applied to the individual components within a ready-made kit.

G. Samples
Health authorities may advise that samples of medicinal or consumable products, or certain medical devices should be supplied to the appropriate regulatory authority. The regulatory body will impose requirements for samples needed in quality control testing or for the retention of a reference sample.

The requirement for samples applies mainly to pharmaceuticals and sterile consumable products. Rarely would the authorities require samples of expensive capital equipment, such as X-ray machines, preferring to inspect the products at the point of manufacture or wholesale. Ensure familiarity with any requirements and request the supplier to provide samples whenever possible.

Sample invoice: The supplier will raise an invoice of all required samples for the attention of customs. The invoice must show that the goods are for sample purposes only, and that they are free-of-charge to the customer, and have no commercial value. There should be no requirement to pay duty on samples. However, this should be verified through the customs office.

Terms and definitions for medical equipment

Capital Equipment: This term is used loosely to describe whatever medical equipment has required considerable capital to finance its procurement. For example, a self-financing primary health care centre may describe forceps as capital equipment, whereas a referral hospital may not. Therefore, it depends on the buyer to define what is meant by 'capital equipment'.

Consumable Products: This term refers to non-medical products. These products are 'consumed' and require regular replacement. This term can apply to disposable sterile items such as syringes, needles, cannulae, etc.

ISO Standards: These are standards of general quality assurance issued by the International Organization for Standardization (ISO), a non-governmental organization. The standards are not official standards and may be seen as voluntary, unless a government adopts them as part of regulatory legislation. ISO standards apply to manufacturing systems, or the creation and provision of a service, with a view to assuring customer satisfaction.

ISO 9000 to 9004: refer to Quality Management and Quality Systems. In this group, other related ISOs are 8402 and 1013. These standards recommend modern approaches to management and how to assure general product quality. They therefore cover issues such as quality policy, manufacturing process, design and development, construction, installation and services.

European Norms (EN): These are standards similar to ISOs set by the European Union. For example, EN 29000 is identical to ISO 9000; EN 45001 is similar to ISO 9001.
The European Committee for Standardization (CEN): The CE symbol (which is the CEN’s seal of approval) indicates that the products are manufactured in accordance with ISO 9001 and EN 46001. This specifically applies to medical devices and surgical products for use within the EU.

In the same way that the manufacture of pharmaceutical products is subcontracted, a number of manufacturers of medical devices and surgical products (cannulae, catheters, etc) based in the EU subcontract the manufacture of these products outside the EU (either through pure subcontracting, or through joint venture agreements). In this event, the subcontracted party must meet the same rigour of quality assurance as expected of an EU-based manufacturer.

While many buyers use the CE symbol as the highest indicator of quality, they miss out on a number of excellent and good quality products produced specifically for non-European markets by manufacturers outside the EU.

Electrical Safety: With electrical equipment, it is worth asking what safety and performance standards the item you are buying meets. This information will tend to appear on technical specification sheets and in operation and service manuals, but if in doubt, ask the supplier to clarify. The main accepted international standards for both electrical safety and performance are those set by the IEC (International Electrotechnical Commission) in Geneva.

Uninterruptible Power Supply (UPS): When ordering electrical equipment, you should not forget the importance of obtaining a stabilizer or UPS as appropriate, to protect electrical equipment from possible damage due to uncontrolled fluctuations in electrical supply.

When looking at complex or expensive capital equipment, it is prudent to stick to well-known and reputable manufacturers. Check which ones can offer technical support in the region where the equipment will be in operation. It is wise to buy from suppliers who have both the technical capacity and the ability to support you with accessories, spare parts, advice, technical backup and support as well as in troubleshooting, maintenance, servicing and repair.

Responsibilities of the parties

The following categories of responsibilities are important with respect to claims being made if goods are damaged during storage at any one point or during transit. The point handling cold storage items would be liable in the event the goods were damaged due to being kept at the wrong temperature, or under wrong storage conditions.

The supplier

The supplier is expected to:

- Ensure that appropriate storage facilities for heat-sensitive products are available and in working order;
- Store the products at the recommended temperature;
- Ship the goods at the recommended temperature (documentation and information on packs to follow); and
- Inform the freight forwarder and the customer about the storage and transit requirements and recommendation for heat-sensitive products being shipped as set out in the shipping documents.

Freight forwarder

- Ensures that appropriate storage facilities for heat-sensitive products are provided;
- Refers to shipping documents for information on heat-sensitive products;
- Stores the goods at the recommended storage temperature, as advised on documents and on packs;
- Ships the goods at the recommended temperature; and
- Ensures that the delivery period will be within the recommended transit time and temperature requirements will be respected.

Freighter or carrier

- Ensures that appropriate storage facilities for heat-sensitive products are available at their premises;
- Ensures that they have appropriate storage facilities for heat-sensitive products on board the chosen vessel or aircraft;
• Refers to shipping documents for information on heat-sensitive products; and

• Ensures that the delivery period will be according to the recommended transit time and temperature.

**Customs**

• Will ensure that they have appropriate storage facilities for heat-sensitive products;

• Will refer to shipping documents for information on heat-sensitive products;

• Will receive heat-sensitive goods upon arrival;

• Will store heat-sensitive goods at recommended temperature as advised by the supplier (shipping documents); and

• Will inform the end-user of the arrival and storage of heat-sensitive products at customs.

**Customer (end-user)**

• Ensures that appropriate cold storage facilities are available;

Depending on the freight contract:

• Refers to shipping documents for information on heat-sensitive products;

• Clears through customs all heat-sensitive products upon arrival in a timely manner;

• Stores heat-sensitive products at recommended temperature.

**Freight: shipping goods and the risks involved**

Shipping of goods is a cost to be considered as part of the overall price. A variety of freight contracts are available to both the buyer and seller when shipping goods. Knowing the types of contracts available enables an informed choice in freighting of goods. Knowing and selecting the appropriate contract may often reduce the cost of procurement.

The method or mode selected to ship goods to the end-user or buyer’s destination must be seen as a contract to supply. This is the second part of the procurement exercise, the first being the actual placing of the order for the goods. Various freight contracts are available, based on the International Chamber of Commerce terms: the current edition being INCOTERM 2000. These terms have historically applied to shipping of goods by sea and carriage by road. However, they now apply to air; where a shipper or carrier is used, terms will apply to both ‘ship for sea freight’ and ‘airfreight’ carrier.

It is important to note that INCOTERMS are voluntary and provide importers and exporters with guidelines on the responsibilities to be borne by the parties. Being terms that are reviewed annually, it is important to keep and refer to current terms in use.

**Costs**

It is important to define the term ‘Free’ as set out in some of the contracts. This does not mean that the buyer is exempt from paying for the service. As with all other freight contracts, the cost of shipping is to be borne by the buyer. In this event, it may be prudent to request the separation of freight and insurance charges from the cost of goods.

**Risks of loss or damage to goods**

A number of freight contracts require that insurance is taken out against loss or damage of goods. In these contracts, the risk and the cost of covering such a risk is borne either by the seller (in the event the buyer has not requested insurance) or by the buyer. Risk is, however, passed on from seller to buyer once the goods become the responsibility of the buyer.

**Terms and definitions**

The following are the most common freight contract terms:

**Ex Works (at sellers’ premises):** The seller’s only obligation is to provide goods at his premises for collection by the buyer. It is the buyer’s responsibility and obligation to load the goods and transport them to the buyer’s destination.

**FCA (Free Carrier to a named port of carriage):** The seller’s obligation is to deliver goods into the hands of the first or only carrier, present at a named port of carriage (seaport or airport). The buyer’s responsibility is to pay for the onward shipment of goods to the destination.

**FAS (free alongside ship):** The seller’s obligation is to ensure that the goods are placed alongside the ship, on the loading platform (or quay). The seller will be charged up to this point and it is for the buyer to pay for the loading and onward shipping. This generally applies to sea freight.

**FOB (free on board the carrier at a named port of shipment):** The seller is responsible for placing...
the goods on board the first ship or carrier at a stated port of shipment. Once the goods pass the rails of the ship and are on the ship’s platform, the risks and responsibility pass onto the buyer, and so does the cost of onward shipping.

CFR (cost and freight to a named port of destination): The seller covers all cost for freight of goods to a named destination port. Once the goods leave the ship, the risk and other costs become the responsibility of the buyer.

CIF (cost, insurance and freight to a named port of destination): As above, but the seller also pays for the insurance on behalf of the buyer against loss or damage to goods. This cost is passed onto the buyer. Where insurance is not included, the seller may take out additional insurance cover for loss or damage to goods.

CPT (carriage paid to a named place of destination): The sellers’ responsibility is to pay for freight of goods to the destination, loading onto the first carrier at the destination port. Costs of using subsequent carriers will be borne by the buyer.

CIP (carriage, insurance paid to a named place of destination): As under CPT, but that the seller has insured against loss or damage to goods during transportation to the first carrier.

DAF (delivered at frontier of a named port of entry): The seller’s obligation (cost and risk) terminate once the goods arrive at the port of entry of a named country, and the export clearance has been granted. The buyer is obliged to pay for customs clearance and onward transportation in the country.

DES (delivered ex-ship, at port of destination): This means that the seller will bear the cost of shipping the goods up to the docking of the ship at the port of destination, making the goods available to the buyer. It is then the buyer’s responsibility for customs clearance and unloading the goods, and for onward carriage.

DEQ (delivered ex-quay at port of destination): The seller is obliged to present the goods to the buyer at the quay or wharf at the destination port. That is, the seller pays for unloading of goods off the ship and onto the quayside, bearing all risks. The buyer is responsible for customs clearance. DEQ is further subdivided into:

- Ex-quay duty paid: where the seller pays customs duty; or
- Ex-quay duty on buyer’s account: where the duty is paid by the seller, but is then reimbursed by the buyer.

DDU (delivered duty unpaid to named port of destination): The seller covers all costs and risks for taking the goods to the port of destination, the goods remaining uncleared, import arrangements to be administered by the buyer. The seller is not responsible for duty or taxation.

DDP (delivered duty paid to named place of destination): This is where the seller delivers the goods to the buyers’ door, meeting all costs and risks incurred, including duties. Of course, this contract may be negotiated to exempt the seller from paying local value added tax (VAT) and taxes. Where one has no experience in freighting goods, it is best to contract an established freight forwarder who can act on your behalf and make these arrangements for you (at a fee). Using established freight forwarders can result in great savings in costs, as they have access to price cuts that may not be available to the small or inexperienced buyer.

Taxes and duties

Value added tax (VAT): An added cost to the procurement of medical products is VAT or value-added tax, collected by the government. It is a percent charge of the value of the goods being sold. This VAT affects those buyers based in the country of the seller (manufacturer or wholesaler). Many organizations based in Europe, purchasing medical products in Europe for use overseas, are charged VAT. They can claim this fee back from customs at the time of export of goods. A quality supplier will provide you with all documents relating to reclaiming VAT. However, an organization can be VAT-exempt (i.e., it has this notification), and may not be charged this tax if the goods procured are for charitable work in-country, or for use overseas.

Many charitable and nongovernmental organizations providing health care services in developing countries qualify for VAT-exemption. A buyer should be aware of the VAT status. If this status is unknown, VAT may be charged by the seller, thus increasing costs unnecessarily.
Customs duty: A duty is charged on all types of goods exported and imported. The organization exporting goods to its projects overseas will have to pay duty at the time of export, and duty in the country of import. In some cases, an organization offering charitable or free-of-charge health care services, may be exempt from paying these duties. However, this is an exception rather than the rule.

As a buyer, you need to be familiar with the duties to be paid. Do find out if you are exempt from paying duties in the recipient country. In some cases, religious organizations offering health care are also exempt from duties and VAT.

Conclusion

Many quality assurance processes are involved before medical products are finally delivered to the end-user. Procurement is a complex system, which does not end at the point of needs assessment and placing an order. Awareness of various aspects of procurement, such as product quality, country regulations, etc., is crucial to carrying out the task successfully.

The same need to be knowledgeable applies to manufacturers and more so to wholesalers. Medical suppliers nowadays come in a variety of shapes and sizes, and with varying levels of expertise, understanding and quality assurance capability. A supplier’s competence in terms of understanding and quality assurance of the products which are offered should always be questioned rather than assumed. A competent and professional supplier will be able to give you details not only of their own quality controls on the products that they sell, but also provide you with basic documentary evidence from the manufacturer confirming that they are authorized, competent and manufacturing to certain specifications. A supplier unable to provide this basic evidence is not fulfilling a crucial element of their responsibility which is the consistent and reliable supply of quality products.

Knowledge of related policy issues is important, as economic and political matters become increasingly intertwined in health care provision. Information is needed in order to understand the issues. While arguments persist about the role of industry in public health care, it is important to understand the background to these discussions.

Further reading and sources of information:

4. World Health Organization. Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce. WHO/P HARM 82.4 Rev.5.
10. IFPMA Code of Pharmaceutical Marketing Practices and International Conference of Harmonisation (ICH). International Federation of Pharmaceutical Manufacturers Associations (IFPMA), 1211 Geneva 18, Switzerland. Tel: +41 (22) 340 12 00 Fax +41 (22) 340 13 80 at: admin@ifpma.org or: www.ifpma.org
11. CEN Management Centre, 36 rue de Stassart, B-1050 Brussels, Tel: +32 2 550 08 19; Fax: +32 2 550 08 11; at: infodesk@cenorm.be or: www.cenorm.be.
12. The American Society for Quality, 611 East Wisconsin Avenue, P. O. Box 3005, Milwaukee, WI 53201-3005 www.asq.org
13. ECHO International Health Services Limited, Ullswater Crescent, Coulsdon, Surrey, CR5 2HR, UK. Tel: +44 (0)20 8660 2220; Fax: +44 (0)20 8668 0751; at: cs@echohealth.org.uk or: www.echohealth.org.uk.


Recent Publications and Sources of Information

**NIH guidelines for stem cell research**

The US National Institutes of Health (NIH) has published its Guidelines for Research Involving Human Pluripotent Stem Cells. The Guidelines describe the documentation and assurances that must accompany requests for NIH funding for research using human pluripotent stem cells from human embryos or fetal tissue. They state specific criteria for informed consent and establish a review group to decide on compliance with the guidelines, thereby ensuring that NIH-funded research is conducted in an ethical and legal manner. Only cells derived from frozen embryos that were created for the purposes of fertility treatment and were in excess of clinical need may be utilized. The Guidelines prohibit the use of inducements for donation of an embryo. The Guidelines set out those areas where NIH will not provide funding, including research which creates or contributes to a human embryo, utilizes human pluripotent stem cells derived using somatic cell nuclear transfer, or those combined with an animal embryo.

Human pluripotent stem cells can give rise to many different types of cells, such as muscle, nerve, heart and blood cells. Research in this area could help scientists to generate cells and tissue for use in transplantation to treat many diseases or to improve understanding of the complex events that occur during normal human development and what causes diseases and conditions such as birth defects and cancer.


**Opioid control policy: self assessment guidelines**

The purpose of these self-assessment guidelines is to encourage governments to achieve better pain management of cancer patients by identifying and overcoming regulatory barriers to opioid availability. The guidelines are intended for those who decide national drug control policy and those who implement it. Balance is needed to prevent illegal trafficking and diversion of opioids, while ensuring availability for medical and scientific purposes.

Information is provided on the global problem of inadequate cancer pain relief and why opioids are needed. There are three barriers to adequate pain management: economic, medical and regulatory. While the Guidelines focus solely on regulatory issues, it is well understood that other barriers play major roles, such as the inappropriate prescribing of expensive medication which is ineffective in late-stage cancer.


**Australian therapeutic guidelines on antimicrobials**

The Eleventh edition of Therapeutic Guidelines: Antibiotics has now been published. The guidelines are endorsed by the Royal Australian College of General Practitioners and the National Prescribing Service. They cover principles of antimicrobial use and contain in-depth information on infections and diseases and the way they should be treated. Adverse reactions, interactions and the dangers of resistance are set out in the appendices.

Therapeutic Guidelines: Antibiotics. Available from: Therapeutic Guidelines Ltd., Melbourne, Australia by e-mail: sales@tg.com.au or on http://www.tg.com.au

**Reliable quality information and the Internet**

Guidelines for medical and health information sites on the Internet have been published by the American Medical Association (AMA). Access to medical information through the Internet has the potential to...
speed the transformation of the patient-physician relationship from that of a physician providing advice and treatment to that of shared decision making between patient and physician.

Barriers to the provision of independent information through the Internet include wide variations in quality of information, commercial interests which influence Web site content, and uncertain preservation of personal privacy. For example, insurers or employers could monitor what diseases Web users research.

To address these issues, the AMA has developed principles to guide development and posting of Internet content, govern acquisition of information and posting of online advertising and sponsorship, ensure site visitor and patient rights to privacy and confidentiality and provide effective and secure means of e-commerce. Although developed for the AMA Web sites, these principles may also be useful to other providers and users of medical information on the Internet.


Standards for Internet pharmacies

The Council of the Royal Pharmaceutical Society in the United Kingdom has published standards of good professional practice for those who wish to provide pharmaceutical services via the Internet. For some time the Council has been aware of the development of on-line pharmacy services and has been working to identify the specific issues such developments raise. The standards will be updated as required.

The standards deal with protection of the confidentiality and integrity of patient information and require that all information must be encrypted and comply with National Health Service security standards. Pharmacists providing on-line pharmacy services must advise patients to seek consultation whenever this is judged necessary. A questionnaire appropriate to the product must be completed and advice offered on all purchases. All information provided must comply with the marketing authorization, patient advertising leaflet and advertising regulations. A record should be kept of any recommendations made, and the pharmacy must retain records for two years of all purchasers and the medicines sold.

Available from: Royal Pharmaceutical Society, 1 Lambeth High Street, London SE1 7J N, United Kingdom
International Nonproprietary Names for Pharmaceutical Substances (INN)

RECOMMENDED International Nonproprietary Names (Rec. INN): List 44

Notice is hereby given that, in accordance with paragraph 7 of the Procedure for the Selection of Recommended International Nonproprietary Names for Pharmaceutical Substances [Off. Rec. Wld Health Org., 1955, 60, 3 (Resolution EB15.R7); 1969, 173, 10 (Resolution EB43.R9)], the following names are selected as Recommended International Nonproprietary Names. The inclusion of a name in the lists of Recommended International Nonproprietary Names does not imply any recommendation of the use of the substance in medicine or pharmacy. Lists of Proposed (1–73) and Recommended (1–35) International Nonproprietary Names can be found in Cumulative List No. 9, 1996.

Dénominations communes internationales des Substances pharmaceutiques (DCI)

Dénominations communes internationales RECOMMANDÉES (DCI Rec): Liste 44


Denominaciones Comunes Internacionales para las Sustancias Farmacéuticas (DCI)

Denominaciones Comunes Internacionales RECOMENDADAS (DCI Rec.): Lista 44

De conformidad con lo que dispone el párrafo 7 del Procedimiento de Selección de Denominaciones Comunes Internacionales Recomendadas para las Sustancias Farmacéuticas [Act. Of. Mund. Salud, 1955, 60, 3 (Resolución EB15.R7); 1969, 173, 10 (Resolución EB43.R9)], se comunica por el presente anuncio que las denominaciones que a continuación se expresan han sido seleccionadas como Denominaciones Comunes Internacionales Recomendadas. La inclusión de una denominación en las listas de las Denominaciones Comunes Recomendadas no supone recomendación alguna en favor del empleo de la sustancia respectiva en medicina o en farmacia. Las listas de Denominaciones Comunes Internacionales Propuestas (1–73) y Recomendadas (1–35) se encuentran reunidas en Cumulative List No. 9, 1996.
<table>
<thead>
<tr>
<th>Proposed INN (Latin, English, French, Spanish)</th>
<th>Chemical name or description: Action and use: Molecular formula</th>
<th>Chemical Abstracts Service (CAS) registry number: Graphic formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>DCI Proposée</td>
<td>Nom chimique ou description: Propriétés et indications: Formule brute Numéro dans le registre du CAS: Formule développée</td>
<td></td>
</tr>
<tr>
<td>DCI Propuesta</td>
<td>Nombre químico o descripción: Acción y uso: Fórmula empírica Número de registro del CAS: Fórmula desarrollada</td>
<td></td>
</tr>
<tr>
<td><strong>adalimumabum</strong></td>
<td>immunoglobulin G 1 (human monoclonal D2E7 heavy chain anti-human tumor necrosis factor), disulfide with human monoclonal D2E7k-chain, dimer</td>
<td></td>
</tr>
<tr>
<td><strong>adalimumab</strong></td>
<td>immunoglobuline G1, anti-(facteur a de nécrose tumorale humain) (chaîne lourde de l’anticorps monoclonal humain D2E7), dimère du disulfure avec la chaîne κ de l’anticorps monoclonal humain D2E7</td>
<td></td>
</tr>
<tr>
<td><strong>adalimumab</strong></td>
<td>inmunoglobulina G1 (anti-factor α de necrosis tumoral humano), dimero del disulfuro de la cadena pesada D2E7 monoclonal humana con la cadena κ D2E7 monoclonal humana</td>
<td></td>
</tr>
<tr>
<td><strong>adrogolidum</strong></td>
<td>(5aR,11bS)-4,5,5a,6,7,11b-hexahydro-2-propylbenzo[f]thieno[2,3-c]quinoline-9,10-diol diacetate (ester)</td>
<td></td>
</tr>
<tr>
<td><strong>adrogolide</strong></td>
<td>diacétate de (5aR,11bS)-2-propyl-4,5,5a,6,7,11b-hexahydrobenzo[f]thieno= [2,3-c]quinoléine-9,10-diyle</td>
<td></td>
</tr>
<tr>
<td><strong>adrogolida</strong></td>
<td>diacetato (éster)de (5aR,11bS)-4,5,5a,6,7,11b-hexahidro-2-propilbenzo= [f]thieno[2,3-c]quinolina-9,10-dilo</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C_{22}H_{25}NO_{4}S</td>
<td></td>
</tr>
<tr>
<td><strong>alemcinalum</strong></td>
<td>8,9-didehydro-N-demethyl-9-deoxo-4&quot;--6,12-trideoxy-6,9-epoxy-N-ethylerythromycin</td>
<td></td>
</tr>
<tr>
<td><strong>alemcinal</strong></td>
<td>(2R,3S,4R,5R,8R,9S,10S,11R,12R)-5-éthyl-11-[(3-(éthylméthylamino)-3,4,6-tridésoxy--β--xýlo-hexopyranosyloxy)--3-hydroxy-2,4,8,10,12,14-hexaméthyl-9-[(3-C-méthy-3-O-méthyl-2,4,6-tridésoxy--L--erythro-hexopyranosyloxy)oxy]-6,15-dioxabicyclo[10.2.1]pentadec-1(14)-én-7-one</td>
<td></td>
</tr>
</tbody>
</table>
alemcinal 8,9-dideshidro-N-desmetil-9-desoxo-4",6,12-tridesoxi-6,9-epoxi-N-etilertromicina

\[ C_{38}H_{67}NO_{10} \]

altiniclinum
altinicline (-)-5-ethynlincotine
altinicline (-)-3-éthynyl-5-[(2S)-1-méthylpyrrolidin-2-yl]pyridine
altiniclina (-)-5-etinilnicotina

\[ C_{12}H_{14}N_{2} \]

amiglumidum
amiglumide (R)-4-(2-naphthamido)-N,N-dipentylglutaramic acid
amiglumide acide (4R)-5-(dipentylamino)-4-[(naphtalén-2-ylcarbonyl)amino]-5-oxopentanoïque
amiglumida (R)-4-(2-naftamido)-N,N-dipentilglutarámico

\[ C_{28}H_{36}N_{2}O_{4} \]
anisperimusum
anisperimus [(6-guanidinoheptyl)carbamoylmethyl 4-[[((R)-3-aminobutyl)amino]butyl]=
carbamate

anispérimus [4-[[((3R)-3-aminobutyl)amino]butyl]carbamate de
2-[[6-guanidinoheptyl]amino]-2-oxoéthyle

anisperimus [4-[[((R)-3-aminobutyl)amino]butyl]carbamato de
[[6-guanidinoheptiI]carbamoiI]metilo

\[ C_{18}H_{39}N_{7}O_{3} \]

ataquimastum
ataquimast 1-ethyl-3-(methylamino)-2(1H)-quinoxalinone
ataquimast 1-éthyl-3-(méthylamino)quinoxalin-2(1H)-one
ataquimast 1-etil-3-(metilamino)-2(1H)-quinoxalinona

\[ C_{11}H_{13}N_{3}O \]

axitiromum
axitirome ethyl (±)-4'-'[[α-(p-fluorophenyl)-α,4-dihydroxy-m-tolyl]oxy]-
3',5'-dimethyloxanilate

axitirome [[4-3-[(RS)-(4-fluorophényl)hydroxyméthyl]-4-hydroxyphénoxy]-
3,5-diméthylphényl]amino]oxoacétate d'éthyle

axitiromo (±)-4'-[[α-(p-fluorofenil)-α,4-dihidroxi-m-tolil]oxi]-3',5'-dimetiloxanilato de etilo

\[ C_{25}H_{24}FNO_{6} \]
**bilastinum**

*bilastine*

\[p\{-[4\{-[1-(2-ethoxyethyl)-2-benzimidazolyl]piperidino}ethyl\}-\alpha\text{-methylhydratropic acid}\]

*bilastine*

\[acide\ 2\{-[4\{-[1-(2-éthoxyéthyl)-1H-benzimidazol-2-yl]pipéridin-1-yl\éthyl}phényl\}-2-méthylpropanoïque\]

*bilastina*

\[ácido\ \(p\{-[4\{-1-(2-etoxietil)-2-bencimidazolil]piperidino}etil\}-\alpha\text{-metilhidratrópico}\]

\[C_{28}H_{37}N_3O_3\]

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**binetrakinum**

*binetrakin*

interleukin 4 (human)

*binétrakine*

interleukine 4 humaine

*binetraquina*

interleuquina 4 (humana)

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**cangrelorum**

*cangrelor*

\(N\{-[2-(methylthio)ethyl]-2\{-[3,3,3-trifluoropropyl]thio\}-5\text{-adénylic acid, monoanhydride with (dichlorométhylène)diphosphonic acid}\]

*cangrélor*

monoanhydride dichlorométhylènediphosphonique \(N\{-[2-(méthylsulfanil)éthyl]-2\{-[3,3,3-trifluoropropyl)sulfanil\}-5\text{-adénylique}\]

*cangrelor*

monoanhidrido del ácido \(N\{-[2-(metiltio)etil]-2\{-[3,3,3-trifloweropropil]tio\}-5\text{-adenilico con ácido (diclorometileno)difosfónico}\]
cetuximabum
cetuximab
immunoglobulin G 1 (human-mouse monoclonal C225 \( \gamma 1 \)-chain anti-human epidermal growth factor receptor), disulfide with human-mouse monoclonal C225 \( \kappa \)-chain, dimer

cétuximab
immunoglobuline G1, anti-(récepteur du facteur de croissance humain de l’épiderme) (chaîne \( \gamma 1 \) de l’anticorps monoclonal chimérique homme-souris C225), dimère du disulfure avec la chaîne \( \kappa \) de l’anticorps monoclonal chimérique homme-souris C225

cetuximab
immunoglobulina G 1, anti-(receptor del factor humano de crecimiento de la epidermis)(cadena \( \gamma 1 \)-del anticuerpo monoclonal químérico hombre-ratón C225), dímero del disulfuro con la cadena \( \kappa \) del anticuerpo monoclonal químérico hombre-ratón C225

cilomilastum
cilomilast
cis-4-cyano-4-[3-(cyclopentyl)oxy]-4-methoxyphenyl]cyclohexanecarboxylic acid

cilomilast
acide cis-4-cyano-4-[3-(cyclopentyl)oxy]-4-méthoxyphényl]cyclohexanecarboxylique

cilomilast
ácido cis-4-ciano-4-[3-(ciclopentiloxi)-4-metoxifenil]ciclohexanocarboxílico

C\(_{20}\)H\(_{25}\)NO\(_4\)

conivaptanum
conivaptan
4\(''\)-[(4,5-dihydro-2-methylimidazo[4,5-\(d\)[1]benzazepin-6(1\(H\))-yl]carbonyl]-2-biphenylcarboxanilide

conivaptan
\(N\)-[4-[(2-méthyl-4,5-dihydropyrimidazo[4,5-\(d\)[1]benzaépin-6(1\(H\))-yl]carbonyl]phényl]biphényle-2-carboxamide

conivaptán
4\(''\)-[(4,5-dihidro-2-metilimidazo[4,5-\(d\)[1]benzazepin-6(1\(H\))-il]carbonil]-2-bifenilcarboxanilida

\[\text{C}_{17}\text{H}_{25}\text{Cl}_{2}\text{F}_{3}\text{N}_{5}\text{O}_{12}\text{P}_{3}\text{S}_{2}\]
crobenetinum

crobenetine

\((2R,6S)-3-[(2S)-2-(benzylloxy)propyl]-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocin-10-ol\)

crobéntine

\((2R,6S)-3-[(2S)-2-(benzylloxy)propyl]-6,11,11-trimethyl-1,2,3,4,5,6-hexahydro-2,6-méthano-3-benzazocin-10-ol\)

crobenetina

\((2R,6S)-3-[(2S)-2-(benciloxi)propil]-1,2,3,4,5,6-hexahidro-6,11,11-trimeti-2,6-metano-3-benzazocin-10-ol\)

cystinum

cystine

\(-cystine\)

cystine

\(-cystine\)

cistina

\(-cistina\)

darusentanum

darusentan

\((+)-(S)-2-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-3-methoxy-3,3-diphenylpropionic acid\)

darusentan

\((+)-acide (2S)-2-(4,6-diméthoxypyrimidin-2-yloxy)-3-méthoxy-3,3-diphénylpropanoïque\)

daruséntán

\(ácido (+)-(S)-2-[(4,6-dimetoxi-2-pirimidinil)oxi]-3-metoxi-3,3-difenilpropiónico\)
**donatriptanum**
donatriptan  
1-[[3-(2-aminoethyl)indol-5-yl]oxy]acetyl]-4-(p-cyanophenyl)piperazine

donatriptan  
1-[2-[[3-(2-aminoethyl)-1H-indol-5-yl]oxy]acetyl]-4-(4-cyanophényl)pipérazine

donatriptán  
1-[[3-(2-aminoetil)indol-5-il]oxi]acetil]-4-(p-cianofenil)piperazina

**doxercalciferolium**
doexcaciferol  
(5Z,7E,22E)-9,10-secoergosta-5,7,10(19),22-tetraene-1α,3β-diol

doexcaciférol  
(5Z,7E,22E)-9,10-sécoergosta-5,7,10(19),22-tétraène-1α,3β-diol

doexcaciferol  
(5Z,7E,22E)-9,10-secoergosta-5,7,10(19),22-tetraeno-1α,3β-diol

**emfilerminum**
emfilermin leukemia-inhibiting factor (human)

emfilermine facteur d’inhibition leucémique humain

emfilermina factor inhibidor de leucemia (humano)
emivirinum
emivirine 6-benzyl-1-(ethoxymethyl)-5-isopropyluracil
émivirine 6-benzyl-1-(éthoxyméthyl)-5-(1-méthyléthyl)pyrimidine-2,4(1H,3H)-dione
emivirina 6-bencil-1-(etoximetil)-5-isopropiluracilo

\[ \text{C}_{17}\text{H}_{22}\text{N}_{2}\text{O}_{3} \]

entecavirum
entecavir 9-\{1S,3R,4S\}-4-hydroxy-3-(hydroxymethyl)-2-methylenecyclopentyl[guanine]
entécavir 2-amino-9-\{1S,3R,4S\}-4-hydroxy-3-(hydroxyméthyl)-2-méthylène cyclopentyl]-1,9-dihydro-6H-purin-6-one
entecavir 9-\{1S,3R,4S\}-4-hidroxi-3-(hidroximetil)-2-metilenociclopentil]guanina

\[ \text{C}_{12}\text{H}_{15}\text{N}_{5}\text{O}_{3} \]

epitumomabum
epitumomab mouse IgG 1 monoclonal antibody which binds the human muc-1 gene product
épitumomab immunoglobuline G2a, anti-(antigène CD20 humain) (chaîne \( \gamma \)2a de l’anticorps monoclonal de souris B1R1), dimère du disulfure avec la chaîne \( \lambda \) de l’anticorps monoclonal de souris B1R1
epitumomab

immunoglobulina G2a, anti-(antígeno CD20 humano) (cadena γ2a del anticuerpo monoclonal de ratón B1R1), dímero del disulfuro con la cadena λ del anticuerpo monoclonal de ratón B1R1

epratuzumab

epratuzumab

immunoglobulina G (human-mouse monoclonal IMMU-hLL2 γ-chain anti-human antigen CD22), disulfide with human-mouse monoclonal IMMU-hLL2 κ-chain, dimer

epratuzumab

immunoglobuline G, anti-(antigène CD22 humain) (chaîne γ de l’anticorps monoclonal de souris IMMU-hLL2 humanisé), dimère du disulfure avec la chaîne κ de l’anticorps monoclonal de souris IMMU-hLL2 humanisé

epratuzumab

immunoglobulina G, anti-(antígeno CD22 humano)(cadena γ del anticuerpo monoclonal humanizado de ratón IMMU-hLL2) dímero del disulfuro con la cadena κ del anticuerpo monoclonal humanizado de ratón IMMU-hLL2

eptapironum

eptapirone

4-methyl-2-[4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl]-1,2,4-triazine-3,5(2H,4H)-dione

eptapirone

4-méthyl-2-[4-[4-(pyrimidin-2-yl)pipérazin-1-yl]butyl]-1,2,4-triazine-3,5(2H,4H)-dione

eptapirona

4-metil-2-[4-[2-pirimidinil]-1-piperazinil]butil]-as-triazina-3,5(2H,4H)-diona

C_{16}H_{23}N_{7}O_{2}

escitalopramum

escitalopram

(+)-(S)-1-[3-(dimethylamino)propyl]-1-(p-fluorophenyl)-5-phthalancarbonitrile

escitalopram

(+)-(1S)-1-[3-(dihéthylamino)propyl]-1-(4-fluorophényl)-1,3-dihyroisobenzofurane-5-carbonitrile

escitalopram

(+)-(S)-1-[3-(dimetilamino)propil]-1-(p-fluorfenil)-5-fftalancarbonitrilo

C_{20}H_{21}FN_{2}O
evernimicinum
evernimicin

\( O(1R)-2,3-O\text{-methylene}-4-O(6\text{-methyl-}\beta\text{-resorcyllo})\text{-d-xylopyranosylidene}(1\rightarrow3)-\alpha\text{-L-lyxopyranosyl} O(2,3,6\text{-trideoxy}-3-C\text{-methyl}-4-O\text{-methyl}-3\text{-nitro-}\alpha\text{-L-arabino}-\text{hexopyranosyl}(1\rightarrow3)-O(2,6\text{-dideoxy}-4-O(3,5\text{-dichloro}-6\text{-methoxy}-4,2\text{-cresotyl})\text{-d-arabino-hexopyranosyl}(1\rightarrow4)-O(1R)-2,6\text{-dideoxy-}\alpha\text{-arabino-hexopyranosylidene}(1\rightarrow3)-O(6\text{-deoxy-}3\text{-C-methyl-}\beta\text{-d-mannopyranosyl}(1\rightarrow3)-O(6\text{-deoxy-}4\text{-O-methyl-}\beta\text{-d-galactopyranosyl}(1\rightarrow4)-2,6\text{-di-O-methyl-}\beta\text{-d-mannopyranoside}

évernimicine

\( O(3\text{-C-}\text{methyl}-4\text{-O-methyl-3-nitro-}2,3,6\text{-trideoxy-}\alpha\text{-L-arabino-hexopyranosyl}(1\rightarrow3)-O(4\text{-O}(3,5\text{-dichloro-4-hydroxy-2-methoxy-6-methylbenzoyl})-2,6\text{-dideoxy-}\beta\text{-d-arabino-hexopyranosyl}(1\rightarrow4)-O(1R)-2,6\text{-dideoxy-}\beta\text{-d-arabino-hexopyranosylidène}(1\rightarrow3)-O(3\text{-C-}\text{methyl-6-désoxy-}\beta\text{-d-mannopyranosyl}(1\rightarrow3)-O(4\text{-O-méthyl-6-désoxy-}\beta\text{-d-galactopyranosyl}(1\rightarrow4)-2,6\text{-di-O-méthyl-}\beta\text{-d-mannopyranoside de } O(1R)-4\text{-O}(2,4\text{-dihydroxy-6-méthylbenzoyl})-2,3\text{-O-méthylène-}\text{-d-xylopyranosylidène}(1\rightarrow3)-\alpha\text{-L-lyxopyranosyle}

evernimicina

\( O(2,3,6\text{-trideoxi-}3-C\text{-metil-4-O-metil-3-nitro-}\alpha\text{-L-arabino-hexopiranosil}(1\rightarrow3)-O(2,6\text{-didesoxi-}4-O(3,5\text{-dichloro-6-metoxi-4,2-cresotilo})\text{-d-arabino-hexopiranosil}(1\rightarrow4)-O(1R)-2,6\text{-didesoxi-d-arabino-hexopiranosilideno}(1\rightarrow3)-O(6\text{-desoxi-}3-C\text{-metil-}3\text{-nitro-}\beta\text{-d-manopiranosil}(1\rightarrow3)-O(6\text{-desoxi-}4-O\text{-metil-}\beta\text{-d-galactopiranosil}(1\rightarrow3)-2,6\text{-di-O-metil-}\beta\text{-manopiranósido de } O(1R)-2,3-O\text{-metileno-}4-O(6\text{-metil-}\beta\text{-resorcióilo})\text{-d-xilopiranosilideno}(1\rightarrow3)-\alpha\text{-L-lixopiranosilo}

\( C_{70}H_{79}Cl_{2}NO_{38} \)
everolimusum

everolimus


évérolimus


everolimus


\[C_{53}H_{83}NO_{14}\]

ezlopirantum

ezlopirant

\[(2S,3S)-2-(diphenylméthyl)-3-[(5-isopropyl-2-méthoxybenzyl)amino]=quinuclidine\]

ezlopirant

\[(2S,3S)-2-(diphénylméthyl)-N-[2-méthoxy-5-(1-méthyléthyl)benzyl]-1-azabibyclo[2.2.2]octan-3-amine\]

ezlopirant

\[(2S,3S)-2-(difenilmetil)-3-[(5-isopropil-2-metoxibencil)amino]quinuclidina\]
**fiduxosinum**

fiduxosin


fiduxosine


fiduxosina


\[ C_{30}H_{29}N_{5}O_{4}S \]

**figopitantum**

figopitant

(S)-N-[bis(3,5-trifluorométhyl)phenéthyl]-4-(cyclopropylméthyl)-N-méthyl-\( \alpha \)-phenéthyl-1-piperazinaacetamide

figopitant

(2S)-N-[2-[3,5-bis(trifluorométhyl)phényl]éthyl]-2-[4-(cyclopropylméthyl)=piperazin-1-yl]-N-méthyl-2-phénylacétamide

figopitant

(S)-N-[bis(3,5-trifluorométhil)fenëtil]-4-(ciclopropilmetil)-N-metil-\( \alpha \)-fenil-1-piperazinaacetamida

\[ C_{27}H_{31}F_{6}N_{3}O \]
**implitetapidum**

**(αS)-α-[α-(2,4-dimethyl-9H-pyrido[2,3-b]indol-9-yl)-p-tolyl]-N-(α-hydroxymethyl)benzyl]cyclopentaneacetamide**

**implitapide**

**(2S)-2-cyclopentyl-2-[4-[(2,4-dimethyl-9H-pyrido[2,3-b]indol-9-yl)methyl]phenyl]-N-[1R]-2-hydroxy-1-phényléthyl]jacetamide**

**implitapida**

**(αS)-α-[α-(2,4-dimethyl-9H-pyrido[2,3-b]indol-9-yl)-p-tolyl]-N-[α-(hydroxymethyl)benzyl]cyclopentaneacetamida**

C$_{35}$H$_{37}$N$_3$O$_2$

![Chemical structure](image)

**irampanelum**

**irampanel**

5-[α-[2-(dimethylamino)ethoxy]phenyl]-3-phenyl-1,2,4-oxadiazole

**irampanel**

$N,N$-diméthyl-2-[2-(3-phényl-1,2,4-oxadiazol-5-y1)phényloxéthamine

**irampanel**

5-[α-[2-(dimetilamino)etoixi]fenil]-3-fenil-1,2,4-oxadiazol

C$_{18}$H$_{19}$N$_3$O$_2$

![Chemical structure](image)

**irofulvenum**

**irofulven**

(R)-6'-hydroxy-3'-{(hydroxymethyl)-2',4',6'-trimethylspiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one

**irofulvente**

(6'R)-6'-hydroxy-3'-{(hydroxyméthyl)-2',4',6'-triméthylspiro[cyclopropane-1,5'-[5H]indén]-7'(6'H)-one

**irofulveno**

(R)-6'-hidroxi-3'-{(hidroximetil)-2',4',6'-trimetilsipo[ciclopropano-1,5'-[5H]inden]-7'(6'H)-ona
**itriglumidum**

*itriglumide*  
(R)-2'-(8-azaspiro[4.5]dec-8-ylcarbonyl)-4',6'-dimethyl-3-(1-naphthalen-1-yl)glutaranic acid

**Iliciceminum**

*lalicemine*  
(+)-2-[(S)-β-aminophenethyl]pyridine

**lusaperidonum**

*lusaperidone*  
3-[2-(3,4-dihydrobenzofuro[3,2-c][pyridin-2(1H)-yl]ethyl]-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one
metreleptinum
metreleptin  
N-methionyleptin (human)

métréleptine
  
N-méthionyleptine humaine

metreleptina
  
N-metionileptina (humana)

\[ C_{22}H_{21}N_{3}O_{2} \]

\[
\begin{align*}
\text{N} &- \text{methionyl} \\
\text{N} &- \text{methionyl} \\
\text{CH}_3 &
\end{align*}
\]

\[
\begin{align*}
\text{KTLIKTIVTR} & \\
\text{INDISHTQSV} & \\
\text{SSKQKVTLGD} & \\
\text{YQQILSMPS} & \\
\text{RNVIQISNDL} &
\end{align*}
\]

mitumomab
mitumomab  
immunoglobulin G2b (mouse monoclonal BEC2 γ2b-chain anti-GD3 ganglioside), disulfide with mouse monoclonal BEC2 κ-chain, dimer

mitumomab  
immunoglobuline G2b, anti-(ganglioside GD3) (chaîne γ2b de l’anticorps monoclonal de souris BEC2), dimère du disulfure avec la chaîne κ de l’anticorps monoclonal de souris BEC2

mitumomab  
imunoglobulina G2b,anti-(gangliósido GD3)(cadena γ2b del anticuerpo monoclonal de ratón BEC2) dímero del disulfuro con la cadena κ del anticuerpo monoclonal de ratón BEC2

motexafinum
motexafin  
9,10-diethyl-20,21-bis[2-[2-(2-methoxyethoxy)ethoxy]ethoxy]-4,15-dimethyl-8,11-imino-3,6:16,13-dinitrilo-1,18-benzodiazacycloeicosine-5,14-dipropanol

motéxafine  

motexafina  
**nebostinelum**
- **nebostinel**
  - \((S)-4\text{-amino-}N-(4,4\text{-dimethylcyclohexyl})\text{glutaramic acid}\)
- **nébostinél**
  - \(\text{acide } (4S)-4\text{-amino-5-[}(4,4\text{-diméthylcyclohexyl})\text{amino]}-5\text{-oxopentanoïque}\)
- **nebostinel**
  - \(\text{ácido } (S)-4\text{-amino-}N-(4,4\text{-dimetilciclohexil})\text{glutarámico}\)
  - \(C_{13}H_{24}N_{2}O_{3}\)

**onerceptum**
- **onercept**
  - \(\text{glycoprotein TNF-BP (tumor necrosis factor-binding protein) (human disulfide variant 1)}\)
- **onercept**
  - \(\text{20-180-récepteur } 1\text{ humain du facteur de nécrose tumorale, protéine glycosylée (partie du domaine extracellulaire)}\)
- **onercept**
  - \(\text{glicoproteína TNF-BP (proteína de unión al factor de necrosis tumoral) (disulfuro de la variante 1 humana)}\)
  - \(C_{753}H_{1156}N_{228}O_{247}S_{25}\)

```
DSVCPQKYI HPQNSICCT KCHKTYLYN DCPGPGQDID
CRECESGSFT ASENHLRCL SCSKCRKMEG QVEISSCTVD
RDTVGCRCRN QYRHYWSENLR QCFNCILSGL NGTVHLSQEU
KQNTVCTCHA GFLRENQCV SCSNKKSLE CTKLSCPQIE
```
- * glycosylation sites
- * sites de glycosylation
- * posiciones de glicosilación
pegvisomantum  
**pegvisomant**  

pegvisomant  

pegvisomant  

```
FPTIPLSRLF DNAMLRADRL NQLAFDTYQE FEEAYIPKEQ
KYSFLQNPQT SLCFSESIPHT PSNREETYQK SNLELLRISL
LLIQSWLEPV QFLRSVFANS LVYGASDNSV YDLKDEEKL
IQTLMGRLED GSPRTGQIFK QTYSKFDTNS HNDDALLKNY
GLLYCNADM SRVSTFLRTTV QCRSGECSGF
```

* pegylation sites  
* sites de pegylation  
* posiciones de pegilación

perflexanum  
**perflexane**  
tetradecafluorohexane

**perflexane**  
tétradécfluorohexane

**perflexano**  
tetradecafluorohexano

\[\text{C}_6\text{F}_{14}\]

\[
\begin{array}{c}
F_3C \\
\text{F} \\
\text{F} \\
\text{F} \\
\end{array}
\]

perflutrenum  
**perflutren**  
octafluoropropane

**perflutrène**  
octafluoropropane

**perflutreno**  
octafluoropropano

\[\text{C}_3\text{F}_8\]

\[
\begin{array}{c}
F_3C \\
\text{CF}_3 \\
\end{array}
\]
pinokalantum

(±)-3,4-dihydro-6,7-dimethoxy-α-phenyl-\(N,\)\(N\)-bis(2,3,4-trimethoxyphenethyl)-1-isoquinolineacetamide

pinokalant

(2\(RS\))-2-(6,7-dimethoxy-3,4-dihydroisoquinoléin-1-yl)-2-phényl-\(N,\)\(N\)-bis[2-(2,3,4-triméthoxyphényl)éthyl]acétamide

pinokalant

(±)-3,4-dihydro-6,7-dimetoxi-α-fenil-\(N,\)\(N\)-bis(2,3,4-trimetoxifenetil)-1-isoquinolinacetamida

\(C_{41}H_{48}N_{2}O_{9}\)

posaconazolum

posaconazole

4-[\(p\)-[\([3R,5R]\)-5-(2,4-difluorophenyl)tetrahydro-5-(1\(H\)-1,2,4-triazol-1-ylmethyl)-3-furylmethoxy]phenyl]-1-piperazinyl[phenyl]-1-\:[(1\(S\),2\(S\))-1-ethyl-2-hydroxypropyl]-\(\Lambda^{2}\)-1,2,4-triazolin-5-one

posaconazole

4-[\(p\)-[\([3R,5R]\)-5-(2,4-difluorophényl)-5-(1\(H\)-1,2,4-triazol-1-ylméthyl)= tétrahydrofurán-3-ylméthoxy][phényl]pipérazin-1-yl][phényl]-2-\:[(1\(S\),2\(S\))-1-éthyl-2-hydroxypropyl]-2,4-dihydro-3\(H\)-1,2,4-triazol-3-one

posaconazol

4-[\(p\)-[\([3R,5R]\)-5-(2,4-difluoroënil)tetrahydro-5-(1\(H\)-1,2,4-triazol-1-ilmetil)-3-furil]metoxi]fenil]-1-piperaziniil]fenil]-1-\:[(1\(S\),2\(S\))-1-etil-2-hidroxiëropriil]-D\(^2\)-1,2,4-triazolin-5-ona

\(C_{37}H_{42}F_{2}N_{8}O_{4}\)
prinomastatum
prinomastat
(S)-2,2-dimethyl-4-[[p-(4-pyridyloxy)phenyl]sulfonyl]-3-thiomorpholinecarboxylic acid

prinomastat
(3S)-N-hydroxy-2,2-dimethyl-4-[[4-(pyridin-4-yloxy)phenyl]sulfonyl]thiomorpholine-3-carboxamide

prinomastat
ácido (S)-2,2-dimetil-4-[[p-(4-piridiloxi)fenil]sulfonil]-3-tiomorfolinacarboxidroxámico

C₁₈H₂₁N₃O₅S₂

pumafentrinum
pumafentrine
(-)-p-[(4aR*,10bS*)]-9-ethoxy-1,2,3,4,4a,10b-hexahydro-8-methoxy-2-methylbenzo[c][1,6]napthyridin-6-yl]-N,N-diisopropylbenzamide

pumafentrine
(-)-4-[(4aR*,10bS*)]-9-éthoxy-8-méthoxy-2-méthyl-1,2,3,4,4a,10b-hexahydrobenzo[c][1,6]napthyridin-6-yl]-N,N-bis(1-méthyléthyl)benzamide

pumafentrina
(-)-p-[(4aR*,10bS*)]-9-etoxi-1,2,3,4,4a,10b-hexahidro-8-metoxi-2-metilbenzo[c][1,6]naftiridina-6-il]-N,N-diisopropilbenzamida

C₂₉H₃₉N₃O₅

relovaptanum
relovaptan
(2S)-1-[[2R,3S]-5-chloro-3-(o-chlorophenyl)-1-[[3,4-dimethoxyphenyl]=sulfonyl]-3-hydroxy-2-indolyl]carbonyl]2-pyrrolidinecarboxamide

relovaptan
(2S)-1-[[2R,3S]-5-chloro-3-(2-chlorophényl)-1-[[3,4-diméthoxypyényl]=sulfonyl]-3-hydroxy-2,3-dihydro-1H-indol-2-yl]carbonyl]pyrrolidine-2-carboxamide

relovaptán
(2S)-1-[[2R,3S]-5-cloro-3-(o-clorofenil)-1-[[3,4-dimetoxxifenil)sulfonil]-3-hidroxi-2-indolinil]carbonil]-2-pirrolidinacarboxamida
**repiferminum**  
repifermin 33-172-keratinocyte growth factor 2 (human)  
répifermine 33-172-facteur 2 humain de croissance du kératinoctye  
repifermina 33-172-factor 2 de crecimiento de queratinocitos (humano)

C_{28}H_{27}Cl_{2}N_{3}O_{7}S

SYNLQGDVR \ WRKLFSFTKY \ FLKIEKNGKV \ SGTKKENCYPY  
SILEITSVEI \ GVVAVKAINS \ NYYLAMNKKG \ KLYGSKEFNN  
DCKLKERIEE \ NGNITYASFN \ WQHNGRQMYV \ ALNGKGAPRR  
GQKTRRKNTS \ AHFLPMVVHS

**resiquimodum**  
resiquimod 4-amino-2-(ethoxymethyl)-α,α-dimethyl-1H-imidazo[4,5-c]quinoline-1-ethanol  
résiquimod 1-[4-amino-2-(éthoxyméthyl)-1H-imidazo[4,5-c]quinoléin-1-yl]-2-méthylpropan-2-ol  
resiquimod 4-amino-2-(etoximetil)-α,α-dimetil-1H-imidazo[4,5-c]quinolina-1-etanol

C_{17}H_{22}N_{4}O_{2}

**risarestatum**  
risarestat (±)-5-[3-ethoxy-4-(pentyloxy)phenyl]-2,4-thiazolidinedione  
risarestat (5RS)-5-[3-éthoxy-4-(pentyloxy)phényl]thiazolidine-2,4-dione
risarestat  
$(\pm)$-5-[3-etoxy-4-(pentiloxy)fenil]-2,4-tiazolidinadiona  
\[ C_{16}H_{21}NO_4S \]

rubitecanum  
rubitecan  
9-nitrocamptotecin  

rubitécan  
$(4S)$-4-éthyl-4-hydroxy-10-nitro-1,12-dihydro-14\(H\)-pyrano[3',4':6,7]indolizino[1,2-b]quinoléine-3,14(4\(H\))-dione  

rubitecán  
9-nitrocamptotecina  

sulamserodum  
sulamserod  
\(N\)-[2-4-[2-[(8-amino-7-chloro-1,4-benzodioxan-5-yi)carbonyl]ethyl)piperidino]ethyl]metanesulfonamide  

sulamsérod  
\(N\)-[2-4-[3-(8-amino-7-chloro-2,3-dihydro-1,4-benzodioxin-5-yi)-3-oxopropyl]pipérídin-1-yi]éthyl]méthanesulfonamide  

sulamserod  
\(N\)-[2-4-[2-[(8-amino-7-cloro-1,4-benzodioxan-5-il)carbonil]etil]piperidino]=étilymetanosulfonamida  

\[ C_{19}H_{28}ClN_3O_5S \]

tanomastatum  
tanomastat  
$(S)$-3-[(4'-chloro-4-biphenyl)carbonyl]2-[(phenylthio)methyl]propionic acid  

tanomastat  
acide (2S)-4-(4'-chlorobiphényl-4-yi)-4-oxo-2-[(phénysulfanyl)méthyl]=butanoïque
tanomastat  ácido (2S)-4-(4'-clorobifenil-4-il)-4-oxo-2-[(fenilsulfanilo)metil]butanoico
C_{23}H_{19}ClO_3S

tebipenemum  tebipenem  (+)-hydroxymethyl (4R,5S,6S)-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-3-[(1-(2-thiazolin-2-yl)-3-azetidinyl)thio]-1-azabiciclo[3.2.0]hept-2-ene-2-carboxylate, 2-pivalate

tébipénem  (+)-(4R,5S,6S)-3-[[1-(4,5-dihydrothiazol-2-yl)azetidin-3-yl]sulfanyl]-6-[(1R)-1-hydroxyéthyl]-4-méthyl-7-oxo-1-azabiciclo[3.2.0]hept-2-éne-2-carboxylate de [(2,2-diméthylpropanoyl)oxy]métyle

tebipenem  2-pivalato y (4R,5S,6S)-6-[(1R)-1-hidroxietil]-4-metil-7-oxo-3-[(1-(2-tiazolin-2-il)-3-azetidinil)thio]-1-azabiciclo[3.2.0]hept-2-eno-2-carboxilato de metileno
C_{22}H_{31}N_{3}O_{6}S_{2}

tenofovirum  tenofovir  [[(R)-2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]phosphonic acid

ténofovir  acide [[(1R)-2-(6-amino-9H-purin-9-yl)-1-méthyléthoxy]méthyl]phosphonique

C_{9}H_{14}N_{5}O_{4}P
**tiplimotidum**

**tiplimotide**


**tiplimotide**

\[ \text{D-} \text{l-lysyl-L-prolyl-L-valyl-L-valyl-L-histidyl-L-leucyl-L-phenylalanyl-L-alanyl-L-asparaginy}- \text{l-L-thr}^{\text{é}} \text{onyl-L-prolyl-L-arginyl-L-thr}^{\text{é}} \text{onyl-L-threonyl-L-prolinamide} \]

**tiplimotida**


\[ \text{C}_{87}\text{H}_{143}\text{N}_{25}\text{O}_{20} \]

D-Ala—Lys—Pro—Val—Val—His—Leu—Phe—Ala—Asn—
Ile—Val—Thr—Pro—Arg—Thr—Pro—NH\(_2\)

**valrocehidum**

**valrocemide**

\( N \)-\( (\text{carbamoylmethyl}) \)-2-propylvaleramide

**valrocémide**

\( N \)-\( (2\text{-amino-2-oxéthyl}) \)-2-propylpentanamide

**valrocehidama**

\( N \)-\( (\text{carboamoyimetil}) \)-2-propilvaleramida

\[ \text{C}_{10}\text{H}_{20}\text{N}_{2}\text{O}_{2} \]

\[ \text{H}_{3}\text{C} \]
\[ \begin{array}{c}
\text{N} \\
\text{H} \\
\text{O} \\
\text{NH}_{2} \\
\text{OH} \\
\text{CH}_{3}
\end{array} \]

**vardenafilum**

**vardenafil**

1-\[\text{[3-(3,4-dihydro-5-methyl-4-oxo-7-propylimidazo}[5,1-f]as-triazin-2-yl)-4-ethoxyphenyl]sulfonil]-4-ethylpiperazine

**vardénafil**

2-\[\text{[2-éthoxy-5-[(4-éthylpipérasin-1-yl)sulfonyl]phényl]-5-méthyl-7-propylimidazolo}[5,1-f][1,2,4]triazin-4(3H)-one

**vardenafil**

1-\[\text{[3-(3,4-dihidro-5-metil-4-oxo-7-propilimidazo}[5,1-f]as-triazin-2-il)-4-etoxyfenil]sulfonil]-4-etilpiperazina

\[ \text{C}_{23}\text{H}_{32}\text{N}_{6}\text{O}_{4}\text{S} \]
vofopitantum

vofopitant

(2S,3S)-3-[[2-methoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]benzyl]amino]-2-phenylpiperidine

vofopitant

(2S,3S)-N-[2-méthoxy-5-[5-(trifluorométhyl)-1H-tétrazol-1-yl]benzyl]-2-phénylpipéridin-3-amine

vofopitant

(2S,3S)-3-[[2-metoxi-5-[5-(trifluorometil)-1H-tetrazol-1-il]bencil]amino]-2-fenilpiperidina

C_{21}H_{23}F_{3}N_{6}O
AMENDMENTS TO PREVIOUS LISTS
MODIFICATIONS APPORTÉES AUX LISTES ANTÉRIEURES
MODIFICACIONES A LAS LISTAS ANTERIORES

Recommended International Nonproprietary Names (Rec. INN): List 43
Dénominations communes internationales recommandées (DCI Rec.): Liste 43
Denominaciones Comunes Internacionales Recomendadas (DCI Rec.): Lista 43


p. 50  **eledoisinum**
eledoïsite

remplacer le nom par le suivant:
elédoïsite

p. 57  **idremcinalum**
idremcinal

remplacer le nom chimique par le suivant:
(2R,3R,4S,5R,8R,9S,10S,11R,12R)-5-éthyl-3,4-dihydroxy-2,4,8,10,12,14-hexaméthyl-9-[(3-C-méthyl-3-O-méthyl-2,6-didésoxy-α-L-ribo-hexopyranosyl)oxy]-11-[[3-[(méthyl(1-méthyléthyl)amino]-3,4,6-tridésoxy-β-D-xylo-hexopyranosyl]oxy]-6,15-dioxabicyclo[10.2.1]pentadec-1(14)-én-7-one

p. 59  **lasofoxifennum**
lasofoxifène

remplacer le nom chimique par le suivant:
(-)-(5R*,6S*)-6-phényl-5-[4-[(pyrrolidin-1-yl)éthoxy]phényl]-5,6,7,8-tétrahydronaphtalén-2-ol

p. 64  **pimecrolimusum**
pimécrolimus

remplacer le nom chimique par le suivant:

p. 66  **sarakalimum**
sarakalim

remplacer le nom chimique par le suivant:
N-[2,2-diméthyl-4-(2-oxopyridin-1(2H)-yl)-6-(trifluorométhyl)-2H-1benzopyran-3-yl)méthyl]-N-hydroxyacétamide
Procedure and Guiding Principles / Procédure et Directives / Procedimientos y principios generales

The text of the Procedures for the Selection of Recommended International Nonproprietary Names for Pharmaceutical Substances and General Principles for Guidance in Devising International Nonproprietary Names for Pharmaceutical Substances will be reproduced in uneven numbers of proposed INN lists only.

Les textes de la Procédure à suivre en vue de choix de dénominations communes internationales recommandées pour les substances pharmaceutiques et des Directives générales pour la formation de dénominations communes internatio-nales applicables aux substances pharmaceutiques ont été publiés avec la liste 81 des DCI proposées et seront, à nouveau, publiés avec la prochaine liste des DCI proposées.

El texto de los Procedimientos de selección de denominaciones comunes internacionales recomendadas para las sustancias farmacéuticas y de los Principios generales de orientación para formar denominaciones comunes internacio-nales para sustancias farmacéuticas aparece solamente en los números impares de las listas de DCI propuestas.