WHO Drug Information

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http://www.who.int/druginformation
Quality Assurance Issues

Good pharmaceutical trade and distribution practices

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Over the past sixty years, there have been over 500 reported cases of fatal incidents due to the accidental but also fraudulent incorporation of diethylene glycol into pharmaceuticals (1). About 80 children died in Haiti in 1996 as a result of contaminated paracetamol syrup containing diethylene glycol in glycerol used as an excipient. A similar case of diethylene glycol poisoning was identified in India between April and June 1999 (2). The WHO Drug Information has also published articles on other cases reported worldwide (3).

WHO has developed guidelines on good manufacturing practices (GMP) for both finished pharmaceutical dosage forms and starting materials (4), while other regulations and guidelines continue to be issued. A Guideline on Good Manufacturing Practice for Active Pharmaceutical Ingredients has also been approved by the International Conference on Harmonization (ICH) (5). Other bodies, such as the International Pharmaceutical Excipients Council or the United States Pharmacopeia, have published recommendations (6–7). WHO Guidelines for the Manufacture of Pharmaceutical Excipients were published in 1999 (8) although no equivalent ICH guideline yet exists. Although high quality production standards will guarantee a good quality product, they do not confirm that high quality starting materials are indeed delivered to the pharmaceutical manufacturers.

Industry has engaged in a voluntary programme of responsible care and product stewardship, as set out on the following page. Such programmes should ensure that only safe products are used. However, the best programmes cannot defeat all fraudulent practices. Unscrupulous individuals concerned with making quick and easy money will continue to seek out any loopholes in regulations and circumvent systems in particular when regulations are absent or not enforced (9).

How do these products reach the consumer?

When company A buys from manufacturing company B, does company A really receive a product made by company B? Hopefully, yes. But this is not always the case. The commercial practices described below are considered normal transactions in many countries and demonstrate the difficulties encountered in operating effective control systems.

• Producer A has more orders on the books for active ingredients than he can handle. Therefore, he orders products from company B to be delivered in neutral drums (no labels, or peelable labels). He will then relabel these drums with his own labels and reissue the certificate of analysis.

• Export company XYZ exports products bearing with its own labels, without reference to the original producer. Additionally, the company may source from several different producers at the same time.

• A distributor repackages a product in smaller containers under its own name, without traceability to the original producer. Such practice is also fairly common in some European companies which are not obliged to communicate the origin of the goods.

• A technical product or a food-grade product is reanalysed by the broker/distributor and found compliant with a given pharmacopoeia, and relabelled as being of pharmaceutical quality.

The above practices, and many more, have a potential impact because these products are eventually administered to humans for sometimes quite serious health conditions. In all the cases above, there is no way to guarantee that the product originates from a plant where appropriate GMP standards have been implemented. Absent cleaning validations, the use of low quality water, the use

*Authors alone are responsible for views expressed in signed contributions.
of unacceptable solvents such as benzene, or process changes which go unreported and unvalidated, can result in unsafe medicinal products. Recent FDA warning letters indicate that some facilities who claim GMP compliance have never carried out the corrections they committed to make in writing. Are these exceptions to the rule, or are they the tip of the iceberg?

Furthermore, if there is lack of traceability, a variable or unknown origin of the goods, all process validation files of the medicinal producer are — by definition — meaningless, and this includes all the stability data. Processing conditions may vary depending on the source of the starting materials, which has a direct impact on bioavailability and hence on the efficacy of the medicinal product.

Another frequent observation is that products are being offered against obsolete pharmacopoeial standards. For example, at the end of the year 2000, acetylsalicylic acid was reported to have been offered, with compliance stated against BP–80 although the British Pharmacopoeia monograph was changed in 1986 and again in 2000. The monograph change concerned related substances, suspected to be mutagenic and now limited at 0.1%. The samples of the product offered had over 0.2 % of the principal impurity.

These are not the only recurring fraudulent practices by far. Several constructions are known, often related to the registration process or patent infringement. A lot of money can be made by committing fraud, and the risks taken are sometimes significantly lower than those, for example, of narcotics dealers for which capital punishment is often the penalty. Yet fraud with medicinal products can be as devastating to the end user as narcotics!

PRODUCT STEWARDSHIP*

• Product stewardship is the responsible and ethical management of health, safety and environmental aspects of a product throughout its total life cycle. Product Stewardship is Responsible Care® applied to products.

• Product stewardship improves market confidence. By defining and pursuing common goals throughout the supply chain, we can achieve benefits for all businesses involved.

• No company operates in isolation. Everyone involved in the production, handling, use and disposal of chemicals has a shared responsibility to ensure their safe management and use.

• By adopting a programme of Product Stewardship, every company can play its part in protecting humans and the environment from potential harm.

WHY PRODUCT STEWARDSHIP?

• Every company, up and down the supply chain, should be concerned about the impact of chemicals on human health and the environment, throughout their life cycle.

• Each of us is confronted with a multitude of safety, health, and environmental issues regarding our products. These may be voiced by our customers, environmental groups, and regulatory authorities. They may arise from special expectations and public concern or from the industry’s own internal assessment.

• Implementing Product Stewardship helps us to manage these issues more effectively, taking into account health, safety and environmental as well as technical and economic aspects to ensure best customer value.

• Chemical products must be managed and used safely along the supply chain, through manufacture, packaging, distribution, use and ultimate disposal.

*The European Chemical Industry Council (CEFIC) definition,
Supply chain characteristics of excipients

During the past decade, the excipient market has changed from a regional to a global market. Companies have become international, manufacturing products from only a small number of sites for the whole global market. New competitors have appeared, especially in Eastern Europe and Asia. This situation has led to a movement of excipients throughout the world. In this environment, distributors become more involved in the supply chain.

The incident in Haiti of contaminated paracetamol illustrates the extent and dramatic consequences of improper handling of excipients by supply chain brokers. Several distributors were involved in this incident, the product was shipped all around the world — from Asia via Europe to Haiti, with no traceability, insufficient controls and documentation lacking. Other similar incidents have also been reported (10).

In many countries, distributors are in charge of the excipients business because pharmaceutical companies have low consumption of these products compared to the large quantities used in food production, or for cosmetic and technical applications. Of course, some exemptions exist concerning particular excipients used exclusively for pharmaceutical applications. However, most distributors dealing with excipients are involved in trading to businesses with technical applications and often supply similar products for different uses. In these other business lines, processes involving mixing or minor cross contamination, are not viewed with the same precision as they are in pharmaceutical production. Traceability and documentation are not strictly required, nor do customers wish to pay for this service when using such materials for technical, food or cosmetic applications.

Given this situation, managing the distribution of pharmaceuticals requires sensitivity of the issues and knowledge of how to deal with the different requirements for the many similar products and their different applications. Incidents with contaminated excipients in the past showed that there is a lack of good practice in this area but no detailed regulation yet exists that provides standards for industry and regulatory authorities.

Current legislation and guidelines on good distribution practices (GDP)

The latest harmonized ICH Guideline: Good Manufacturing Practice for Active Pharmaceutical Ingredients (Q7a), approved in November 2000 includes a chapter entitled “Agents, brokers, traders, distributors, repackers, and relabelers”. Within that chapter, special requirements for distributors are defined regarding traceability, stability, repackaging, transfer of information, complaints and recalls (5).

The French Medicines Agency (AFSSAPS) is currently preparing an exhaustive guide for good distribution practices covering both active pharmaceutical ingredients and excipients. This is still a draft working document, but it is likely to be published and implemented before the end of 2001. The International Pharmaceutical Excipients Council (IPEC) has also issued an audit-style questionnaire specifically designed for assessing distributors of excipients and is based on IPEC GMP Guidelines for Bulk Pharmaceutical Excipients (11). This document is intended to be used by pharmaceutical companies for auditing their supply distributors as part of their supplier evaluation system, as well as certifying distributors against IPEC standards. It should be used as a tool to assess the actual GMP/GDP level of distributors, to raise awareness and improve knowledge of supply chain actors, and thereby improve GMP compliance.

The European Association of Chemical Distributors (FECC) and other traders’ organizations have also published a discussion paper entitled GMP for Active Pharmaceutical Ingredients in Distributive Trade (12). However, there is so far no final agreement amongst traders and brokers on these requirements and on the implementation of the principles set out in the document. Furthermore, there have been substantial comments made by some trader’s organizations on the GDP requirements of ICH Draft Q7a, claiming that these requirements will lead to substantial price increases in Europe.

The European Chemical Industry Council (CEFIC) has published Guidelines for Handling and Distribution of Propylene glycol USP/EP (13) as part of their Responsible Care Program. The Guidelines were created by European manufacturers of propylene glycol USP/EP and contain relevant instructions and procedures to ensure safety and quality of propylene glycol from the manufacturing site down to the end user, bearing in mind special applications in pharmaceuticals, and consumer health protection measures. Similar ideas and strategies are included in the European Single Assessment Document for Chemical Distributors (ESAD), a document published by CEFIC and FECC in 1999.
(14). In this document, specific guidance is given for the distribution of excipients, food and cosmetic ingredients. It can be used either by manufacturers to assess their distribution partners, or by customers to find out what level of GMP/GDP distributors of excipients have achieved.

**Do these regulations suffice to safeguard public health?**

Maintaining quality standards and product safety has a price, but negating the need for requirements with purely commercial arguments is unacceptable when the implicit risks to human health are considered. The need for global recommendations and control is crucial: if the expense of applying quality and safety practices risks forcing the compliant companies out of business because they charge higher prices than their unscrupulous rivals, then this is obviously a horrifying prospect! It is possible that the current GMP practices dealing with active pharmaceutical ingredients (API), excipient trading and distribution are not sufficient to guarantee product quality and safety.

Several guidance documents require full traceability back to the original producers. However, a repacker or re-labeller is also often considered to be a manufacturer, so that traceability to the last “manufacturing step” is clearly insufficient. Other guidelines require a reference to the original producer on the certificate of analysis. The traceability requirement clearly needs to be bi-directional and is best reflected in section 17.60 of ICH Q7a which states: “Agents, brokers, distributors, re-packers, or re-labellers should transfer all quality or regulatory information received from an active pharmaceutical ingredient (API) or intermediate manufacturer to the customer, and from the customer to the API or intermediate manufacturer.”

The API industry endorses these requirements. However, as long as there are no stringent verification and enforcement regulations in place, it is likely that fraudulent practices will continue to prosper. Europe intends to amend its Starting Materials Directive (75/319 EC) which will create a legal basis for the implementation of these GMP / GDP requirements. This will also create a legal basis for inspections covering manufacturers that are exporting products into the European Union, or intend to do so. However, in the current draft text of the Amendment, the decision to inspect is being left to the discretion of each Member State. Considering current budget restrictions in several countries, industry fears that substandard products, or products made by different processes to those declared in regulatory filings, will continue to enter into the European Union. This particularly concerns generics and over-the-counter (OTC) products, for which controls are minimal. OTC products are generally not even inspected, so similar concerns apply to imports of these products.

Recently, market prices of pharmaceutical ingredients for generics and OTC products have been forced to below economic levels. The inroad onto the market of products manufactured under inadequate — or even in the absence of — systems that should secure their quality and safety seems to be one important causative factor for this development. Omitting the use of such systems allows for lower manufacturing costs and therefore offers an important competitive edge. The implicit risks to humans are evident: such products are often sold to very large populations. For example, it is estimated that annually about 70,000 tons of paracetamol (acetaminophen) are consumed worldwide, representing a total of 150 billion tablets. A sub-standard product could have a more lethal impact than an atom bomb in such cases!

Similar requirements will certainly also be needed with regard to trade in pharmaceutical ingredients worldwide. The first steps that have been taken in this direction by WHO will hopefully lead to increased safety of medicines on a global scale.

In conclusion, the API manufacturing industry looks forward to presentation of a final text for Amendment of 75/319/EC for approval by the European Council and European Parliament. After all, it is the safety of patients which is at stake.

**References**

5. International Conference on Harmonization (ICH) documents available on http://www.ifpma.org


Personal Perspectives

Risk assessment as an element of drug control

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The responsibility of governments to establish systems which assure that all pharmaceutical products used in a given country are both safe and effective is now generally accepted, even if the extent of such responsibility may differ between countries. The operation of such systems may be supervised by a special department within the Ministry of Health or delegated to a drug regulatory authority. In either case, such activities are carried out in close collaboration with those parties involved in drug manufacture and distribution, including manufacturers, wholesalers, hospitals, retail pharmacies and other drug distribution outlets.

The main purpose of a drug regulatory system is to prevent the occurrence of harmful drug related events which may have the potential to attain catastrophic proportions. Because of the need to maintain public confidence in pharmaceutical products for the general health of the population, a system of government-imposed regulations is often in operation, while responsible institutions and enterprises endeavour to ensure that no harmful negligence occurs during manufacture, distribution and use of medicinal products. Such additional activities ensure that all precautions are faithfully implemented by all those involved.

Medicines have important consequences for health and their regulation may involve decisions with international implications. As such, the advice of WHO in relation to these issues is considered highly relevant. Drug regulatory systems operate within the economic environment of the country as a whole and the level of development differs enormously between countries, with regard to the particularities of the restrictions encountered.

Drug-related hazards

While harmful events and risks are inherent in the nature of drugs, many risks can be avoided or at least minimized through implementation of effective preventive measures. For the purposes of the present article, three types of risk may be distinguished.

1. Risks related to the introduction of new medicines

Risks related to the introduction of new medicines are linked to the possibility that an unknown harmful effect of a new substance will appear when the product is used extensively in the general population. Elaborate systems have now been developed for the prevention of such risks based on early detection of harmful effects in the course of pre-clinical testing or during clinical studies. Separate sets of requirements are established for new chemical entities and for new products obtained from biotechnology where additional kinds of risks can be expected. However, even highly elaborate systems cannot be completely foolproof, as is evidenced from cases where rapid withdrawal from the market of recently approved products was necessary (1).

2. Risks related to drug production

Risks that are related to the production of drugs include events resulting from improper manufacturing processes or cases of mix-ups and mislabelling during production. This type of hazard is not related to the intrinsic pharmacological property of the active substance or excipient but to the manufacturing process. Improper production includes the use of inadequate (substandard) starting materials as well as deficiencies in the technological processes of drug formulation. Such deficiencies could result, for example, in the manufacture of products of inadequate bioavailability, or may lead to the appearance of unexpected contaminants in the final product.

Risks related to the use of incorrect starting materials may have serious adverse consequences, as in the well-known cases of ethylene glycol being used in place of glycerol or as an admixture to an excipient (2). Similarly, the risk of contamination by adventitious impurities has also to be considered in the case of starting materials. Risks related to mix-ups may also occur within the drug distribution chain if re-packaging or re-labelling of products is
undertaken by traders, wholesalers or at retail level. Fraudulent production of counterfeit or adulterated drugs is a serious problem which should be considered separately (3). This criminal activity is linked to immense health risks.

3. Risks related to improper use of drugs
The improper use of drugs may lead to scenarios where harm is caused instead of expected relief. This includes mistakes made by physicians in the selection of drugs, irrational prescribing, over-prescribing (leading to over-consumption, particularly of antibiotics) (4), mistakes by auxiliary staff when administering medicines, lack of patient compliance, or mistakes made when taking medication. Some of those situations may also be created by unethical promotional practices which influence prescribing and consumption decisions. Effective drug information and education is essential to counter such practices. It is debatable to what extent drug regulatory authorities are able to take remedial action, since rational prescribing is primarily the responsibility of institutions which supervise medical practitioners.

Drug regulatory authorities
There have been few attempts to establish a classification of drug regulatory authorities into specific groups, although the notion of a small drug regulatory authority has been introduced by the WHO document Guiding Principles for Small National Drug Regulatory Authorities (5). The three following levels of drug regulation were identified in a recent report on global harmonization of regulatory requirements of pharmaceuticals (6). These categories often reflect the degree of economic development of countries, which confirms that the importance of economic factors in the health area extends also to drug regulation.

1. A sophisticated level of drug regulation
Countries with sophisticated drug regulatory activities are generally well equipped to prevent most types of risks related to medicines. Appropriate drug regulatory institutions exist to confirm the safety and efficacy of new drug entities. The majority of these activities are now carried out according to guidelines established by the International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH). A brief review of ICH activities was recently published in WHO Drug Information (6).

High-income countries with sophisticated drug regulatory activities have properly functioning systems for the establishment of drug quality requirements. This will include activities of pharmacopoeia commissions and well established surveillance systems on the manufacture and distribution of pharmaceuticals such as pharmaceutical inspection and national drug control laboratories. All institutions function effectively in order to reduce to a minimum the risks related to drug production and distribution.

Administrative regulations related to the introduction of new medicines and control of drug production can be properly implemented in high-income countries because the pharmaceutical industry, to which they are addressed, is well developed and drug distribution services are staffed by fully qualified personnel. Full implementation of the rules of good manufacturing practices (GMP) is also much simpler in facilities with high manufacturing standards and having at their disposal well-equipped and well-staffed analytical laboratories. The same can be said of institutions providing information on drug use for health professionals and the general public.

2. Drug regulation at the intermediate level
The medicines control situation is less sure in countries at the intermediate level. Countries in this group rely heavily on the evaluation of new drug entities carried out in countries with a sophisticated level of regulatory activity, avoiding, to some extent, the risks associated with unexpected harmful effects of new medicines. However, as the main source of pharmaceutical products will normally be the domestic manufacture of generic pharmaceuticals, the main risk encountered is that related to production processes.

Because of the country’s economic situation, drug regulatory authorities have only moderate financial means at their disposal. Activities are mainly based on the use of national resources, not on outside aid, even if a measure of external advice is usually available. Local pharmaceutical manufacture in the majority of countries in this group, with a few notable exceptions, is based on the importation of raw materials, which gives rise to particular kinds of risk. Furthermore, the technical equipment of local pharmaceutical enterprises may be more rudimentary in comparison with pharmaceutical manufacture in the high-income countries. Drug distributors may also be more moderately equipped. Some countries in this group are also victims of fraudulent production of adulterated drugs. There is, therefore, a whole range of combinations of risk areas within drug regulation that exists in countries of this group.
3. Inadequate drug regulation
Countries with inadequate regulatory activity are quite numerous and comprise nearly all low-income countries where there is no infrastructure for regulatory activity or, where such infrastructure does exist, it is too weak to achieve effective regulation. Typically, there is little local pharmaceutical manufacture, the drug distribution chain is only moderately equipped, while conditions at drug retail level can be described as quite rudimentary. These countries, using mostly imported pharmaceuticals, are highly vulnerable to risks that can occur during drug distribution including fraudulent distribution of adulterated drugs. As countries in this group are not able to create independent, effective drug regulation, they require strong external assistance.

The influence of drug risks on control strategies
As an intergovernmental institution responsible for all matters related to health, the World Health Organization provides advice to its Member States from both the international and national perspective. This is carried out through recommendations and suitable documentation for implementation by countries. Such advice is intended for global application and has been founded on an underlying notion that similar approaches can be applied all over the world in many health related areas. Such a notion also includes issues concerning drug regulation. This integral approach has gradually became diffused through the creation, for example, of essential drug programmes intended primarily for low-income countries. Furthermore, countries at different levels of economic development have become more and more conscious of the various types of risks inherent in providing medicines to their populations.

The lack of proper evaluation of potential hazards and the effectiveness of administrative countermeasures remains a serious obstacle for the selection of an appropriate strategy. Data collection that could help such evaluations is poorly organized, if it exists at all, and is further complicated by the need for greater transparency.

Control strategies of high-income countries
The activities of drug regulatory authorities in high-income countries are directed towards prevention of all types of risks, both those relevant to the introduction of new medicines and those that can occur during manufacture and distribution. To maintain a sophisticated level of drug regulation, considerable financial outlays are necessary from governments and the pharmaceutical industry with the result that risks related to the production of drugs and drug distribution are kept at the lowest level. Major activities are now focused on a comprehensive maintenance strategy of prevention of hazards linked to the introduction of new medicines. Consequently, less attention is being paid to risks linked to drug production and distribution since this was achieved at earlier stages of development.

Control strategies for other countries
Unfortunately, the favourable situation existing in high-income countries does not exist in countries where risks linked to the production and distribution of drugs remain a problem. It may even be that the situation is becoming worse — in part due to the presence of counterfeit products. Appropriate advice is needed from WHO because, for economic reasons, a direct transposition of institutions and procedures which operate in high-income countries is not possible.

In countries at an intermediate level, the operation of drug regulatory institutions is reflected by national resources rather than outside aid operating within the constraints imposed by the economic situation of the country in question. In countries at medium and low-income level, such constraints are much more restrictive than those existing in economically developed countries. In such circumstances, to be fully effective, activities should be oriented where the risks are highest. The assessment of risks is therefore of primary importance in establishing effective drug control strategies.

Assessment of risks linked to the production of drugs should be based on a separate review of each of the main elements of the drug supply system as follows.

- local manufacture;
- sources of raw materials;
- production facilities;
- importation;
- products in final containers; and
- products to be repackaged and re-labelled.
Existing literature on quality assurance of pharmaceuticals, which includes numerous WHO documents, describes in detail the activities related to drug quality assurance in respect of each of these elements. The advice given in that literature is fully appropriate in a situation where adequate resources are available. What is usually missing, however, is a listing of priority risk areas to be considered in cases when insufficient economic resources do not permit a full implementation of all recommendations.

**Alternative control strategies**

An assessment of individual risks related to specific products and raw materials, and recognition of hazards at specific stages of production or distribution would permit national regulatory authorities to better plan a drug control strategy and render its activities more effective within available resources. The main element to be considered is the extent of reliance on documentary evidence concerning the quality of products against confirmation of their quality (identity, purity and strength) through testing of samples. This applies equally to preparations and to raw materials, either of domestic or foreign origin.

Documentary evidence is much cheaper to procure, but it confirms nothing more than the results obtained by the manufacturer’s analytical laboratory at the time the product was released onto the market. Obviously, it requires an additional assurance that it indeed pertains to the product in question. A confirmatory testing of samples is much more expensive, as it requires the maintenance of a suitable testing laboratory added to the costs of analysis. Such confirmatory testing is therefore only carried out on a random basis. None the less, testing of actual samples taken from the market can confirm whether regulatory authority action is adequate and it will remind the manufacturers and importers of the existence of control. A proper combination of the two approaches should also take into account the specificity of risk situations, examples of which are given below.

In many countries, local manufacture of pharmaceutical preparations is based on imported raw materials, both for active materials and excipients. Assurance of the identity and purity of these materials can be based either on certificates of analysis issued by the manufacturer or trader, or on the results of confirmatory testing done locally by the manufacturer of the pharmaceutical preparation. When such confirmatory testing is done locally, the size of the consignment is of importance as in most cases raw materials are shipped in a number of containers, not a single one. The risks that may occur here include those due to natural deterioration of the substance, to mix-ups caused by mistakes in labelling of containers or to contamination of the material by foreign substances. Such presence of adventitious impurities may occur by accident or may be intentional.

When assessing the level of risk of an individual substance, numerous factors have to be considered: the stability — intrinsic properties, or improvements made by the use of stabilizers or adequate containers; price of materials — expensive substances are particularly the target of fraudulent activity; and any other possible dangers related to use. The high-risk category also includes such deceptively innocuous substances as polyols (e.g. glycerol), where mix-ups or inept use as excipients have, as already mentioned, been the cause of many tragedies (1).

Requirements concerning production facilities and processes are the subject of recommendations related to good manufacturing practices (GMP). The assessment of risk is also needed here to indicate those elements of the production process where mistakes can have the most harmful consequences. For example, the risks related to mix-ups are the highest during the labelling stage, while the risk of cross-contamination (but also of mix-ups) is highest at weighing areas. Risk assessment should also take into account the type of products that are manufactured in a given production facility.

**Situation of low-income countries**

The existence of countries with insufficient drug regulation is an unfortunate situation which has been deplored by many authors (6). In such countries, the prevention of risks cannot be achieved through local efforts and appropriate strategies have to be developed to draw on outside assistance. This is especially valid in relation to imported pharmaceuticals on which these countries are usually heavily dependent. In the case of donated products, the assurance of quality should be the responsibility of the donor organizations. The use of certificates issued according to WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce is a possible solution and special procedures exist also for assessing the acceptability of vaccines for purchase by United Nations agencies. Unfortunately, low-income countries are also highly vulnerable to risks related to counterfeited products.
Conclusions
Recognition of the risks that may occur in the drug area is fundamental for the establishment of effective preventive strategies. Although some risks are inherent in the utilization of pharmaceutical products, the majority of such risks are avoidable. Drug regulatory authorities need to match control requirements to the available resources. In high-income countries, resources for drug control activities are considerable, hence eventual risks can be effectively kept at a very low level. In other countries, where more limited resources are at the disposal of regulatory authorities, the assessment of risks and designation of high-risk products, areas and situations will be a priority in designating priorities for control measures. WHO recommendations on drug regulatory and control activities should indicate, to the extent possible, the level of risk linked to specific elements and stages of the production and distribution of pharmaceuticals as this could improve the modalities of their implementation in practice.

References
Message to drug regulatory authorities:

Tenth International Conference of
Drug Regulatory Authorities (ICDRA)

The Tenth International Conference of Drug Regulatory Authorities (ICDRA) will be hosted and co-sponsored by the People’s Republic of China (PRC) in collaboration with the World Health Organization from 5-8 November 2001 in Hong Kong, China. The Department of Health of the Government of the Hong Kong Special Administrative Region of PRC is the organizer of the Conference. Information materials and registration form of the 10th ICDRA are available at the website: http://www.mvdmc.com/icdra

Please note that this conference is reserved exclusively for drug regulatory officials from WHO Member States.

The following travel agent has been appointed to handle registration and arrange hotel accommodation for participants. For further information please contact:

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The WHO Model List of Essential Drugs: latest developments

The WHO Model List of Essential Drugs has been successful in establishing and promoting the concept of essential drugs. For more than twenty years, it has served as the gold standard for countries wishing to develop their own lists and has been adapted for use in more than 150 WHO Member States. From a public health perspective, priorities for the pharmaceutical system can be identified through the use of an essential drugs list. For example, national lists are often linked to national standard treatment guidelines used for training of health workers, and can serve as a guide for the procurement of needed drugs, for reimbursement purposes in health insurance schemes and for encouraging local pharmaceutical production.

The WHO Model List has been updated every two years since it was first published in 1977. The current Model List contains a little over 300 active ingredients and is divided into a main list and a complementary list. At the last meeting of the WHO Expert Committee on the Use of Essential Drugs held in November 1999, several recommendations were made concerning the process of updating both the methodology for selecting drugs for inclusion in the Model List and the List itself. These recommendations included linking the selection of drugs on the Model List to standard treatment guidelines developed by WHO. It was also agreed that decisions on selection of essential drugs should be based on properly-identified evidence. It was recommended that the Model List should prioritize those conditions and drugs for which equitable availability and affordability should be ensured before resources are spent on other treatments. A recommendation on the need for more explicit criteria was also made.

Updating and disseminating the WHO Model List of Essential Drugs

As a result of these recommendations, a draft discussion paper “Updating and disseminating the WHO Model List of Essential Drugs: the way forward” was prepared. This was the subject of discussion at an informal consultation held by WHO in March 2001. The discussion paper highlighted various perceived problems.

The range of diseases for which essential drugs are selected is not clear
Some drugs for very rare diseases are included on the Model List, while some second-line drugs for more common diseases are not. For example, should the Model List include essential drugs for cystic fibrosis?

The selection criteria are insufficiently clear
There is much confusion about the extent to which cost, cost-effectiveness and affordability criteria are being used during selection. For example, the decision not to include antiretroviral drugs (ARVs) for HIV/AIDS has provoked global discussion. The Committee had decided not to include ARVs for the treatment of HIV/AIDS because there was insufficient evidence of their long-term effectiveness in resource-poor settings. Others believed that exclusion was based on cost considerations, and have argued that inclusion of ARVs on the Model List would create the necessary pressure to bring prices down.

Selection has been based on experience rather than evidence
In the past, the Committee has taken a decision based on the material presented and on their own professional experience. However, there is no standard format application and no systematic search for and review of evidence prior to submission before the Committee in support of decisions. Furthermore, there is no external review of the Committee’s draft recommendations.

There are discrepancies between the WHO Model List and WHO treatment guidelines
About 250 of the 306 active ingredients on the current Model List are also recommended in various treatment guidelines published by different WHO programmes and departments. There are a few therapeutic categories where no WHO treatment guidelines exist (e.g. cytotoxics, hormones, diagnostic agents and gastrointestinal drugs).
However, 155 drugs recommended in the total body of WHO treatment guidelines are not on the WHO Model List of 1999. If WHO recommends that national essential drugs lists should be based on national treatment choices and guidelines, the WHO Model List could be developed in a similar way.

**Drugs are included for which there is no pharmacopoeial standard, or no supplier**

In 1997, there were several substances on the Model List for which there was no pharmacopoeial standard. Examples are eflornithine hydrochloride, heparin sodium, methylene blue, permethrin and primaquine. There are several drugs on the Model List for which there is only one supplier, or for which the supply of quality products has always been problematic. Examples of such “abandoned” essential drugs are oily chloramphenicol injection, suramin injection, ether and eflornithine.

**The reasons underlying the decisions of the committee are insufficiently recorded**

The reasons for the recommendations of the Committee are summarized in footnotes to the report. However, these extensive footnotes are not reproduced in *WHO Drug Information* or on the WHO Medicines Website (http://www.who.int/medicines), which implies that this information is only available to the public through the Technical Report Series which is published by WHO much later. In addition, notes from earlier meetings are only available through copies of old Committee reports and are in practice difficult to find. Recently, WHO has made a data base of the recorded reasons for recent Committee decisions which is available on request. However, for many earlier decisions no records are available.

**The recommendations of the committee are final and not open for review**

According to the rules and procedures for WHO expert committees, the report of the Committee is prepared and approved before the end of the meeting. There are no provisions for internal and external review of the report or recommendations after the meeting. The Chair of the Committee may decide to omit a statement from the report but may only change the wording on the basis of written agreement by all members. In practice, the recommendations of the Committee and the text of the report are rarely changed after the meeting and are accepted by the Director-General of WHO.

**The official report of the Committee is published late**

Publication of each of the last three official reports in English in the WHO Technical Report Series has taken over a year. As the Committee meets every two years, the report of the previous meeting and the new WHO Model List therefore came out just before the next meeting, which seriously undermines the usefulness of the report and even of the meeting itself. The French, Spanish and Russian translations of the 1997 report came out even later.

In recent years, this problem has partly been solved by publishing the Model List (without notes, and only in English) in *WHO Drug Information* and on the WHO Medicines Website.

**Recommendations from the informal consultation**

A series of questions was presented during the informal consultation in March 2001 and the following recommendations were issued.

1. The definition of essential drugs is still adequate and does not need to change: “Essential drugs are those drugs that satisfy the health care needs of the majority of the population. They should therefore be available at all times in adequate amounts and in appropriate dosage forms, at a price the individual and the community can afford (1).”

2. The WHO Model List should continue to be presented in two levels. The core list should indicate the minimum drug needs for a basic health care system, listing the most cost-effective drugs for priority conditions; while the complementary list should consist of drugs for priority diseases which are cost-effective but not necessarily affordable, or which may need specialized health care facilities, and should include essential drugs for less frequent diseases. The section on reserve anti-infective agents could thus be integrated into the complementary list.

3. The process of updating the Model List should be more systematic and transparent. A revised standardized format for applications should be drawn up, to include a systematic review of comparative efficacy, safety and cost-effectiveness. An external review of these draft applications and systematic

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1 The full list quoted by WHO in 1997 was: asparaginase, dasozin mesilate, eflornithine hydrochloride, heparin calcium and heparin sodium, methylene blue, permethrin, polygeline, potassium ferric hexacyanoferrate, and primaquine.
reviews should be undertaken prior to submitting them to the Expert Committee.

4. The report of the Expert Committee should specify the reasons for the decision, link the drug to the relevant WHO treatment guideline and summarize the evidence. The report and the Model List should be published both electronically and in hard copy.

5. Several sections of the current Model List need to be reviewed systematically and as a whole; this process should be undertaken in close collaboration with the disease programmes concerned, drawing on the expertise of all the relevant WHO Expert Advisory Panels. Development of this process will require several meetings of the Expert Committee over the next two years.

6. An essential drugs library should be created on the WHO Website, which should include at least: summaries of WHO clinical guidelines for priority diseases; the Model List, with reasons for inclusion of drugs, and linked references to systemic reviews; WHO clinical guidelines and cost information; the WHO Model Formulary; and quality assurance information such as Basic Tests, The International Pharmacopoeia and reference standards.

7. The health care industry and patient advocacy groups could contribute to the work of the Expert Committee with relevant technical and other information as needed. Consideration should be given to the question of whether their representatives could attend the meetings of the Committee as observers.

Outline of the review process
The discussion paper with full details of the above recommendations, including the proposed procedures and information requirements, has been issued for wider consultation among WHO Member States and national essential drug programmes, United Nations agencies, the World Bank, members of WHO Expert Advisory Panels, and interested nongovernmental organizations.

All comments will be taken into consideration and the final recommendations will be reviewed by the WHO Global Cabinet later in 2001.

Reference

Sequencing of the Anopheles gambiae genome
Representatives of an international network of Anopheles gambiae researchers and genome sequencing centres met at the Pasteur Institute in Paris in March 2001 and agreed on the general principles and method of operation for sequencing the genome of Anopheles gambiae — the mosquito responsible for the spread of malaria in sub-Saharan Africa — and for making this information freely available through a public data base, together with all ancillary genomic, genetic and biological information concerning the mosquito. The mosquito genome sequence will join those of the Plasmodium parasite and the human host to provide malaria researchers with the opportunity to identify new mechanisms for controlling the malaria disease cycle and transmission of the malaria parasite to its human host. Each year, this cycle results in three hundred million cases of malaria and approximately one and a half million deaths, primarily African children.

The network operates under the auspices of the UNDP/WORLD BANK/WHO Special Programme for Research and Training in Tropical Diseases and includes the Pasteur Institute, the European Molecular Biology Laboratory (EMBL, headquartered in Germany), the University of Notre Dame (USA), the French National Sequencing Center (Genoscope, France), Celera Genomics (USA), The Institute for Genomic Research (TIGR, USA), the Institute of Molecular Biology and Biotechnology (IMBB, Greece), the ONSA network (Sao Paolo, Brazil) and leading mosquito researchers from around the world.

The participating organizations are collaborating in a programme to sequence the entire A. gambiae genome, with the first version to be completed in 2001. The network looks forward to expanding this collaborative approach to the genomic analysis of other Anopheles species that are important malaria vectors in other parts of the world. The French Government has guaranteed financial support for a portion of this international sequencing project and additional funding is being sought from other sources including the National Institute of Allergy and Infectious Diseases, National Institutes of Health (NIH), an agency of the United States Department of Health and Human Services.

The proposed project will sequence the 260 million base pair Anopheles gambiae genome using the “Whole Genome Shotgun” technique perfected by
Celera Genomics. The initial sequencing would be done by Celera Genomics and Genoscope, the French National Sequencing Center and assembled at Celera Genomics while sequence closure and finishing would be provided by Genoscope, The Institute for Genomic Research (TIGR) and others. Sequence annotation would be carried out by participating organizations.

The genome sequencing effort will build on the initial genomic research. Participation of additional agencies, laboratories and sequencing centres to contribute to genome finishing and annotation will be sought. All interested public and private sector parties active in the field of *Anopheles* genomics, are welcome to participate, subject to technical feasibility and quality assurances. The European Union programme for action on HIV/AIDS, malaria and tuberculosis in the context of poverty reduction may also provide support.

Malaria, with one and a half million deaths per year, and 300 million clinical cases in sub-Saharan Africa, is a serious medical, economic and social problem. Rather than decreasing, the incidence of malaria is mounting due to increased insecticide resistance in mosquitoes and drug resistance in the parasites. Malaria spreads when the parasite is passed from an infected person to an uninfected person by the bite of an *Anopheles* mosquito. Control of human exposure to the insect vector has been and continues to be the surest way to control malaria. In sub-Saharan Africa, *Anopheles gambiae* is the major mosquito vector and *Plasmodium falciparum* is the principal malaria parasite. The hope of eliminating malaria through the application of insecticides to destroy the mosquito vector has receded as the mosquito population has become more and more resistant to chemical agents. New methods of controlling the disease vector are needed and the *Anopheles gambiae* genome project is the fastest way to obtain the basic information which, when combined with field research, can lead to control of malaria transmission.

Reference: Dr Ayo Oduola, UNDP/WORLD BANK/WHO Special Programme for Research and Training in Tropical Diseases, World Health Organization, Switzerland. Email: oduolaa@who.ch

### Multilateral Initiative on Malaria: benefits to the global community

Malaria is responsible for enormous disease and economic burdens in malaria-endemic regions. A high percentage of those who die of malaria are African children under the age of five. Unfortunately, cases of malaria are on the rise due to insecticide resistance, antimalarial drug resistance, and environmental changes. Unless new strategies are developed, death and illness due to malaria will increase, and the disease will continue to be a substantial barrier to the economic and social development of malaria-endemic regions as well as a threat to the millions of people who travel to those regions each year.

In 1997, an international alliance of research and public health agencies and African scientists launched the Multilateral Initiative on Malaria (MIM). MIM is stimulating collaborative research to answer the needs of public health programmes in malaria-endemic countries, modernizing communication systems used by the African research community, and strengthening research capacity and human resources where malaria takes its greatest toll — sub-Saharan Africa. MIM supports 23 collaborative malaria research projects between African laboratories that are also in partnership with laboratories in Europe and the United States (1).

MIM will hold its Third MIM Pan-African Conference on Malaria in November, 2002, in Arusha, Tanzania. This conference will bring together malaria researchers who battle *Plasmodium falciparum* malaria, which causes the most severe illness and which is the dominant form of malaria in sub-Saharan Africa. In addition, MIM is organizing a conference to focus on a second form of malaria, *Plasmodium vivax*, in January 2002 in Bangkok, Thailand, together with partners in Asia. *Plasmodium vivax* malaria significantly contributes to malaria morbidity in Africa, Asia, and Latin America. Both conferences will bring together malaria researchers and malaria control experts with the aim of transferring malaria research advances into critically needed control, prevention, and treatment programmes. Malaria research and capacity building in malaria-endemic regions are essential, integrally linked components in an effective approach to addressing malaria.
The Fogerty International Center (FIC) of the National Institutes of Health (NIH) currently serves as the MIM Secretariat (1). NIH, primarily through the National Institute of Allergy and Infectious Diseases (NIAID), supports malaria research to address critical needs related to vaccine development, vector biology and control, health economics, health information systems, and other research areas, while FIC promotes capacity building through its malaria research training programmes for scientists from malaria-endemic countries. In addition to the two international scientific conferences announced today, other activities of the MIM Secretariat at NIH includes:

- Expanding the capabilities of malaria researchers, through the International Malaria Research and Training Program (IMRTP). The scarcity of trained malaria researchers in the regions most severely impacted by the disease is a major impediment to successful malaria research. In 2000, the IMRTP began supporting collaborative training programmes between US institutions and malaria researchers in endemic countries (2).

- Addressing malarial anaemia by fostering research on the interaction between malaria and anaemia. MIM, NIAID, FIC and the National Heart, Lung, and Blood Institute (NHLBI) organized meetings of haematologists, nutritionists, and malaria researchers to discuss these interactions. Subsequently, NIAID and FIC developed a joint research and training programme to support research in malaria-endemic countries on the pathogenesis of severe malarial anaemia (3, 4).

References


2. More information about this programme, which is currently accepting applications, is available on the FIC website at http://www.nih.gov/fic/programs/malaria.html.


4. Information about MIM is available on the MIM Website at http://mim.nih.gov

China revises its pharmaceutical law

The Chinese National People’s Congress adopted a new pharmaceutical law on 28 February 2001 aiming to standardize China’s pharmaceutical drug procurement and distribution system, to further encourage open market competitiveness in the pharmaceutical industry, and to combat drug counterfeiting. The new law provides for stricter controls on price management, manufacturing registration, import inspections, and law enforcement.

A centralized administration will promote a uniform code of conduct for manufacturers and importers and strengthen law enforcement. One of the new changes being introduced is a clear and wide ranging definition of counterfeit drugs. This now includes drugs prohibited by official order, expired drugs, and drugs whose advertised benefits do not reflect their actual efficacy. Drug production and distribution will now be more aggressively managed and the licensing system for manufacturers has been simplified. It is hoped that this will have a positive impact on imported drugs. Although imported drugs must go through new cumbersome approval procedures before being released on the open market, once approved, pharmaceutical companies will enjoy unrestricted access to the Chinese market.

The new legislation cancels batch inspection of drugs except for drugs that will be sold in China for the first time, biological products, and for drugs designated by the State Drug Administration. Importers will now require a registration certificate, import permit, and customs entry permission at a designated port. The new law has also given strong legal powers to drug inspectors based at ports and airports. It is expected that the inspectors to have a strong impact on the legal and illegal drug markets. Routine sample inspections of imported drugs and mandatory inspections will also be clearly delineated under the new law. Previously, manufacturers paid fees for each inspection but new regulations have eliminated the fee paying system for routine inspections. Now, a graded scale of inspection fees will be imposed on manufacturers and importers of drugs and biological products.

Regulatory and Safety Matters

New formulation of DTP vaccine

United States of America — The Food and Drug Administration (FDA) has approved a new, preservative-free formulation for a diphtheria and tetanus toxoid and acellular pertussis (DTaP) vaccine (Tripedia®). The reformulated product contains less than 0.3 µg mercury per dose (as thiomersal), which is less than 5% of the amount of thiomersal in the original version that the FDA approved in 1992.

Although no harmful effects have been reported from thiomersal in vaccines when used at the recommended dosages, Federal public health agencies, the American Academy of Pediatrics, and vaccine manufacturers have agreed to reduce or eliminate its use in vaccines to protect children against the potential cumulative health risks of mercury.

Since 1999, the FDA has approved pediatric formulations of hepatitis B vaccines that contain no thiomersal (Recombivax HB®) or only trace amounts of the ingredient (Engerix B®). Thiomersal-containing Haemophilus influenzae type b conjugate vaccine (HibTITER®) has been replaced by a thiomersal-free, single-dose formulation. With the reformulated DTaP vaccine, all routinely recommended pediatric vaccines in distribution will soon be free of thiomersal or will contain it in only trace amounts.

References

Bupropion safety reminder

United Kingdom — Bupropion (Zyban®) was licensed in June 2000 as an aid to smoking cessation in combination with motivational support in nicotine-dependent individuals aged 18 years or over. The initial dose is 150 mg twice daily. The maximum single dose should not exceed 150 mg and the total daily dose should not exceed 300 mg.

It is estimated that approximately 276 000 patients have received bupropion in the United Kingdom in the first six months of marketing. A total of 3457 reports of suspected adverse reactions have been received. The most frequently reported reactions include:

- CNS reactions (e.g. insomnia, dizziness, depression, tremor, anxiety, agitation); and
- skin and hypersensitivity reactions (urticaria, rash, pruritus).

Other reported recognized reactions include angioedema, chest pain, increased blood pressure, erythema multiforme and Steven-Johnson syndrome.

It is important to note that the reactions are suspected and may relate to other factors. Eighteen reports have had a fatal outcome although the contribution of bupropion is unproven.

Bupropion is associated with a dose-related risk of seizure with an estimated incidence of approximately 0.1% based on doses up to the recommended daily dose of 300 mg. There have been 74 reports in the United Kingdom of seizures suspected as being associated with the use of bupropion.

Bupropion inhibits metabolism of cytochrome P450 2D6. Caution is therefore advised when other medicines predominantly metabolized by these enzymes are co-administered. These include certain antidepressants, antipsychotics, beta-blockers and type 1C antiarrythmics.


Propofol: reactions to long-term high doses

United Kingdom — Propofol (Diprivan®) is a short-acting intravenous anaesthetic also used for sedation of ventilated adults receiving intensive care.
A recently published study (1) suggests an association between long-term high-dose infusion used for sedation and cardiac failure in adult patients with head injuries. Seven patients are described who developed metabolic acidosis, hyperkalaemia or rhabdomyolysis. Similar reports, including hyperlipaemia and hepatomegaly have previously been reported in children administered propofol infusion for sedation in intensive care units (2).

Doctors are reminded that the recommended dose range for sedation (up to 4 mg/kg/hour) should not be exceeded (3).

References

Propofol: not for paediatric use

**United States** — The manufacturer of propofol (Diprivan®) has informed Health Care Providers of the safety concerns of propofol injectable emulsion if used for sedation of intensive care paediatric patients.

Propofol is currently not approved for sedation in intensive care paediatric patients in the USA and should not be used for this purpose.


Leflunomide: hepatic reactions

**European Union** — The Committee for Proprietary Medicinal Products (CPMP) of the European Agency for the Evaluation of Medicines (EMEA) has evaluated reports of serious liver injuries, including hepatitis, hepatic failure and rare cases of acute hepatic necrosis, some with fatal outcome, in patients treated with leflunomide (Arava®). Leflunomide is a disease-modifying antirheumatic drug which inhibits the enzyme dihydro-orotate dehydrogenase and exhibits antiproliferative activity.

Prescribers are reminded that leflunomide should only be prescribed by specialists experienced in the treatment of rheumatoid diseases. The EMEA wishes to draw attention to the following information.

- Leflunomide is contraindicated in patients with impaired liver function.
- Rare cases of severe liver injury, including cases with fatal outcome, have been reported during treatment. Most cases occurred within 6 months of initiation of treatment. Although confounding factors were present in many cases a causal relationship with leflunomide cannot be excluded.
- Concomitant treatment with methotrexate and/or other hepatotoxic medications is associated with an increased risk of serious hepatic reactions.

The full revised product information is available on the EMEA Website (2).

References

Rapacuronium bromide voluntarily withdrawn

**United States of America** — The injectable drug rapacuronium bromide (Raplon®) is being voluntarily withdrawn from the market following reports, five of which were fatal, that the drug may be associated with bronchospasm.

Rapacuronium bromide is used as a muscle relaxant for breathing tube placement and surgery. Other drugs are on the market which may be prescribed for the same purpose. Although the approved labelling does note the occurrence of bronchospasm in a small percentage of clinical trial patients, post-marketing reports indicate that the risk of injury may be greater than suggested.

Levacetylmethadol withdrawn

European Union — The European Agency for the Evaluation of Medicinal Products (EMEA) has issued a public statement regarding the suspension of the marketing authorization for levacetylmethadol (Orlaam®), a long-acting opiate used for the treatment of drug addition.

Levacetylmethadol is known to cause QTc prolongation. Ten cases of life-threatening heart rhythm disturbances have been reported since July 1997. The Committee for Proprietary Medicinal Products (CPMP) has given an opinion, based on a review of risk benefit, that levacetylmethadol should be suspended.

Health professionals involved in the care of patients currently receiving levacetylmethadol have been advised to immediately review patients who should be switched to alternative treatment. It is recommended that methadone should be started on a daily dose of 80% of the levacetylmethadol dose with subsequent adjustments of 5 to 10 mg according to the clinical status of each patient. The initial methadone dose must be given no sooner than 48 hours after the last levacetylmethadol dose. Patients are advised not to stop levacetylmethadol suddenly without seeking medical advice.

Pharmacists have been advised that existing drug supplies should be disposed of in accordance with procedures relating to controlled drugs.


Isotretinoin and depression

Canada — An increasing number of reports suggest a temporal association between isotretinoin (Accutane®) and depression and/or suicidal ideation in young people. As a result, additional information is being provided to patients and the safety information reinforced.

The majority of patients with severe acne are young people. This group is also at increased risk of depression, suicidal ideation and suicide. However, some young people treated with isotretinoin have been reported with depression which has subsided after discontinuation of isotretinoin therapy. Although a causal relationship has not been established, all patients should be monitored for depression and if symptoms develop during treatment, the drug should be discontinued and the patient referred for appropriate psychiatric treatment if necessary.

Complete information on prescribing Accutane® is available on www.roche canada.com.


New glucose test for adult diabetics

United States of America — The Food and Drug Administration has approved a wristwatch-like device that provides adult diabetics with more information for managing their disease. It is intended for use along with, not as a replacement for, finger-prick blood tests to monitor glucose.

The GlucoWatch Biographer® extracts fluid through the skin by sending out tiny electrical currents. Glucose levels are measured using this fluid every 20 minutes for 12 hours — even during sleep. The device sounds an alarm if the patient’s glucose reaches dangerous levels.
Clinical studies conducted by the manufacturer show that GlucoWatch® measurements are generally consistent with the results from traditional finger-prick blood tests. However, up to 25% of the time the results differed by more than 30% and sometimes gave erroneous readings. The GlucoWatch also caused mild to moderate skin irritation in at least 50% of patients. Because of this potential for error, patients should never use an individual GlucoWatch® reading alone to make changes in insulin doses. The device has not been tested in children.


Anti-inflammatory analgesics: hepatic reactions

Finland — Liver damage caused by anti-inflammatory analgesics is very rare and the incidence of symptomatic liver damage is estimated to be less than 0.05%. However, a symptom-free, mild increase in hepatic enzymes is more common and may occur in as many as 5–15% of patients. The frequency and pattern of liver damage varies between the different anti-inflammatory analgesics and damage is classified as hepatocellular, cholestatic or a mixture of these.

The mechanisms of liver damage caused by anti-inflammatory analgesics are not well known. The reactions may be idiosyncratic, host-dependent and lacking precise correlation with the dose. The damage may be caused by a reactive/toxic metabolite formed from the drug. Sometimes the liver damage may be associated with symptoms indicative of a hypersensitivity reactions (e.g. fever, eosinophilia, rash, arthralgia).

The register of adverse reactions maintained by the National Agency for Medicines has received a total of about 15 200 reports between 1973 and November 2000 concerning suspected adverse reactions in association with the use of drugs. About 1000 (6.6%) of these reports involved a variety of effects on the liver. A total of 59 cases have been reported in association with the use of anti-inflammatory analgesics. The majority of cases only involved a change in liver function tests.


Gentamicin ear drops: ototoxicity

Canada — The Canadian Adverse Drug Reaction Monitoring Program (CADRMP) warns that aminoglycoside ear drops can cause ototoxicity when used in patients with tympanic membrane perforation.

Between 1981 and October 2000, the CADRMP received 18 reports of suspected ototoxicity associated with use of gentamicin + betamethasone (Garasone®) ear drops in patients with tympanic membrane perforation or tympanoplasty tubes; 16 of these reports involved vestibular disorders and 2 involved hearing loss. At the time of reporting, 15 patients had not recovered from their ototoxicity. In addition to these 18 reports, the CADRMP has received 1 report of dizziness and vertigo associated with use of gentamicin ear drops and another report of temporary hearing loss in a patient with Ménière disease following treatment with gentamicin ear drops and high-dose infusion. The CADRMP reminds prescribers that the labelling was changed in 1996 to limit the indications and clinical uses, to expand the contraindications to include patients with absent or perforated tympanic membranes, and to recommend patient monitoring during treatment.


Tetracycline and benign intracranial hypertension

New Zealand — Benign intracranial hypertension (BIH) is a rare but potentially serious condition. BIH has been documented in association with a variety of medications, particularly the tetracyclines.

The New Zealand Centre for Adverse Reactions Monitoring (CARM) has received its second report of benign intracranial hypertension (BIH) related to use of minocycline involving a 14-year old girl who was being treated for acne. Other prescribed medicines were fluticasone and salbutamol inhalers. The patient presented with headache unrelieved by analgesics, and had intermittent vomiting. On admission to hospital she suffered from slurred speech, reduced sensation and left sided weakness, with mild lateral rectus palsy on the right. Minocycline, which had been taken for thirteen days, was discontinued. A diagnosis of hemiplegic
migraine was made, and she recovered. The headache then recurred after restarting minocycline. Papilloedema was observed and the diagnosis of benign intracranial hypertension (with hemiplegic migraine) was made. Treatment included acetazolamide. The patient had not fully recovered at the time of reporting.

Physicians should regularly enquire about headache in patients receiving tetracycline therapy in view of the potential risk of benign intracranial hypertension (BIH). BIH has been reported in association with a variety of medications, particularly the tetracyclines and minocycline is the agent most frequently cited. The lipophilic properties of minocycline may be an explanation for the higher number of reported cases.

If drug-induced BIH is suspected, the implicated drug should be discontinued. Tetracyclines should not be prescribed concomitantly with retinoids (e.g. isotretinoin), another drug class associated with BIH.


Ergotamine and erythromycin interaction

Australia — Ergotism is manifested by symptoms and signs of peripheral ischaemia due to constriction of vascular smooth muscle caused by direct action of an ergot derivative. Headache, intermittent claudication, muscle pain, numbness, coldness and pallor of the extremities may occur, and gangrene has been reported. Ergotism is usually associated with excessive dosing of ergot preparations but has also been reported with normal doses of ergotamine preparations when there was concomitant use of macrolides (particularly erythromycin). The mechanism of the interaction is not established but may involve an inhibition of ergotamine metabolism or an increased gut absorption resulting in an increase in serum ergotamine concentration.

In recent years, the Australian Adverse Drug Reactions Committee (ADRAC) has received reports of ergotism arising from the combination of ergotamine with ritonavir and verapamil and has noted published reports of similar interactions with HIV protease inhibitors, particularly ritonavir (1, 2). These reports suggest that the basis of the interaction is inhibition of either cytochrome P4503A4 in the liver or gut P-glycoprotein with subsequent increase in ergotamine concentrations. As most inhibitors of CYP3A4 also inhibit P-glycoprotein, the concomitant use of erythromycin and other known inhibitors of CYP3A4 with ergotamine preparations should be avoided.

References:

Celecoxib and warfarin interaction

Australia — Since the introduction of celecoxib (Celebrex®) onto the market in October 1999, the Australian Adverse Drug Reactions Committee (ADRAC) has received 2218 reports of suspected adverse drug reactions. Of these, 21 cases describe an increase in the INR of patients on treatment with warfarin. In the 16 cases where the value of the INR was specified, it rose from a stable value of around 2.0 to a peak ranging from 4.2 to 12.2 (median: 5.3). In two other cases the INR was described as “high” and “very high”. While most of the reports did not describe complications, bleeding was reported in 6 cases. These included severe oral bleeding, intracranial haemorrhage, epistaxis and gastrointestinal haemorrhage. In most cases, the problem occurred within two weeks of the addition of celecoxib. Of the patients in whom the outcome was known, all recovered after withdrawal of celecoxib and, in some cases, withholding or reducing the dose of warfarin.

In addition to these 21 cases, there have been 11 cases of bleeding in patients taking concomitant celecoxib and warfarin. These reports described purpura (3 cases), gastrointestinal haemorrhage
(2), haematuria (1), haematemeses (1), melaena (1), subdural haematoma (1), unspecified haemorrhage (1) and stroke (1). There was no reference to the INR in these reports except for one in which the INR was reported as unchanged. It is not clear in these cases whether the bleeding was the result of an interaction, an additive effect, an effect of celecoxib alone, or unrelated to the use of celecoxib.

The product information for celecoxib states that in postmarketing experience, bleeding events have been reported, predominantly in the elderly, in association with increases in prothrombin time in patients receiving celecoxib concurrently with warfarin. In the cases of increased INR and bleeding reported to ADRAC, 5 of the 26 patients in whom the age was stated were less than 50 years old.

The product information also describes a study in healthy volunteer subjects given 2 mg to 5 mg warfarin daily in whom celecoxib had no effect on the prothrombin time. However, since warfarin is metabolised mainly by CYP2C9 and this enzyme can be inhibited by celecoxib, it is possible that in some individuals, inhibition of CYP2C9 may be significant, producing higher blood concentrations of warfarin. There have been two recent publications describing this interaction. (1, 2)

References

Cerivastatin: rare effect of rhabdomyolysis

Australia — Cerivastatin (Lipobay®) is the fifth of the HMG-CoA reductase inhibitors (statins) to be marketed in Australia. Rhabdomyolysis is a known but rare effect of the statins and is more likely to occur when a fibrate is taken concomitantly. Its occurrence in association with cerivastatin appears greater than with other statins. Up to January 2001, the Australian Adverse Drug Reactions Committee (ADRAC) had received a total of 95 reports associated with cerivastatin, of which 17 (18%) have described rhabdomyolysis. This can be compared with the other statins for which the percentages range from 0.3 to 1.2%.

The 17 cases of rhabdomyolysis associated with cerivastatin occurred from just over a week to 18 months after the introduction of cerivastatin but most occurred in the first month of therapy. Seven of the 15 cases in which the dose was stated occurred with daily dosages of 400 micrograms or greater and two cases occurred shortly after the dose was increased to 800 micrograms daily.

Of particular interest is the fact that 10 of the 17 patients were also taking gemfibrozil. The sponsor has made the concomitant use of cerivastatin and gemfibrozil a contraindication. ADRAC wishes to alert prescribers to the possibility of rhabdomyolysis with all statins. Cerivastatin should not be used in combination with gemfibrozil.


SSRIs and increased ocular pressure

Australia — From November 1972 to January 2001, the Australian Adverse Drug Reactions Committee (ADRAC) had received 92 reports of raised ocular pressure. Since 1992, there have been 11 reports implicating selective serotonin reuptake inhibitors (SSRIs) involving sertraline (4 reports), fluoxetine (3), paroxetine (3) and citalopram (1). Ages of patients ranged from 32 to 70 years. Onset generally occurred within 6 months of commencing the SSRI but ranged from one week to 5 years. In 2 cases, the SSRI may have aggravated pre-existing glaucoma. In one case, the intraocular pressures, which had previously been stabilized with treatment, almost doubled. Presentations consisted of asymptomatic increases in intraocular pressure noted on routine testing (6 cases), eye pain (2 cases), and blurred vision (3 cases). At the time of reporting, 5 patients had not recovered and the outcome remained unknown for the other 6.

Amfepramone: new cases of primary pulmonary hypertension

Belgium — The Belgian Centre for Pharmacovigilance has recently been informed by a university hospital of the diagnosis of 9 cases of primary pulmonary hypertension (PPH) associated with previous use of amfepramone (diethylpropion) with or without fenfluramine or phentermine. This report has been triggered by the re-authorization of amfepramone in Belgium, and the prolongation of this authorization for a period of 12 months on 27 November 2000. In three of the nine cases, amfepramone was the only risk factor identified.

The Centre considers that this information is highly relevant to the other countries in the world where amfepramone is still marketed and cases show that primary pulmonary hypertension (PPH) can also occur with previous use of amfepramone. In Belgium, the decision to re-authorize amfepramone and other related anorectic agents will be re-assessed.

Reference: EU Rapid Alert, 6 February 2001, Belgian Centre for Pharmacovigilance, Brussels.

Bufexamac and contact eczema

Germany — The Drug Commission of the German Medical Profession has issued a cautionary statement concerning bufexamac, an anti-inflammatory agent used mainly for topical use. Initially, bufexamac was indicated for the relief of skin inflammation due to endogenous eczema (neurodermatitis) and chronic eczema. Subsequently, bufexemac was indicated as a substitute for glucocorticoid therapy to treat atopic dermatitis, but it was also used for the treatment of eczema of various types such as congestion dermatitis in Status varicosus, perianal eczema due to haemorrhoids, and undetermined dermatoses.

It has been known for some time that bufexamac can provoke contact dermatitis. Since 1987, 25 cases have been published in the literature. Such cases of contact eczema have often persisted for several months, sometimes because the symptoms were erroneously attributed to eczema. Since the allergic potential of bufexamac was often not suspected, its extent was not recognized since these allergies were always considered as rare. In recent years, not only spontaneous reports but also the results of epidemiological studies have given an indication of the number of cases of allergy due to bufexamac.

Data collected from 14 dermatological clinics (showing a rate of 1.7% per 8,163 patients) suggest that bufexamac allergy has been very much under-rated and under-reported and that the real figure could be some 10 200 cases a year, or in the worst case, from 28 333 to 68 000 cases.

It has been concluded that bufexamac can itself provoke contact eczema. Since this substance is indicated for skin diseases which are deceptively similar to the adverse reactions there is a real danger that bufexamac allergy may not be recognized. For indications such as congestion dermatitis or perianal eczema, available therapy should be used that is indicated for the causative underlying affliction. Before making a critical assessment of bufexamac-containing topical products, alternative eczema therapies should be considered. In therapy-resistant eczemas which have been treated with bufexamac, the causative role of the active pathogen may also be important.


Droperidol: prolongation of the QT interval

United Kingdom — The Medicines Control Agency (MCA) has issued a safety notice concerning droperidol (Droleptan®) informing health professionals of the decision of the manufacturer to discontinue medicinal products containing droperidol from 31 March 2001. This action has been taken by the company following an extensive risk-benefit assessment. The company concluded that the oral formulations should be discontinued to prevent use in chronic conditions and that the injectable form was no longer commercially viable. The MCA had raised concerns about the potential effect of droperidol on the cardiac QT interval and requested a risk-benefit assessment.

Droperidol is currently indicated for use in psychiatry to calm manic agitation. The injection is also indicated for use in anaesthesia in neuroleptanalgesia, for premedication, post-operative nausea and vomiting, and for treatment of chemotherapy-induced nausea and vomiting.
Prescribers are advised as follows:

- Existing patients currently receiving droperidol as a therapy should be recalled for review by their psychiatrist and switched to an alternative treatment.

- No patient should have droperidol stopped until a suitable alternative treatment plan has been identified.

- Droperidol therapy should be tapered off through a stepwise reduction over a period of one to two weeks whilst replacement antipsychotic therapy is initiated.


Mofezolac: revised data sheet

Japan — Mofezolac (Disopain®) was approved in July 1994 as a nonsteroidal anti-inflammatory analgesic agent which inhibits prostaglandin synthesis.

The data sheet has now been revised to include gastrointestinal haemorrhage, abnormal hepatic function, jaundice and thrombocytopenia as serious adverse reactions. In addition, the contraindications have been extended to include patients with serious hepatic disorders, and the precautions extended to cover patients with, or with a history of, hepatic disorders.

Fifteen cases of gastrointestinal haemorrhage, five cases of abnormal hepatic function and five cases of thrombocytopenia have been reported to the Ministry of Health, Labour and Welfare. A causal relationship between mofezolac and these reactions could not be excluded.


Monoethanolamine oleate: revised data sheet

Japan — Monoethanolamine oleate (Oldamin® Injection) was approved in June 1996 for haemostasis in oesophageal varices, haemorrhage and sclerosis in oesophageal varices.

The contraindications have recently been extended to include patients with haemorrhage due to gastric or duodenal ulcer, or gastric erosion. The section on other adverse reactions was also previously revised to include haemorrhagic gastritis and haemorrhage due to gastric/duodenal ulcer.

Recently, four cases of gastric ulcer have been reported in association with the use of monoethanolamine oleate for which a causal relationship could not be excluded. The Ministry of Health, Labour and Welfare has therefore directed the licence holder to include gastric ulcer in the section on serious adverse reactions.


Rivastigmine: revised product information

United States of America — The manufacturer of rivastigmine (Exelon®), indicated for Alzheimer disease has informed health professionals of recent changes to the prescribing information. These changes provide guidelines for reinitiating therapy in patients who have interrupted treatment with rivastigmine in order to reduce the risk of severe vomiting. (1)

There is limited experience related to restarting rivastigmine after an interruption in therapy at doses higher than the recommended starting dose. However, to reduce the possibility of severe vomiting in patients who have interrupted therapy for longer than several days, treatment should be reinitiated with the lowest daily dose. Patients should then be titrated back to their maintenance dose as described in the product information. There has been one post-marketing case of severe vomiting with oesophageal rupture reported to have occurred after reinitiation of treatment at an inappropriate single dose of 4.5 mg following interruption of treatment for eight weeks (2).

References


Sarpogrelate: revised data sheet

Japan — Sarpogrelate was approved in July 1993 (Anplag®) and March 1999 and is indicated as a platelet aggregation inhibitor to improve peripheral circulation in the treatment of ischaemic symptoms observed in chronic arterial obstruction.

At the time of its approval, gastrointestinal haemorrhage associated with the use of sarpogrelate was included in the section on other adverse reactions. In May 1996, haematemesis, epistaxis and thrombocytopenia were added to the same section.

With respect to hepatic function disorders, this section was extended to include hepatic disorders and increased gamma-GTP in May 1996 and June 1998, respectively.

Reports of cerebral haemorrhage (4 cases), gastrointestinal haemorrhage (2), thrombocytopenia (5) and hepatic dysfunction (6) have been received in association with sarpogrelate. Because causality could not be excluded, the Ministry of Health, Labour and Welfare directed the licence holder to establish a new section in its package insert on serious adverse reactions to include cerebral haemorrhage, gastrointestinal haemorrhage, thrombocytopenia, abnormal hepatic function and jaundice.


Spontaneous monitoring systems are useful in detecting signals of relatively rare, serious and unexpected adverse drug reactions. A signal is defined as "reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously. Usually, more than a single report is required to generate a signal, depending upon the seriousness of the event and the quality of the information". All signals must be validated before any regulatory decision can be made.
ATC/DDD Classification

ATC/DDD methodology: a country perspective

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An interest in drug utilization in both scientific and governmental circles has developed as a result of the rapid increase in drug consumption over the last 30 years. In order to measure drug use, it is important to have both a classification system and a unit of measurement. Medicinal products can be classified using different methods, either in alphabetic order, by manufacturer, or by diseases treated. Different systems have been used at different times and in different countries but the most important contribution has come from the Drug Utilization Research Group (DURG) which has carried out international drug utilization research.

The first studies on drug consumption undertaken in the mid–1960s showed great differences between population groups. The most important result of these studies was consensus that an internationally accepted classification system of medicinal products was needed. By modifying and extending the existing classification system set up by the European Pharmaceutical Market Research Association (EPhMRA), the Norwegian Medicinal Depot developed a system known as the Anatomical Therapeutic Chemical (ATC) classification. At the same time, the defined daily dose (DDD) as a unit of measurement in drug utilization studies was also established. Today, the WHO Collaborating Centre for Drug Statistics Methodology in Norway collaborates with the WHO International Working Group for Drug Statistics Methodology in determining ATC/DDD classification.

The ATC/DDD system in Estonia

The ATC/DDD system is implemented in Estonia and is used for different regulatory and scientific purposes.

Estonia is situated in the North-eastern part of Europe and is the smallest of the three Baltic countries with a population of 1.45 million. In 1991, Estonia re-established its independence after being part of the Soviet Union for 50 years. The requirements and rules for medicinal products were controlled during that period by the central government and were similar for all Soviet republics. Before 1991, all pharmacies, wholesalers and manufacturers were 100% state owned and purchases and distribution of medicines were centralized. During this period, the assortment of medicinal products was limited and trade names mimicked the name of the active substance. As the manufacturing licence of each medicinal product was owned by the State, products of different manufacturers carried one trade name. There was no standardized classification of medicinal products at that time. Products were classified according to alphabetic order, therapeutic groups, chemical structure, or sale and storage conditions.

During the early years of Estonia’s independence, major reforms were carried out in the health care sector. The decision was made for Estonia to develop its own system for the regulation of medical products modelled on those developed and operated by other Nordic countries. The Estonian State Agency for Medicines (SAM) was established in 1991 and began with only six employees. The main tasks of the Agency were to grant marketing authorizations and import/export licences, and carry out inspection of wholesalers, pharmacies and manufacturers. As retail and wholesale enterprises were privatized, the assortment of medicinal products broadened. A new system of classification was needed but financial and human resources were scarce. The ATC classification was chosen as a solution since it was considered to be easy to understand, to have a reasonable structure, and the only expense was the price of the codebook. Furthermore, it was widely used in neighbouring countries and was recommended by WHO.

To introduce the concept, ATC codes were inserted into the marketing authorization application and, to promote the use of the classification by wholesalers, the codes were attached to the import/export certificates. Lists of authorized products including the ATC codes were published in the national pharmaceutical literature. New regulations for the Wholesale Trade of Medicinal Products included
the requirement to use the ATC classification in wholesale activities.

However, several problems arose. Firstly, the ATC classification had been created to cover medicinal products used in Northern Europe and medicinal products manufactured in Russia and other post-soviet countries and used in Estonia in the early 1990s contained active ingredients not included in the ATC classification. To overcome this discrepancy, new ATC codes were created for local use. Active ingredients were classified according to therapeutic groups and chemical structure and a fifth level number commencing at 80 was created. Products containing more than one active ingredient were not listed in the original classification which led to problems in the identification of active ingredients of medicinal products. As different combination products containing only one similar active ingredient might have the same ATC code, special local ATC codes were created for combinations. All active ingredients were listed, and a unique ATC code was created for the different combinations.

The WHO International Working Group on Drug Statistics Methodology publishes the ATC classification once a year in January. There are often changes to the classification – ATC codes of some active ingredients are different from the previous versions. In consequence, two ATC codes are used during a certain period, which creates double classification with difficulties in reporting the data. To make the introduction of the national system easier, the decision was made to introduce these changes only once every 4 years. The ATC codes of 1994 were therefore not used until 1998.

Use of the ATC/DDD system
The ATC system can be used for many purposes in combination with the defined daily dosages (DDD). The defined daily dosages were developed as a tool for presenting drug consumption figures and have been used for many years in drug utilization studies where they are useful for both national and international comparisons of drug consumption and the evaluation of long-term trends in drug use (2). Drug consumption figures serve as a basis for the identification and evaluation of factors influencing the level of drug use. Drug consumption estimates have typically been based on sales data, which do not reflect the actual use of drugs, although for the purposes of comparing countries and looking for trends, sales statistics can provide reliable information.

Routinely performed drug utilization studies are considered to be useful in determining drug policies and in evaluating the quality of pharmacotherapy. Mapping of drug use patterns can be used to identify excessive or inadequate use of medicines. Another important goal of drug utilization studies is to indicate areas where education and/or information are needed in order to improve prescribing and use of drugs.

Drug statistics in Estonia
By the end of 1994, most wholesalers were using the ATC classification, which enabled the SAM to start compiling national drug consumption statistics based on the ATC/DDD system. All wholesalers had to report their sales twice a year to the SAM according to the Procedures for Wholesale Trade of Medicinal Products, valid since 1994. The structure of the sales data was also described in the Procedures. There were 25 licensed medicinal product wholesalers in Estonia in 1994. Since most of them were not able to report their sales electronically, a lot of work had to be completed before summarized statistics could be compiled.

The first Estonian Statistics on Medicines publication was based on wholesalers’ reports for the year 1994. National consumption statistics were expressed as the number of DDDs per 1000 inhabitants per day (DDD/1000/day). Drug consumption expressed in this way can be used to gain a rough estimate of the number of patients exposed to a given drug. The drug consumption statistics were published both in the local language and English to permit international comparison. The DDD methodology correctly describes differences in levels of drug use and choice of drugs. The number of DDDs per 1000 inhabitants per day has been used to measure and document the difference between national and international use of various drugs.

Comparison of drug consumption
Comparison with the data obtained with other Nordic Countries only shows big differences in some therapeutic groups. For example, the use of beta-blockers, anticoagulants and inhalation anti-asthmatic drugs was considerably less frequent compared to the Nordic Countries. Many of the new groups of effective drugs well known in Nordic Countries were used in modest quantities, if at all (for example, antihypertensives, Figure 1). On the other hand, several drugs were widely used in Estonia although they were not considered to be the drugs of choice.
in the Nordic Countries because of their high risk/benefit ratio. As shown in Figure 1, the consumption of antihypertensives in Estonia was compared to the use of the same drugs in Finland and Sweden. In 1994, the most used medicines for treatment of hypertension in Estonia were central adrenergic agents (mostly reserpine), which were no longer actively used in other Nordic countries. The use of antihypertensive drugs in Estonia doubled during the period 1995–1998, but was still lower than in Finland and Sweden in 1998 although there are no data to indicate that the incidence of hypertension is lower in Estonia than in other Nordic countries. Beta-blockers, ACE-inhibitors and calcium-channel blockers had already replaced the older antihypertensive agents.

Annual drug consumption data
Once the national drug use patterns are known, utilization data should be monitored over time, documenting the changes and evaluating the patterns by relevant comparisons. Estonian drug consumption data have been published annually since 1994. The complete data were made available a year later.

As the medicinal products market develops, the statistics available a year later are no longer up to date. As a result, a more timely system had to be developed. In co-operation with wholesalers, it was decided that the SAM would create new software and wholesalers would present data both in monetary value and by volume units quarterly. The aim of the SAM in developing the new programme was to summarize, correct and analyse wholesaler’s data and create statistical reports in different formats.

The new software was introduced at the beginning of 1999 and the wholesale data of 1998 were collected. The software is able to create a variety of different reports quarterly and makes it possible to compare drug consumption and expenses. Some of the reports are available on the SAM web-side at http://www.sam.ee.

Thus, the possibilities of drug utilization studies have been extended, and studies can be carried out in a more timely manner. Quarterly data of drug consumption is available in ATC/DDD format and also in monetary values. The statistics based on

Figure 1. Antihypertensives (expressed as DDD/1000/day)
ATC/DDD can also provide data about the sale of prescription-only medicinal products or over-the-counter (OTC) products, differentiation between retail pharmacies or hospital sales, consumption of medicinal products with marketing authorizations and products used on a named-patient basis.

Regularly obtained drug consumption data can be used for evaluating the influence of different health policy decisions. For example, the importation of medical products containing phenacetin was not allowed in Estonia as of 1997 because of the adverse reaction profile. As a consequence, the use of phenacetin decreased and the consumption of ibuprofen as an alternative OTC analgesic increased very rapidly.

Since 1999, medicinal products containing metamizole were added to the list of prescription-only medicines because of a high risk of serious adverse reactions. Enteral metamizole was widely used in Estonia as an OTC drug and was one of the most popular analgesics. The use of tablets containing metamizole has decreased in 2000 compared to 1999.

The present drug reimbursement scheme based on obligatory patient co-payment was introduced in Estonia in 1993. The drug consumption data of 1994 and 1995 were able to show the impact of the new system, although it was very difficult to explain why the use of prescription only medicines (covered by at least 50% reimbursement) increased more slowly than the use of OTC products.

Drug utilization monitoring has been helpful in follow-up of all changes in the list of reimbursement products, e.g. to evaluate the validity of the assumptions made by the authorities before the change was introduced. Therefore, data from drug utilization studies can be used to measure the effects of drugs on overall health care costs and resource consumption. These data are fundamental to pharmacoeconomic evaluation as they can provide real-life estimates of drug use prevalence, effectiveness, compliance and safety.

Data on the use of drugs have been regularly considered when taking decisions on regulatory matters, in reimbursement policy, in teaching and in the development of formularies. As an example, the use of morphine and other opiates is relatively low.

Figure 2. Morphine (expressed as DDD/1000/day)
in Estonia, but has increased year by year. During the Soviet period, morphine was prescribed for cancer pain only for terminally ill patients and administered mainly by injection. There have been a lot of different workshops and meetings for doctors explaining the need for narcotic analgesics to provide better control of cancer pain. As a result, the consumption of morphine has increased approximately five times and half of the morphine used in 2000 was administrated enterally or rectally (Figure 2). Correct statistics are vital in identifying problem areas and following-up the impact of interventions.

Conclusion

• The ATC classification is essential to drug utilization studies and to support regulatory decisions, reimbursement policy, under- and postgraduate teaching, and in the development of formularies.

• The ATC classification of medicinal products is simple to use.

• Implementation of a classification system on a national basis requires more time and dedication than financial resources.

• The ATC/DDD system provides the means to create national statistics, which can be compared historically with other countries.

References


International Nonproprietary Names for Pharmaceutical Substances (INN)

RECOMMENDED International Nonproprietary Names (Rec. INN): List 45

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 RECOMMENDÉES (DCI Rec): Liste 45


Denominaciones Comunes Internacionales para las Sustancias Farmacéuticas (DCI)

Denominaciones Comunes Internacionales RECOMENDADAS (DCI Rec.): Lista 45

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.
Latín, inglés, francés, español:

**Recommended INN**  Chemical name or description; Molecular formula; Graphic formula

**DCI Recomandée**  Nom chimique ou description; Formule brute; Formule développée

**DCI Recomendada**  Nombre químico o descripción; Fórmula empírica; Fórmula desarrollada

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**adekalantum**

- adekalant  
  tert-butyl 7-\{(S)-3-(p-cyanophenoxy)-2-hydroxypropyl\}-3,7-diazabicyclo[3.3.1] nonane-3-carboxylate

- adékalant  
  7-\{(2S)-3-(4-cyanophénoxy)-2-hydroxypropyl\}-3,7-diazabicyclo[3.3.1] nonane-3-carboxylate de 1,1-diméthyléthyle

- adecalant  
  7-\{(S)-3-(p-cianofenoxi)-2-hidroxipropil\}-3,7-diazabiciclo[3.3.1]nonano-3-carboxilato de terc-butilo

- 
  C_{22}H_{31}N_{3}O_{4}

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**alemtuzumabum**

- alemtuzumab  
  immunoglobulin G 1 (human-rat monoclonal CAMPATH-1H γ1-chain anti-human antigen CD52), disulfide with human-rat monoclonal CAMPATH-1H light chain, dimer

- alemtuzumab  
  immunoglobuline G1 anti-(antigène CD52 humain) (chaîne γ1 de l’anticorps monoclonal de rat CAMPATH-1H humanisé), dimère du disulfure avec la chaîne légère de l’anticorps monoclonal de rat CAMPATH-1H humanisé

- alemtuzumab  
  inmunoglobulina G 1 anti-(antígeno humano CD52) (cadena γ1 del anticuerpo monoclonal hombre-rata CAMPATH-1H), dímero del disulfuro con la cadena ligera del anticuerpo monoclonal hombre-rata CAMPATH-1H
aliskirenum
aliskiren  (2S,4S,5S,7S)-5-amino-N-(2-carbamoyl-2-methylpropyl)-4-hydroxy-2-isopropyl-7-[4-methoxy-3-(3-methoxypropoxy)benzyl]-8-methyl-nonanamide

aliskirène  (2S,4S,5S,7S)-5-amino-N-(3-amino-2,2-diméthyl-3-oxopropyl)-4-hydroxy-7-[4-méthoxy-3-(3-méthoxypropoxy)benzyl]-8-méthyl-2-(1-méthyléthyl)=nonanamide

aliskireno  (2S,4S,5S,7S)-5-amino-N-(2-carbamoil-2-metilpropil)-4-hidroxi-2-isopropil-7-[4-metoxi-3-(3-metoxipropoxi)bencil]-8-metilnonanamida

C_{30}H_{53}N_{3}O_{6}

amiloxatum
amiloxate  isopentyl p-methoxycinnamate

amiloxate  (E)-3-(4-méthoxyphényl)prop-2-énoate de 3-méthylbutyle

amiloxato  p-metoxicinamato de isopentilo

C_{15}H_{20}O_{3}

bevacizumabum
bevacizumab  immunoglobulin G 1 (human-mouse monoclonal rhuMAb-VEGF γ-chain anti-human vascular endothelial growth factor), disulfide with human-mouse monoclonal rhuMAb-VEGF light chain, dimer

bévacizumab  immunoglobuline G1 anti-(facteur de croissance de l’endothélium vasculaire humain) (chaîne γ1 de l’anticorps monoclonal de souris rhuMAb-VEGF humanisé), dimère du disulfure avec la chaîne légère de l’anticorps monoclonal de souris rhuMAb-VEGF humanisé

bevacizumab  inmunoglobulina G 1 anti-(factor de crecimiento del endotelio vascular humano) (cadena γ1 del anticuerpo monoclonal hombre ratón rhuMAb-VEGF), dímero del disulfuro con la cadena ligera del anticuerpo monoclonal hombre-ratón rhuMAb-VEGF

C_{6638}H_{10168}N_{1720}O_{2108}S_{44}
**biotinum**

*biotin*  
5-[(3aS,4S,6aR)-2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl]pentanoic acid

*biotine*  
acide 5-[(3aS,4S,6aR)-2-oxohexahydro-1H-théno[3,4-d]imidazol-4-yl]pentanoïque

*biotina*  
ácido 5-[(3aS,4S,6aR)-2-oxohexahidro-1H-tieno[3,4-d]imidazol-4-il]pentanoico

C_{10}H_{16}N_{2}O_{3}S

**bivatuzumabum**

*bivatuzumab*  
immunoglobulin G 1 (human-mouse monoclonal BIWA4 \(\gamma\)1-chain anti-human antigen CD44v8), disulfide with human-mouse monoclonal BIWA4 \(\kappa\)-chain, dimer

*bivatuzumab*  
immunoglobuline G1 anti-(antigène CD44v8 humain) (chaîne \(\gamma\)1 de l’anticorps monoclonal de souris BIWA4 humanisé), dimère du disulfure avec la chaîne \(\kappa\) de l’anticorps monoclonal de souris BIWA4 humanisé

*bivatuzumab*  
immunoglobulina G 1 anti-(antigeno humano CD44v8) cadena \(\gamma\)1 del anticuerpo monoclonal hombre-ratón BIWA4), dímero del disulfuro con la cadena \(\kappa\) del anticuerpo monoclonal hombre-ratón BIWA4

**capravirinum**

*capravirine*  
5-[(3,5-dichlorophenyl)thio]-4-isopropyl-1-(4-pyridylmethyl)imidazole-2-methanol carbamate (ester)

*capravirine*  
carbamate de [5-[(3,5-dichlorényl)sulfanyl]-4-(1-méthyléthyl)-1-(pyridin-4-ylméthyl)-1H-imidazol-2-yl]méthyle

*capravirina*  
carbamato (éster) de 5-[(3,5-diclorofenil)tio]-4-isopropil-1-(4-piridilmetil) imidazol-2-metanol

C_{20}H_{20}Cl_{2}N_{4}O_{2}S
capromorelinum

2-amino-N-[(1R)-1-[[3aR]-3a-benzyl-2,3,3a,4,6,7-hexahydro-2-methyl-3-oxo-5H-pyrazolo[4,3-c]pyridin-5-yl]carbonyl]-2-(benzoyloxy)ethyl]-2-methylpropionamide

capromoréline

2-amino-N-[(1R)-2-[(3aR)-3a-benzyl-2-méthyl-3-oxo-2,3,3a,4,6,7-hexahydro-5H-pyrazolo[4,3-c]pyridin-5-yl]-1-[(benzoyloxy)méthyl]-2-oxoéthyl]-2-méthylpropanamidine

capromorelina

2-amino-N-[(1R)-1-[[3aR]-3a-bencil-2,3,3a,4,6,7-hexahidro-2-metil-3-oxo-5H-pirazolo[4,3-c]piridin-5-il]carbonil]-2-(benciloxi)etil]-2-metilpropionamida

\[C_{28}H_{35}N_5O_4\]

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cridanimodum

cridanimod 9-oxo-10-acridanacetic acid

cridanimod acide (9-oxoacidin-10(9H)-yl)acétique

cridanimod ácido 9-oxo-10-acridanacético

\[C_{15}H_{11}NO_3\]

doripenemum

doripenem (+)-(4R,5S,6S)-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-3-[[3S,5S]-5-[[sulfamoylamino)methyl]-3-pyrrolidiny]thio]-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid

doripénem (+)-acide (4R,5S,6S)-6-[(1R)-1-hydroxyéthyl]-4-méthyl-7-oxo-3-[[3S,5S]-5-[[aminosulfonylamino)méthyl]pyrrolidin-3-yl][sulfanyl]-1-azabicyclo[3.2.0]hept-2-ène-2-carboxylique

doripenem ácido (+)-(4R,5S,6S)-6-[(1R)-1-hidroxietil]-4-metil-7-oxo-3-[[3S,5S]-5-[[sulfamoilamino)metil]-3-pirrolidinil]tio]-1-azabicyclo[3.2.0]hept-2-eno-2-carboxilico
**ecraprostum**

**ecraprost**  
butyl (4R,5R)-2,4-dihydroxy-5-[(1E,3S)-3-hydroxy-1-octenyl]-1-cyclopentene-1-heptanoate, 2-butyrate

**écraprost**  
7-[(4R,5R)-2-(butanoyloxy)-4-hydroxy-5-[(1E,3S)-3-hydroxyoct-1-ényl]cyclopent-1-ényl]heptanoate de butyle

**ecraprost**  
2-butirato de (4R,5R)-2,4-dihidroxi-5-[(1E,3S)-3-hidroxi-1-octenil]-1-ciclopenteno-1-heptanoato de butilo

**elarofibanum**

**elarofiban**  
(S)-β-[(R)-1-[3-(4-piperidyl)propionyl]nipecotamido]-3-pyridinepropionic acid

**élarofiban**  
acide (3S)-3-[[(3R)-1-[3-(pipéridin-4-yl)propanoyl]piperidin-3-yl]carbonyl]amino]-3-(pyridin-3-yl)propanoïque

**elarofibán**  
ácido (S)-β-[(R)-1-[3-(4-piperidil)propionil]nipecotamido]-3-piridinapropiónico

\[\text{C}_{28}\text{H}_{48}\text{O}_6\]
ensulizolum
ensulizole
2-phenyl-5-benzimidazolesulfonic acid
ensulizole
acide 2-phényl-1H-benzimidazole-5-sulfonique
ensulizol
ácido 2-fenil-5-bencimidazolsulfónico

\[ \text{C}_{13}\text{H}_{10}\text{N}_{2}\text{O}_{3}\text{S} \]

enzacamenum
enzacamene
(±)-3-\((p\)-methylbenzyldene\)camphor
enzacamène
\((E)-(1\text{RS},4\text{SR})\)-1,7,7-triméthyl-3-(4-méthylbenzylidène)bicyclo[2.2.1]heptan-2-one
enzacameno
1,7,7-trimetil-3-(4-metilbencilideno)biciclo[2.2.1]heptan-2-ona

\[ \text{C}_{18}\text{H}_{22}\text{O} \]

eptaplatinum
eptaplatin
\textit{cis-}\{[4\text{R},5\text{R})-2-isopropyl-1,3-dioxolane-4,5-bis(methylamine)-N,N'[malonato(2-)O,O']platinum

eptplatine
\((\text{SP}-4-2)\)-\{[4\text{R},5\text{R})-2-(1-méthyléthyl)-1,3-dioxolane-4,5-diyl\}bis(méthanamine)-N,N'[propanedioato(2-)O,O’]platine

eptplatino
\textit{cis-}\{[4\text{R},5\text{R})-2-isopropil-1,3-dioxolano-4,5-bis(metilamina)-N,N'][malonato=(2-)O,O’]platino

\[ \text{C}_{11}\text{H}_{20}\text{N}_{2}\text{O}_{6}\text{Pt} \]
**Recommended INN: List 45**

**WHO Drug Information, Vol. 15, No. 1, 2001**

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**ezetimibum**

**ezetimibe**

$$(3R,4S)-1-(p\text{-fluorophenyl})-3\{-[(3S)-3-(p\text{-fluorophenyl})-3\text{-hydroxypropyl}]\-4-(p\text{-hydroxyphenyl})\}2\text{-azetidinone}$$

**ézétimibe**

$$(3R,4S)-1-(4\text{-fluorophényl})-3\{-[(3S)-3-(4\text{-fluorophényl})-3\text{-hydroxypropyl}]\-4-(4\text{-hydroxyphényl})\}2\text{-azétidin-2\text{-one}}$$

**ezetimiba**

$$(3R,4S)-1-(p\text{-fluorofenil})-3\{-[(3S)-3-(p\text{-fluorofenil})-3\text{-hidroxipropil}]\-4-(p\text{-hidroxifenil})\}2\text{-azetidinona}$$

$$C_{24}H_{21}F_2NO_3$$

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**fondaparinuxum natricum**

**fondaparinux sodium**

methyl $\text{O-2-deoxy-6-O-sulfo-2-(sulfoamino)-}$\(\text{-d-glucopyranosyl-}

$$(1\rightarrow4)\text{-O-\text{a-d-glucopyranuronosyl-(1\rightarrow4)O-2-deoxy-3,6-di-O-sulfo-2-(sulfoamino)-\text{-d-glucopyranosyl-(1\rightarrow4)O-2-sulfo-\text{-l-idopyranuronosyl-(1\rightarrow4)2-deoxy-6-O-sulfo-2-(sulfoamino)-\text{-d-glucopyranoside, decasodium salt}}$$

**fondaparinux sodique**

$$O\text{-6-O-sulfo-2-(sulfoamino)-2-désoxy-\text{-d-glucopyranosyl-(1\rightarrow4)-}

O\text{-d-glucopyranuronosyl-(1\rightarrow4)-O-3,6-di-O-sulfo-2-(sulfoamino)-2-désoxy-\text{-d-glucopyranosyl-(1\rightarrow4)O-2-sulfo-\text{-l-idopyranuronosyl-(1\rightarrow4)6-O-sulfo-2-(sulfoamino)-2-désoxy-\text{-d-glucopyranoside de méthyle décasodique}}$$

**fondaparinux sódico**

sal decasódica del $\text{O-2-desoxi-6-O-sulfo-2-(sulfoamino)-\text{-d-glucopiranosil-(1\rightarrow4)-O-\text{b-\text{-d-glucopiranuronosil-(1\rightarrow4)-O-2-desoxi-3,6-di-O-sulfo-2-(sulfoamino)-\text{-d-glucopiranosil-(1\rightarrow4)-O-2-sulfo-\text{-l-idopiranuronosil-(1\rightarrow4)-2-desoxi-6-O-sulfo-2-(sulfoamino)-\text{-d-glucopiranósido de metilo}}$$

$$C_{31}H_{43}N_3Na_{10}O_{49}S_8$$

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38
<table>
<thead>
<tr>
<th>INN: List 45</th>
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<tbody>
<tr>
<td><strong>fosamprenavirum</strong></td>
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<td>fosamprenavir</td>
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<td>fosamprénavir</td>
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<td>fosamprenavir</td>
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<tr>
<td>$\text{C}<em>{25}\text{H}</em>{36}\text{N}<em>{3}\text{O}</em>{9}\text{PS}$</td>
</tr>
</tbody>
</table>

| fosfluconazolum |
| fosfluconazole | 2,4-difluoro-α,α-bis(1H-1,2,4-triazol-1-ylmethyl)benzyl alcohol, dihydrogen phosphate (ester) |
| fosfluconazole | dihydrogénophosphate de 1-(2,4-difluorophényl)-2-(1H-1,2,4-triazol-1-yl)-1-(1H-1,2,4-triazol-1-ylméthyl)éthyle |
| fosfluconazol | dihidrógénofosfato (éster) de 2,4-difluoro-α,α-bis(1H-1,2,4-triazol-1-ilmetil) bencilo |
| $\text{C}_{13}\text{H}_{13}\text{F}_{2}\text{N}_{6}\text{O}_{4}\text{P}$ |

| fosvesetum |
| fosveset | $N$-[2-[bis(carboxymethyl)amino]ethyl]-$N$-[(R)-2-[bis(carboxymethyl)amino]-3-hydroxypropyl]glycine, 4,4-diphenylcyclohexyl hydrogen phosphate (ester) |
| fosveset | 4,4-difenilciclohexilhidrógénofosfato (éster) de $N$-[2-[bis(carboximetil)=amino]jetil]-$N$-[(R)-2-[bis(carboximetil)amino]-3-hidroxipropil]glicina |
**gadofosvesetum**

**gadofosvet**

Trihydrogen [N-[2-[bis(carboxymethyl)amino]ethyl]-N-[(R)-2-[bis(carboxymethyl)amino]-3-hydroxypropyl]glycine 4,4-diphenylcyclohexyl hydrogen phosphato(6-)]gadolinate(3-)

**gadofosvéset**


**gadofosveset**

[4,4-difenilciclohexilhidrógenofosfato de (6-)-N-[2-[bis(carboximeti)]amino]- etil]-N-[(R)-2-[bis(carboximetil)amino]-3-hidroxipropl]glicina]gadolinato(3-) de trihidrógeno

\[
C_{33}H_{44}N_3O_{14}P
\]

**gemtuzumabum**

**gemtuzumab**

Immunoglobulin G 4 (human-mouse monoclonal hP67.6 γ4-chain anti-human antigen CD 33), disulfide with human-mouse monoclonal hP67.6 κ-chain, dimer

**gemtuzumab**

Immunoglobuline G 4 anti-(antigène CD 33 humain) (chaîne γ4 de l’anticorps monoclonal de souris hP67.6 humanisé), dimère du disulfure avec la chaîne κ de l’anticorps monoclonal de souris hP67.6 humanisé

**gemtuzumab**

Inmunoglobulina G 4 anti-(antigeno humano CD 33) (cadena γ4 del anticuerpo monoclonal hP67.6 hombre-ratón), dimero del disulfuro con la cadena κ del anticuerpo monoclonal hP67.6 hombre-ratón
idraparinuxum natricum
idraparinux sodium
methyl O-2,3,4-tri-O-methyl-6-O-sulfo-α-D-glucopyranosyl-(1→4)-O-2,3-di-O-methyl-β-D-glucopyranuronosyl-(1→4)-O-2,3,6-tri-O-sulfo-α-D-glucopyranosyl-(1→4)-O-2,3-di-O-methyl-α-L-idopyranuronosyl-(1→4)-2,3,6-tri-O-sulfo-α-D-glucopyranoside nonasodium

idraparinux sodique
O-2,3,4-tri-O-méthyl-6-O-sulfo-α-D-glucopyranosyl-(1→4)-O-2,3-di-O-méthyl-β-D-glucopyranuronosyl-(1→4)-O-2,3,6-tri-O-sulfo-α-D-glucopyranosyl-(1→4)-O-2,3-di-O-méthyl-α-L-idopyranuronosyl-(1→4)-2,3,6-tri-O-sulfo-α-D-glucopyranoside de méthyle nonasodique

idraparinux sódico
O-2,3,4-tri-O-metil-6-O-sulfo-α-D-glucopiranosoil-(1→4)-O-2,3-di-O-metil-β-D-glucopiranuronosil-(1→4)-O-2,3,6-tri-O-sulfo-α-D-glucopiranosoil-(1→4)-O-2,3-di-O-metil-α-L-idopiranuronosil-(1→4)-2,3,6-tri-O-sulfo-α-D-glucopiranósido de metilo nonasódico

C_{38}H_{55}Na_{9}O_{49}S_{7}

isatoribinum
isatoribine
5-amino-3-(β-D-ribofuranosyl)thiazolo[4,5-d]pyrimidine-2,7(3H,6H)-dione

isatoribine
5-amino-3-(β-D-ribofuranosyl)thiazolo[4,5-d]pyrimidine-2,7(3H,6H)-dione

isatoribina
5-amino-3-β-D-ribofuranosiltiazolo[4,5-d]pirimidina-2,7(3H,6H)-diona

C_{10}H_{12}N_{4}O_{6}S

isatoribine
5-amino-3-(β-D-ribofuranosyl)thiazolo[4,5-d]pyrimidine-2,7(3H,6H)-dione

isatoribina
5-amino-3-β-D-ribofuranosiltiazolo[4,5-d]pirimidina-2,7(3H,6H)-diona

C_{10}H_{12}N_{4}O_{6}S
labradimilum

\[ \text{labradimil} \]

\[ N^2\{(S)\}-2-\{\text{L-arginyl-L-prolyl-trans-4-hydroxy-L-prolylglycyl-3-(2-thienyl)-L-alanyl-L-seryl-L-prolinamido}\}-3-\{(\text{p-methoxyphenyl})propyl\}-L-\text{arginine} \]

\[ N^2\{(2S)\}-2-\{\text{L-arginyl-L-prolyl-}(4R)-4\text{-hydroxy-L-prolyl}\}-\text{glycyl}-\{3\text{-}(\text{thiophén-2-yl})-L-\text{alanyl}\}-L-\text{seryl}-L-\text{prolylamino}\}-3-\{(\text{4-méthoxyphényl})propyl\}-L-\text{arginine} \]

\[ N^2\{(S)\}-2-\{\text{L-arginil-L-prolil-trans-4-hidroxi-L-prolilglicil-3-(2-tienil)-L-alanil-L-seril-L-prolinamido}\}-3-\{(\text{p-metoxifenil})propil\}\text{-arginina} \]

\[ C_{49}H_{75}N_{15}O_{12}S \]

ladirubicinum

ladirubicin

\[(1S,3S)\]-3-acetyl-1,2,3,4,6,11-hexahydro-3,5,12-trihydroxy-6,11-dioxo-1-naphthacenyl 3-(1-azidinyl)-2,3,6-trideoxy-\(4\)-\(O\)-(methylsulfonyl)-\(\alpha\)-\(L\)-lyxo-hexopyranoside \]

ladirubicine

\[(7S,9S)\]-9-acétyl-7-[3-(aziridin-1-yl)-4-\(O\)-(méthylsulfonyl)]-2,3,6-tridésoxy-\(\alpha\)-\(L\)-lyxo-hexopyranosyl\]oxy]-6,9,11-trihydroxy-7,8,9,10-tétrahydrotrécène-5,12-dione

ladirubicina

\[(1S,3S)\]-3-acetil-1,2,3,4,6,11-hexahidro-3,5,12-trihidroxi-6,11-dixo-1-naftacenil 3-(1-aziridinil)-2,3,6-tridesoxi-\(4\)-\(O\)-(metilsulfonil)-\(\alpha\)-\(L\)-lixo-hexopiranósido

\[ C_{29}H_{31}NO_{11}S \]
**lerdelimumab**

**lerdelimumab**

immunoglobulin G4, anti-(human transforming growth factor b2) (human monoclonal CAT-152 γ 4-chain), disulfide with human monoclonal CAT-152 λ-chain, dimer

**lérdelimumab**

immunoglobuline G4, anti-(facteur de croissance transformant humain b2) (chaîne γ 4 de l'anticorps monoclonal humain CAT-152), dimère du disulfure avec la chaîne λ de l'anticorps monoclonal humain CAT-152

**lerdelimumab**

inmunoglobulina G4, anti-(factor b2 de crecimiento transformador humano)(cadena γ 4 del anticuerpo monoclonal humano CAT-152), dimero del disulfuro con la cadena λ del anticuerpo monoclonal humano CAT-152

**levmetamfetaminum**

**levmetamfetamine**

(−)-(R)-N,α-dimethylphenethylamine

**levmétamfétamine**

(−)-(2R)-N-méthyl-1-phénylpropan-2-amine

**levmetanfetamina**

(−)-(R)-N α-dimetilfenetilamina

C_{10}H_{15}N

![Molecular structure of levmetamphetamine](image)

**lixivaptanum**

**lixivaptan**

3′-chloro-5-fluoro-4′-(5H-pyrrolo[2,1-c][1,4]benzdiazepin-10(11H)-ylcarbonyl)-o-toluanilide

**lixivaptan**


**lixivaptán**

3′-cloro-5-fluoro-4′-((5H-pirrolo[2,1-c][1,4]benzdiazepin-10(11H)-ilcarbonil)-o-toluanilida

C_{27}H_{21}ClFN_{3}O_{2}

![Molecular structure of lixivaptan](image)
melevodopum
melevodopa
(-)-3,4-dihydroxy-L-phenylalanine, methyl ester
mélévodopa
(-)-(2S)-2-amino-3-(3,4-dihydroxyphényl)propanoate de méthyle
melevodopa
éster metílico de (-)-3,4-dihidroxi-L-fenilalanina

\[ C_{10}H_{13}NO_4 \]

meradimatum
meradimate
\( p \)-menth-3-yl anthranilate
méradimate
2-aminobenzoate de 5-méthyl-2-(1-méthyléthyl)cyclohexyle
meradimato
antranilato de \( p \)-ment-3-ilo

\[ C_{17}H_{25}NO_2 \]

noretgestrominum
noretgestromin
13-ethyl-17-hydroxy-18,19-dinor-17α-pregn-4-en-20-yn-3-one oxime
noretgestromine
13-éthyl-17-hydroxy-18,19-dinor-17α-prégn-4-én-20-yn-3-one oxime
noretgestromina
13-etil-17-hidroxi-18,19-dinor-17α-pregn-4-en-20-in-3-ona oxima

\[ C_{21}H_{29}NO_2 \]
octinoxatum
octinoxate 2-ethylhexyl \( p \)-methoxycinnamate
octinoxate \((E)\)-3-(4-méthoxyphényl)prop-2-énoate de \((2RS)\)-2-éthylhexyle
octinoxato \( p \)-metoxicinamato de 2-etilhexilo

\[ \text{C}_{18}\text{H}_{26}\text{O}_3 \]

\[ \text{C}_{18}\text{H}_{26}\text{O}_3 \]

octisalatum
octisalate 2-ethylhexyl salicylate
octisalate 2-hydroxybenzoate de \((2RS)\)-2-éthylhexyle
octisalato salicilato de 2-etilhexilo

\[ \text{C}_{15}\text{H}_{22}\text{O}_3 \]

\[ \text{C}_{15}\text{H}_{22}\text{O}_3 \]

opaviralinum
opaviraline isopropyl \((S)\)-2-ethyl-7-fluoro-3,4-dihydro-3-oxo-1(2\( H \))-quinoxalinecarboxylate
opaviraline \((2S)\)-2-étyl-7-fluoro-3-oxo-3,4-dihydroquinoxaline-1(2\( H \))-carboxylate de 1-méthyléthyle
opaviralina \((S)\)-2-etil-7-fluoro-3,4-dihidro-3-oxo-1(2\( H \))-quinoxalina carboxilato de isopropilo

\[ \text{C}_{14}\text{H}_{17}\text{F}\text{N}_2\text{O}_3 \]

\[ \text{C}_{14}\text{H}_{17}\text{F}\text{N}_2\text{O}_3 \]
**opebakanum**

opebakan  132-α-alanine-1-193-bactericidal/permeability-increasing protein (human)

opébakan  [132-α-alanine]-1-193-protéine humaine augmentant la perméabilité et à action bactéricide

opebacán  132-α-alanina-1-193-proteína(humana) bactericida/incrementadora de la permeabilidad


\[
\begin{align*}
V & \text{NPGVVVRIS} \\
F & \text{KIKHLGKGH} \\
S & \text{NAIKISGK} \\
T & \text{NPTSGKPTI} \\
K & \text{IESALRNKM}
\end{align*}
\]

\[
\begin{align*}
G & \text{QLDYASQQ} \\
D & \text{QLPSSQISM} \\
L & \text{NGDLSEIG} \\
S & \text{VSHVISKSK} \\
P & \text{VWLIQLFHK}
\end{align*}
\]

\[
\begin{align*}
Q & \text{KLQKELK} \\
R & \text{IKIPDYSDS} \\
E & \text{VPVPLKSFI} \\
\text{MSIA} & \text{DLKLG}
\end{align*}
\]

**oritavacinum**

oritavacin  (4"R)-22-O-(3-amino-2,3,6-trideoxy-3-C-methyl-α-L-arabino-hexopyranosyl)-\(N^\beta\)-[p-(p-chlorophenyl)benzyl]vancomycin


oritavancina  (4'R)-22-O-(3-amino-2,3,6-tridesoxi-3-C-metil-α-L-arabino-hexopiranosil)-\(N^\beta\)-[p-(p-clorofenil)benzil]vancomicina
ozogamicinum

methyl (1R,4Z,8S,13E)-13-[2-[2-[[p-(3-carbamoylpropoxy)-
8-[[4,6-dideoxy-4-[[2,6-dideoxy-4-S-[4-[[6-deoxy-3-O-methyl-
α-L-mannopyranosyl]oxy]-3-ido-5,6-dimethoxy-o-toluoyl]-4-thio-
β-D-ribo-hexopyranosyl]oxy]amino]-2-O-[2,4-dideoxy-4-((N-ethylacetamido)-
3-O-methyl-α-L-threo-pentopyranosyl]-β-D-glucopyranosyl]oxy]-1-hydroxy-
11-oxobicyclo[7.3.1]trideca-4,9-diene-2,6-diyne-10-carbamate

ozogamicin

[(1R,4Z,8S,13E)-8-[[2-O-[4-(acétylethylamino)-3-O-méthyl-2,4-didésoxy-
α-L-théo-pentopyranosyl]-4-[[4-S-[3-ido-5,6-diméthoxy-2-méthyl-4-[[3-O-
méthyl-6-désoxy-α-L-mannopyranosyl]oxy]benzoyl]-2,6-didésoxy-4-thio-
13-[2-[[3-[[4-(4-amino-4-oxobutoxy)phényl]léthylidène]hydrazino]-1,1-diméthyl-3-oxopropyl]disulfanyl]léthylidène]-1-hydroxy-
11-oxobicyclo[7.3.1] tridéca-4,9-diène-2,6-diyne-10-y]l carbamate de méthyle

ozogamicina

(1R,4Z,8S,13E)-13-[2-[[p-(3-carbamoylpropoxi)-α-metilbencilideno]
hidrazino]carbonyl]-1,1-dimetiletil]ditio]etilideno]-8-[[4,6-didesoxi-
4-[[2,6-didesoxi-4-S-[4-[[6-desoxi-3-O-metil-α-L-manopiranosil]oxi]-3-ido-
5,6-dimetoxy-o-toluoyl]-4-tio-[β-D-ribo-hexopiranosil]oxi]amino]-
2-O-[2,4-didesoxi-4-((N-etilacetamido)-3-O-metil-α-L-threo-pentopiranosil]-
β-D-glucopiranosil ox]-1-hidroxi-11-oxobiclo[7.3.1]trideca-4,9-dieno-
2,6-diina-10-carmamate de metilo
paliperidonum

paliperidone
\((\pm)-3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidino]ethyl]-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one\)

palipéridone
\((9RS)-3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)pipéridin-1-yl]éthyl]-9-hydroxy-2-méthyl-6,7,8,9-tétrahydro-4H-pyrido[1,2-a]pyrimidin-4-one\)

paliperidona
\((\pm)-3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-il)piperidino]etil]-6,7,8,9-tetrahidro-9-hidroxi-2-metil-4H-pirido[1,2-a]pirimidin-4-ona\)

\(C_{23}H_{27}FN_4O_3\)

and enantiomer et énantiomère y enantiómero

pitavastatinum

pitavastatin
\((3R,5S,6E)-7-[2-cyclopropyl-4-(p-fluorophenyl)-3-quinolyl]-3,5-dihydroxy-6-heptenoic acid\)

pitavastatine
acide \((6E)-(3R,5S)-7-[2-cyclopropyl-4-(4-fluorophényl)quinoléin-3-yl]-3,5-dihydroxyhept-6-énoïque\)

pitavastatina
ácido \((3R,5S,6E)-7-[2-cicloclopropil-4-(p-fluorofenil)-3-quinolil]-3,5-dihidroxi-6-heptenoico\)
rimonabantum
rimonabant 5-(p-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-N-piperidinopyrazole-3-carboxamide
rimonabant 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-N-(piperidin-1-yl)-1H-pyrazole-3-carboxamide
rimonabant 5-(p-clofenil)-1-(2,4-diclorofenil)-4-metil-N-piperidinopirazol-3-carboxamida
C25H24FNO4

rostaporfinum
rostaporf lin (OC-6-13) dichtoro[ethyl (18RS, 19SR)-3,4,20,21-tetradehydro-4,9,14,19-tetraethyl-18,19-dihydro-3,8,13,18-tetramethyl-20- phorbinecarboxylato (2-) N23,N24,N25,N26]tin
rostaporfine (OC-6-13)-dichloro[(2RS,3SR)-2,7,12,17-tétraéthyl-3,8,13,18-tétraméthyl-2,3-dihydrocyclopenta[a,f]porphyrine-2'-carboxylato(3-) N21,N22,N23,N24] stannate(2-) d'éthyle
rostaporfina (OC-6-13)-dichloro[(18RS, 19SR)-3,4,20,21-tetradehidro-4,9,14,19-tetraetil-18,19-dihidro-3,8,13,18-tetrametil-20-forbinacarboxilato de etilo (2-) N23,N24,N25,N26]estaño
rosuvastatinum
rosuvastatin
(3R,5S,6E)-7-[4-(p-fluorophenyl)-6-isopropyl-2-(N-methylmethane sulfonamido)-5-pyrimidinyl]-3,5-dihydroxy-6-heptenoic acid

rosuvastatine
acide (3R,5S,6E)-7-[4-(4-fluorophényl)-6-(1-méthyléthyl)-2-[méthyl (méthylsulfonyl)amino]pyrimidin-5-yl]-3,5-dihydroxyhept-6-énoïque

rosuvastatina
ácido (3R,5S,6E)-7-[4-(p-fluorofenil)-6-isopropil-2-(N-metilmetano sulfonamido)-5-pirimidinil]-3,5-dihidroz-6-heptenoico

rotigotinum
rotigotine
(-)-(S)-5,6,7,8-tetrahydro-6-[propyl[2-(2-thienyl)ethyl]amino]-1-naphthol

rotigotine
(-)-(6S)-6-[propyl[2-(thiophén-2-yl)éthyl]amino]-5,6,7,8-tétrahydronaphtalén-1-ol

rotigotina
(-)-(S)-5,6,7,8-tetrahidro-6-[propil[2-(2-tienil)etil]amino]-1-naftol

C_{19}H_{25}NOS
ruplizumabum
ruplizumab immunoglobulin G 1 (human-mouse monoclonal 5c8 γ1-chain anti-human CD 40 ligand), disulfide with human-mouse monoclonal 5c8 κ-chain, dimer
ruplizumab immunoglobuline G1 anti-(ligand CD 40 humain) (chaîne γ1 de l’anticorps monoclonal de souris 5c8 humanisé), dimère du disulfure avec la chaîne κ de l’anticorps monoclonal de souris 5c8 humanisé
ruplizumab inmunoglobulina G 1 anti-(ligando CD 40 humano) (cadena γ1 del anticuerpo monoclonal hombre-ratón 5c8), dímero del disulfuro con la cadena κ del anticuerpo monoclonal hombre-ratón 5c8

sitaxentanum
sitaxentan N-(4-chloro-3-methyl-5-isoxazolyl)-2-[[4,5-(methylenedioxy)-o-tolyl]acetyl]-3-thiophenesulfonamide
sitaxentan N-(4-chloro-3-méthylisoxazol-5-yl)-2-[(6-méthyl-1,3-benzodioxol-5-yl)acétyl]thiophène-3-sulfonamide
sitaxentán N-(4-cloro-3-metil-5-isoxazolil)-2-[[4,5-(metilenodioxi)-o-toli]acetil]-3-tiofenosulfonamida

C_{18}H_{15}ClN_{2}O_{6}S_{2}

sulfamazonum
sulfamazone (RS)-(1,5-dimethyl-2-phenyl-3-oxo-2,3-dihydro-1H-pyrazol-4-yl)[4-[(6-methoxy pyridazin-3-yl)sulfamoyl]phenyl]amino]methanesulfonic acid
sulfamazone acide (RS)-(1,5-diméthyl-2-phényl-3-oxo-2,3-dihydro-1H-pyrazol-4-yl)[4-[(6-méthoxy pyridazin-3-yl)sulfamoyl]phényl]amino]méthanesulfonique
sulfamazona ácido (RS)-(1,5-dimetil-2-fenil-3-oxo-2,3-dihidro-1H-pirazol-4-il)[4-[(6-metoxipiridazin-3-il)sulfamoil]fenil]amino]metanosulfónico

C_{23}H_{24}N_{6}O_{7}S_{2}

and enantiomer et énantiomère y enantiómero
**talaporfinum**

N-[[2S,3S]-18-carboxy-2-(2-carboxyethyl)-13-ethyl-2,3-dihydro-3,7,12,17-tetramethyl-8-vinylporphyrin-20-yl]acetyl]-L-aspartic acid

**talaporfine**

(2S)-2-[[7S,8S)-3-carboxy-7-(2-carboxyethyl)-13-éthényl-18-éthyl-2,8,12,17-tétraméthyl-7,8-dihydroporphyrin-5-yl]acétyl]amino]butanedioïque

**talaporfina**

N-[[2S,3S]-18-carboxi-2-(2-carboxietil)-13-etil-2,3-dihidro-3,7,12,17-tetrametil-8-vinilporfirin-20-il]acetil]-ácido-L-aspártico

\[C_{38}H_{41}N_5O_9\]

**ticalopridum**

ticalopride 4-amino-5-chloro-\(N\)-[(3S,4R)-3-méthoxy-4-pipéridin-4-yl]benzamide

ticalopride 4-amino-5-chloro-2-méthoxy-\(N\)-[(3S,4R)-3-méthoxypipéridin-4-yl]benzamide

ticaloprida 4-amino-5-cloro-\(N\)-[(3S,4R)-3-metoxi-4-piperidil]-o-anisamida

\[C_{14}H_{20}ClN_3O_3\]

**tolvaptanum**

tolvaptan (±)-4'-[(7-chloro-2,3,4,5-tetrahydro-5-hydroxy-1H-1-benzazepin-1-yl)carbonyl]-o-tolu-m-toluidide

tolvaptan \(N\)-[4-[[5RS]-7-chloro-5-hydroxy-2,3,4,5-tétrahydro-1H-1-benzázipin-1-yl]carbonyl]-3-méthylphényl]-2-méthylbenzamide

tolvaptán (±)-4'-[(7-cloro-2,3,4,5-tetrahidro-5-hidroxi-1H-1-benzazepin-1-il)carbonil]-o-tolu-m-toluidida
vilazodонum

vilazodone  5-[4-{4-(5-cyanoindol-3-yl)butyl}-1-piperazinyl]-2-benzofurancarboxamide

vilazodone  5-[4-[4-(5-cyano-1H-indol-3-yl)butyl]piperazin-1-yl]benzofurane-2-carboxamide

vilazodona  5-[4-[4-(5-cianoindol-3-il)butil]-1-piperazinil]-2-benzofurancarboxamida

vilazodona  5-[4-[4-(5-cianoindol-3-il)butil]-1-piperazinil]-2-benzofurancarboxamida

vilazodona  5-[4-[4-(5-cianoindol-3-il)butil]-1-piperazinil]-2-benzofurancarboxamida

vilazodona  5-[4-[4-(5-cianoindol-3-il)butil]-1-piperazinil]-2-benzofurancarboxamida
AMENDMENTS TO PREVIOUS LISTS
MODIFICATIONS APPORTÉES AUX LISTES ANTÉRIEURES
MODIFICACIONES A LAS LISTAS ANTERIORES

Recommended International Nonproprietary Names (Rec. INN): List 14
(Who Chronicle, Vol. 28, No. 10, 1974)

p. 1 delete insert
amfebutamonum bupropionum
amfebutamone bupropione

Dénominations communes internationales recommandées (DCI Rec.): Liste 14
(Chronique OMS, Vol. 28, No. 10, 1974)

p. 1 supprimer insérer
amfebutamonum bupropionum
amfetamone bupropione

Denominaciones Comunes Internacionales Recomendadas (DCI Rec.): Lista 14
(Crónica de la OMS, Vol. 28, No. 10, 1974)

p. 1 suprimase insértese
amfebutamonum bupropionum
anfebutamona bupropión

Denominaciones Comunes Internacionales Recomendadas (DCI Rec.): Lista 30
(Informacion farmacutica de la OMS, Vol. 4, No. 3, 1990)

p. 5 suprimase insértese
enalquireno enalkireno

Recommended International Nonproprietary Names (Rec. INN): List 42
Dénominations communes internationales recommandées (DCI Rec.): Liste 42
Denominaciones Comunes Internacionales Recomendadas (DCI Rec.): Lista 42

p. 198 delete/supprimer/suprimase insert/insérer/insértese
olmesartanum olmesartanum medoxomilum
olmesartan olmesartan medoxomil
olmesartan olmesartan médoxomil
olmesartán olmesartán medoxmilo
Denominaciones Comunes Internacionales Recomendadas (DCI Rec.): Lista 44

p. 184 adalimumabum
adalimumab
sustitúyase la descripción por la siguiente:
inmunoglobulina G1 (anti-factor α de necrosis tumoral humano) (cadena pesada del anticuerpo monoclonal humano D2E7), dímero del disulfuro con la cadena κ del anticuerpo D2E7 monoclonal humano

p. 185 amiglumidum
amiglumida
sustitúyase la descripción por la siguiente:
ácido (R)-4-(2-naftamido)-N,N-dipentilglutarámico

p. 193 evernimicinum
evernimicina
sustitúyase la descripción por la siguiente:
O-2,3,6-tridesoxi-3-C-metil-4-O-metil-3-nitro-α-L-arabino-hexopiranosil-(1→3)-O-2,6-didesoxi-4-O-(3,5-dicloro-6-metoxi-4,2-cresotoil)-β-D-arabino-hexopiranosil-(1→4)-O-(1R)-2,6-didesoxi-D-arabino-hexopiranosilideno-(1→3-4)-O-6-desoxi-3-C-metil-β-D-manoopiranósido de O-(1R)-2,3-O-metileno-4-O-(6-metil-β-resorciolil)-α-xilopiranósido de O-(1→3-4)-α-L-lixopiranósido

p. 196 irofulvenum
irofulveno
sustitúyase la descripción por la siguiente:
(R)-6'-hidroxi-3'-(hidroximetil)-2',4',6'-trimetilespirociclopropano-1,5'-[5H]inden-7'(6'H)-ona

p. 201 posaconazolum
posaconazol
sustitúyase la descripción por la siguiente:
4-[(p-[4-[p-[(3R,5R)-5-(2,4-difluorofenil)tetrahidro-5-(1H-1,2,4-triazol-1-ilmetil)-3-furil]metoxi]fenil]-1-piperazinil]fenil]-1-[(1S,2S)-1-etil-2-hidroxipropil]-Å²-1,2,4-triazolin-5-ona

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 du choix de dénominations communes internationales recommandées pour les substances pharmaceutiques et des Directives générales pour la formation de dénominations communes internationales applicables aux substances pharmaceutiques seront publiés seulement dans les numéros impairs des listes des DCIs 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 internacionales para sustancias farmacéuticas aparece solamente en los números impares de las listas de DCI propuestas.