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is now available at:
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Drug and therapeutics committees: a Swedish experience

The development of drug and therapeutics committees (DTCs) in hospitals and for primary health care varies markedly from one country to another within Europe (1) but has been particularly strong in the Nordic countries. Since 1997, Swedish law requires that all twenty-one regions have a drug and therapeutics committee. These committees have played an increasingly important role in implementing the rational use of drugs.

For 40 years, hospital drug formulary committees have existed in Sweden to develop guidelines for the selection of the pharmacotherapeutic armamentarium. Committees were primarily established to evaluate drugs available for use in routine care and to recommend drugs of choice for common diseases. Selection was based on therapeutic value, therapeutic tradition, and price. The right of an individual physician to prescribe according to his own judgement was fully recognized as a fundamental element of health care delivery, but the difficulty of maintaining oversight of the increasing number of drugs on the market was also acknowledged (2). The committee's primary objective was thus to improve rational use while decreasing the cost of drug treatment.

Four important prerequisites relating to the work of the committee were emphasized (2):

- Work should be a collaborative effort between clinicians, pharmacists and clinical pharmacologists.
- Selection of recommended drugs should be based on relevant statistics on the use of drugs in a hospital setting.
- The committee should work through "ambassadors" to inform prescribers about committee evaluations and conclusions.
- The drug committee should inspire a sophisticated and intense pharmacotherapeutic debate in hospitals.

The success of the first committees within university hospitals was instrumental in extending rational use throughout the country. As a result of initial work, the number of standard solutions for infusion was reduced from 25 to four, and the number of pharmacotherapeutic hypnotics from 37 to six (2). During the early seventies, follow-up of the outcome of drug recommendations through drug utilization statistics was emphasized, and educational initiatives were implemented when prescribing was found to deviate from recommendations (3). By 1975, the concept of generic substitution had been successfully introduced in Stockholm hospitals. Major events in the development of drug selection are summarized in Table 1 on page 208.

In the 1980s, a special guideline focusing on drug choices in primary health care was developed to increase the commitment of general practitioners. In 2000, a single guideline with some 200 recommended first-line drugs for the most common diseases was agreed upon for the entire population of 1.8 million inhabitants in Stockholm. During the early 1990s, the scope of the committees was broadened to include drug information and education of prescribers. The number of committees in Sweden now reached almost one hundred.

In 1997, drug and therapeutics committees became obligatory under law and instructions were issued (see Table 2 on page 208). Counties now had to provide a budget to support committee activities. The number of coordinating DTCs was reduced to 21 regional committees, performing their work through expert groups on different diseases and through local committees.

Functions of drug and therapeutics committees
Since the 1997 Swedish Drug Reform Act, the function of drug and therapeutics committees has
been regulated by the local county councils as the main providers of public health care. As the principal source of expertise, the overall aim of the committees is to promote the rational use of drugs at all levels of the health care system, whether at specialized clinics or primary health care centres. The committees have become a core facility for evidence-based principles of drug therapy within the health care system. Clinical pharmacologists, pharmacists, and district nurses (who have restricted prescribing rights in Sweden) are also represented. Members must declare any conflict of interest and acting as a consultant to industry is not allowed if this would lead to the promotion of an individual drug product. However, scientific collaboration at the institutional level is acceptable and even desirable.

Regional DTCs gather and evaluate knowledge on drugs and drug therapies through screening of scientific documentation systematically retrieved from the literature. Local networks of experts representative of the various health care levels are responsible for implementation of the recommendations. The committees are urged to improve the quality of drug therapy at all levels of health care within a given county, including the private sector, and collaborate with other experts from regional

Table 1. Major development of drug and therapeutics committees in Sweden

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1961</td>
<td>First committee set up at the Karolinska Hospital, Stockholm.</td>
</tr>
<tr>
<td>1975</td>
<td>Generic substitution encouraged.</td>
</tr>
<tr>
<td>1980s</td>
<td>Committees for primary health care and hospitals join forces. Stronger influence from primary health care. Newsletters.</td>
</tr>
<tr>
<td>1997</td>
<td>Drug and therapeutic committees required by law. Instructions issued, budget provided. Number of committees reduced to 21 regional committees.</td>
</tr>
<tr>
<td>2000</td>
<td>Information campaigns to public about recommended drugs of choice.</td>
</tr>
</tbody>
</table>

Table 2: Swedish law concerning drug and therapeutics committees (28 November 1996)

1. There shall be one or several drug committees in each county.
2. Each drug committee shall engage medical and pharmaceutical expertise.
3. A drug committee shall work towards the rational use of drugs through its recommendations to health care personnel. The recommendations should be based on scientific evidence and well-tried experience.
4. The National Corporation of Swedish Pharmacies shall provide drug committees with drug utilization statistics. If the committee realizes that there are shortcomings in the use of drugs it should provide education to prescribers.
5. Each committee shall, when required, collaborate with other committees and with relevant authorities and universities.
6. The County shall issue an instruction for the drug committee.
clinical pharmacology departments, telepharmacological services, local pharmacies, the Medical Products Agency, the pharmaceutical industry, and drug formulary committees. Other important functions are to provide the county council administrations with medical expertise in drug purchasing, develop policy documents for drug information, and provide education and follow-up on drug utilization and prescription patterns.

**Selection of recommended drugs**
Selected drugs should be well documented and appropriate from the pharmaceutical, pharmacological and therapeutic point of view, and considered essential in the treatment of common diseases. Evaluation of documentation follows the principles of evidence-based medicine. In order to gather experience about the safety of the compound, a new drug should have been registered and available on the market for at least two years. However, there is a trend towards quicker decisions and earlier acceptance of new drugs if they have shown potential to improve therapy.

Treatment costs are taken into account and an economic evaluation is demanded both for initial drug cost and the total treatment schedule. Recommended drugs should have high delivery guarantees from the producer/distributor, with relevant and up-to-date product information. Maintaining drug selection requires continuous follow-up of newly registered drugs, evaluation of the literature with respect to new guidelines, clinical trials and reports on adverse reactions. Expert groups are expected to stay in touch with specialist organizations preparing national treatment guidelines as well as with the Medical Products Agency, which regularly initiates and coordinates workshops.

**Education and information**
The rapidly expanding number of new drugs and treatment principles has created an increased need for independently evaluated drug information and education. The drug and therapeutics committee plays a central role here and supports a bilateral exchange of information with prescribers. Education is mostly problem-oriented, being initiated and organized by the medical community based on the needs of prescribers. Different models are being tested and an important idea is “drug education by prescribers for prescribers”. Primary health care physicians in academic drug detailing have been engaged at primary health care centres as “Drug Watchers” (4). Regional drug information centres based within clinical pharmacology departments provide independent and evaluated problem-oriented drug information to prescribers (5) through a database — Drugline — containing more than 10 000 evaluated documents on drug-related issues (6).

In several counties, DTCs regularly inform the public of their recommendations. In Stockholm, mass media campaigns focusing on the list of recommended drugs have been directed at prescribers and their patients. The campaigns have helped to establish the regional committee as an independent and reliable expert organization. Both DTCs and the regional drug information centres collaborate actively with the Medical Products Agency, which publishes excellent monographs on individual drugs and reviews on the treatment of different diseases.

**Electronic prescribing**
In Stockholm, a computer-based prescription support system, JANUS telepharmacology, has been developed (http://www.janusinfo.org) aimed at providing all prescribers within a county with easily accessible, clinically relevant and updated information on drugs. The system includes (mainly in Swedish):

- information and recommendations from the regional and local drug committees in the county;
- recent guidelines from the Medical Products Agency;
- links to the Physicians Desk Reference (FASS) and Drugline; and
- recent drug news with comments and evaluations by specialists.

JANUS also provides access to information on drug interactions, with evaluated literature references to each interaction (7). The key objective is to provide appropriate information and prescribing tools to simplify the selection and dosage of drugs.

Graphic presentations of local drug prescription patterns are also included to allow quick feedback to and between prescribers. Within the next few years, electronic prescribing is expected to replace old-fashioned prescriptions, and the prescriber will then have access to real time information while prescribing. Integrated into the JANUS prescription
system is a website (http://www.janusinfo.org) that serves as the electronic channel for all DTCs in Stockholm. Representative examples of the site pages in JANUS are set out in Figures 1 and 2.

**Follow-up and feedback of drug utilization**

Increasing drug costs, together with the transfer of the drug budget from the government to the county councils, emphasizes the need for follow-up of drug use, prescription patterns and cost trends. Drug committees play a key role in developing pharmacoepidemiological tools. The 1997 Drug Reform Act required bar codes for prescriptions, indicating workplace and prescriber identity. The feedback provided serves as an ideal self-audit system for primary health care centres, clinics, and individual prescribers (10).

Local auditing of prescription patterns and cost development in relation to the committee’s recommendations is an important strategy and stimulates feedback on rationality, prescribing and cost-awareness. Such data also form the basis for revision of drug recommendations, educational and informational activity needs, or intervention studies. Before drug reform, physicians were relatively unaware of the costs that prescribing generated, since the government paid the bill. This will now change dramatically and drug costs will become an integrated and visible part of the entire budget for a clinic or primary health care centre.

A new indicator of the quality of drug prescribing has recently been introduced in Stockholm County (8): Drug Utilization 90% (DU90%). The term refers

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**Fig. 1. JANUS prescription system:**

Drug statistics:

Drug sales (1 million Swedish Kroner= 0.1 million Euros) by ACT class for 1st. quarter 1995–2000 in Stockholm. This function is updated monthly at the website: http://www.janusinfo.org
to the number of drugs accounting for 90% of drug use, measured in defined daily doses (DDDs). The Swedish Medical Quality Council (9) has suggested using the DU90% as a general quality indicator of drug prescribing, and this has also been adopted in Stockholm (10). Adherence to guideline recommendations or other consensus documents is reflected by the percentage of recommended drugs within the DU90% segment. This measure can easily be used for comparisons over time between hospitals, clinics, primary health care centers and geographical regions and may identify problem areas where educational interventions are required. The method can be applied to all drugs or to different therapeutic classes (ATC groups). It also provides data for economic follow-up and analysis, as the drug costs are also included. By sorting on “costs” the corresponding Drug Costs 90% – DC90% – profile is obtained.

The combined DU90%/DC90% profile has turned out to be of considerable interest to prescribers and physicians responsible for health care costs, including drugs. Figure 3 on page 212 describes DU90% profile by brand name based on prescriptions dispensed to the population of Stockholm during the three months of October–December 2000 ranked by number of defined daily doses (DDD), according to the recommendations by the Swedish Medical Quality Council (9). The drug utilization 90% (DU90%) segment (the area below the curve) corresponds to 311 of a total of 1,317 brand names with DDDs dispensed at pharmacies. Adherence to

**Fig. 2. JANUS prescription system:**

The JANUS prescribing tool contains 24 different drug information databases. Patient data are automatically retrieved from electronic records. A bullet shows that the drug is recommended by the drug and therapeutics committee (arrow a). Arrow b indicates an automatic pregnancy alert for drugs with potential effects on the foetus. Arrow c shows an automatic interaction alert for warfarin. [http://www.janusinfo.org](http://www.janusinfo.org)
Fig. 3. DU90% Drug use profile

PHARM. PRODUCT | (DDD) | DDD | % | Rx | COST (SEK) | SEK/D
1. TROMBYL | 1 tabl. | 6,569,005 | 4.5% | 64,425 | 2,186,994 | 0.33
2. LEVAXIN | 0.15 mg | 2,952,441 | 2.0% | 41,535 | 3,059,630 | 1.04
3. ZOCORD | 15 mg | 2,816,558 | 1.9% | 24,749 | 25,618,330 | 9.10
4. PLENDIL | 5 mg | 2,409,584 | 1.7% | 23,319 | 11,072,443 | 4.60
5. CIPRAMIL | 20 mg | 2,372,289 | 1.6% | 27,362 | 19,325,240 | 8.15
6. RENITEC | 10 mg | 2,335,146 | 1.6% | 18,642 | 9,841,277 | 4.21
7. SELOKEN ZOC | 0.15 g | 2,304,272 | 1.6% | 47,073 | 12,493,554 | 5.42
8. IMOVANE | 7.5 mg | 2,097,315 | 1.4% | 42,237 | 4,831,678 | 2.30
9. LASIX RETARD | 40 mg | 1,957,065 | 1.4% | 19,505 | 2,666,956 | 1.36
10. LIPITOR | 10 mg | 1,935,550 | 1.3% | 12,783 | 13,528,542 | 6.99
11. FURIX | 40 mg | 1,863,001 | 1.3% | 10,919 | 751,774 | 0.40
12. PULMICORT TURBUH. | 0.8 mg | 1,779,825 | 1.2% | 22,903 | 11,065,400 | 6.22
13. PROPAVAN | 25 mg | 1,640,487 | 1.1% | 20,353 | 1,791,482 | 1.09
14. TRIATEC | 2.5 mg | 1,558,301 | 1.1% | 6,778 | 4,615,226 | 2.96
15. FUROSEMID NM | 40 mg | 1,525,293 | 1.1% | 7,629 | 549,500 | 0.36
16. IMDUR | 40 mg | 1,498,186 | 1.0% | 11,996 | 3,645,951 | 2.43
17. LOSEC MUPS | 20 mg | 1,464,548 | 1.0% | 23,961 | 23,312,114 | 15.92
18. BEHEPAN TABL. | 1 mg | 1,445,912 | 1.0% | 13,635 | 2,106,438 | 1.46
19. ZOLOFT | 50 mg | 1,404,284 | 1.0% | 15,813 | 13,158,324 | 9.37
20. TENORMIN | 75 mg | 1,303,954 | 0.9% | 19,172 | 1,863,095 | 1.43
21. STILNOCT | 10 mg | 1,234,150 | 0.9% | 27,991 | 3,918,260 | 3.17
22. BRICANYL TURBUH. | 2 mg | 1,179,700 | 0.8% | 22,369 | 3,696,018 | 3.13
23. DESOLETT | * | 1,114,876 | 0.8% | 6,255 | 1,822,517 | 1.06
24. LANZO | 30 mg | 1,005,654 | 0.7% | 23,132 | 10,677,362 | 10.62
25. CITODON | 3 t/supp | 985,687 | 0.7% | 33,107 | 3,013,438 | 3.06
26. ATROVENT | * | 971,489 | 0.7% | 10,421 | 3,914,818 | 4.03
27. CALCICHEW D3 | 2 tabl | 953,687 | 0.7% | 22,315 | 3,696,018 | 3.13
28. FLUDENT | 1.1 mg | 925,260 | 0.6% | 4,564 | 411,151 | 0.44
29. ALVEDON | 3 g | 922,590 | 0.6% | 34,307 | 2,247,339 | 2.44
30. LAKTULOS P&U | 6.7 g | 919,890 | 0.6% | 8,732 | 909,068 | 0.99

DU90% 1-311 130,278,408 90.0% 2,022,457 555,509,919 4.26
312-1317 14,464,452 10.0% 439,649 282,849,843 19.55

TOTAL 1-1317 144,742,860 100.0% 2,462,106 838,359,762 5.79
Guideline 2000 issued in January 2000 was 59% in the DU90% segment. The technical unit of comparison (DDD) is given in mg, or number of tablets, etc. Rx = number of prescription items. Cost (SEK) in Swedish kronor. Corresponding ranking by cost provides a drug cost 90% profile – DC90%. SEK/DDD is the actual costs per DDD.

**Resources**

The drug and therapeutics committees have an annual budget which varies between the 21 regions. In the most progressive counties it has been considered appropriate to invest a sum corresponding to 1% of the total drug expenditure. The annual budget for the DTCs in Stockholm is about 4 million Euros, with drug expenditure about 0.4 billion Euros annually.

In Stockholm, the budget is spent on salaries and for engaging clinical expertise. With the existing financial system for the health care budget it is impossible to engage clinical experts for this intellectual work unless they can have leave of absence from their pressing daily work with patients. Much of the budget is spent on continuing education of prescribers and to implement the recommendations of the drug committee.

The committees can also use the competence of existing units in clinical pharmacology as well as regional and local pharmacies. The regional drug information centres (6) offer a service to retrieve, evaluate and summarize the documentation of different drug products.

**The future of drug and therapeutics committees**

A number of circumstances make it clear that the individual prescriber will be in great need of unbiased, consultative support in the selection and use of drugs in the future. The aims of drug treatment should be that the right drug is prescribed to the right patient in the right dose with the right information and at the right (affordable) cost (11). This implies competence, integrity and cost-awareness on behalf of the prescriber.

Prescribers, then, will accept advice from the organization paying the drug bill and not from the manufacturer alone, while providers of health care have to take responsibility for the continued drug education of the prescribers. This will probably be an invaluable investment in view of the alarming annual increase of expenditure for drugs, and adverse drug effects now reported worldwide.

For drug and therapeutics committees to be effective, it is vital to broadly engage the prescribing professions in the work and to base the selection of the therapeutic choice on advice from the most competent experts in pharmacotherapeutics.

**References**


Current Topics

Tenth International Conference of Drug Regulatory Authorities

The Tenth International Conference of Drug Regulatory Authorities (ICDRA) took place in Hong Kong SAR, People's Republic of China from 24 to 27 June 2002. Two hundred and twenty senior drug regulatory officials from over one hundred countries participated in this international forum established in 1980. The objectives of the ICDRA are to address issues of immediate concern, strengthen communication and develop collaboration among regulatory authorities. As a platform set up to develop international consensus, the ICDRA has been an important tool for WHO in its efforts to harmonize regulation and improve the safety, efficacy and quality of medicines. Regulatory authorities are continually faced with new issues brought about by globalization and development of free trade, while increased responsibilities — such as those covering control of alternative medicines and the introduction of innovative treatments — place heavy demands on regulatory systems and knowledge bases. The development of sophisticated technologies and techniques in health care and extensive use of the Internet impose new challenges.

The conference programme was developed by a planning committee of representative drug regulators and provided the impetus for discussion of the many current issues facing authorities. As a result of the four days of debate, drug regulators made recommendations (as set out below) on issues covering herbal medicines, homeopathy, regulatory reform, medicines safety, counterfeiting, access to drugs and vaccines, regulation of clinical trials, harmonization, new technologies and e-commerce. These recommendations have been proposed to serve as a basis for future collaboration and efforts among Member States, drug regulatory authorities, WHO, and interested agencies and institutions.

Recommendations from the Tenth International Conference of Drug Regulatory Authorities

Herbal medicines

1. Member States, together with WHO, should define criteria and standards for herbal medicines, health or functional foods, and dietary supplements. WHO should continue to develop guidelines on the assessment of safety, efficacy and quality control of herbal medicinal products and herbal combinations.

2. The safe use of herbal medicines is a major concern for governments and consumers. WHO should provide guidance to countries wishing to establish safety monitoring systems or to expand existing systems to monitor and report adverse reactions to herbal medicines. Member States should strengthen their post-marketing surveillance systems for herbal medicines. Such systems should involve health care providers, consumers and manufacturers.

3. WHO should support countries in developing sources of information on herbal medicines while facilitating information-sharing among countries. WHO should provide guidance to governments and nongovernmental organizations (NGOs) on how to develop information and educational programmes on the proper use of herbal medicines for the public.

4. WHO should provide guidance for governments and NGOs on training of traditional medicine providers, and promote communication with other health workers.

5. Member States should seek funds to support research on herbal medicines.

6. Progress should be reported back to the ICDRA.
Safety of Blood-derived Products

Plasma-derived medicinal products, as well as blood and blood components, should be regulated in the same way as other biological products and fall under the responsibility of regulatory authorities. The importance of good manufacturing practice (GMP) was emphasized. The main problem identified was how best to minimize the risk of transmitting currently known and emerging blood-borne diseases. Developing countries in particular, had difficult choices to make in planning balanced regulatory action.

1. WHO should promote the regulation of blood and plasma collection centres, with emphasis on ensuring GMP compliance.

2. Regional co-operation and training should be promoted and WHO should facilitate the development of educational programmes and training opportunities for staff involved in regulation and control of blood products.

3. WHO should collaborate with Member States to strengthen the technical expertise of regulatory authorities (especially those countries with plasma fractionation activities/facilities) to assure adequate quality, safety and efficacy of plasma products. Special emphasis should be placed on viral testing, viral inactivation procedures, and surveillance for viral and other transfusion-transmitted diseases. Special attention should be given to the possible risk of transmission of vCJD and appropriate validation studies should be carried out.

4. In those countries where contract fractionation of plasma is a common option, WHO should develop guidance on the regulatory issues involved.

5. In order to facilitate approval by regulatory authorities of importation of plasma products, WHO should promote the use of batch release certificates, with a clear description of the procedures used.

6. Progress should be reported back to the ICDRA.

Antimicrobial resistance: new initiatives

Antimicrobial resistance is a threat to effective treatment of infectious diseases. Since the topic was first discussed at the ICDRA in 1996, much has been accomplished in this area. However, if the emergence of resistance is to be slowed, much more needs to be done. The following are urgent recommendations for all regulatory authorities to implement.

1. All countries should make containment of antimicrobial resistance a national priority by creating an intersectoral task-force to bring together all interested parties and ensure collaboration among the various professional groups.

2. National systems should be created to monitor and analyse antimicrobial usage in food animals and humans by collecting data from hospitals and in the community and linking these findings to resistance and disease surveillance data.

3. Efforts should continue in regulating antimicrobials, while addressing the need for availability at all levels of the health care system.

4. Promotional activities should continue to be regulated by ensuring adherence to guidelines for ethical promotion of medicines.

5. Education of health professionals in rational prescribing and of patients in compliance should be encouraged. Awareness of antimicrobial resistance should be raised within regulatory authorities.

6. The pharmaceutical industry should pay particular attention to GMP and quality issues in relation to the production of antimicrobials, as well as to labelling of their products.

7. Regional and international collaboration should continue and progress reported back to the ICDRA.

Harmonization I

1. WHO should continue involvement in the ICH Steering Committee, adopting a more proactive role by proposing topics for guideline development and expressing opinions on the potential public health implications of the guidelines proposed by ICH.

2. In the light of the wide range of regulatory environments, WHO should support non-ICH Member States and regional harmonization initiatives by evaluating the usefulness, feasibility and impact of implementing ICH guidelines.

3. WHO should continue to produce briefing notes on ICH meetings for regulatory officials of non-ICH countries and consider ways of making them widely available, including use of the Internet.
4. In order to improve access to essential drugs of good quality, especially in developing countries, WHO should assess the benefits and risks to public health of implementing selected ICH drug quality guidelines on manufacturing standards for generic products in non-ICH countries, and intensify its efforts to develop international standards and guidelines for the regulatory assessment of generic products. WHO should offer specific advice to national authorities in non-ICH countries.

5. Progress should be reported back to the ICDRA.

Harmonization II

It was recognized that international harmonization is characterized by a number of initiatives undertaken in different parts of the world. Such initiatives reflect specific local or regional needs and circumstances. Although these activities and their products may be useful examples and supply important technical knowledge, no single initiative can currently be considered a model for international application or implementation.

1. Countries should take into account local factors, priorities, possible implications, and implementation capacity when evaluating harmonization initiatives and guidance materials produced elsewhere.

2. The development of international regulatory requirements and guidelines should be based on demonstrated public-health needs and should not be driven by technological progress alone.

3. WHO should continue to support regional and local harmonization initiatives aimed at strengthening regulatory capacity and achieving public health goals.

4. Progress should be reported back to the ICDRA.

Protection of subjects in clinical trials

1. Drug regulatory authorities have an important role in protecting trial subjects. Drug regulatory authorities are required to keep a complete register of trials carried out in the country and, when possible, these registers should be made public (e.g. through the agency website).

2. When trials are carried out in several countries or where part of a study is carried out in a different country, direct communication between the regulatory authorities of the countries involved should be established. Contact data of responsible people should be available on the agency website.

3. Drug regulatory authorities should pay attention to the informed consent procedure and ensure that complete information is provided to the trial subjects in conformity with international guidelines, in addition to requiring national or local ethical review.

4. WHO should develop guidelines for the effective control of trials by the regulatory authority.

5. WHO should strengthen protection of human trial subjects by developing good clinical practices (GCP) training tools for drug regulatory authorities, promoting training of GCP inspectors, and providing assistance to Member States in setting up GCP inspectorates.

6. Progress should be reported back to the ICDRA.

Regulating biotechnology products

The need to make optimal use of the products of new biotechnologies in the prevention, diagnosis and treatment of diseases that are the major causes of morbidity and mortality throughout the world, especially in developing countries, was recognized. However, it was emphasized that these are highly complex products, often manufactured using novel biotechnologies, and the need for careful evaluation and regulation was vital. Issues relating to the comparability of biotechnology products, including those of scale-up, were highlighted as needing particular attention.

Rapid growth of the biotechnology industry in a number of developing countries was noted, as was the science-based regulatory oversight already in place in some instances. However, effective regulatory oversight, as well as adequate resources to deal with biotechnology products, was still needed in the majority of developing countries. Full support was expressed for the application of biotechnology to the development of vaccines, therapeutic biologics and diagnostics for the prevention, treatment or diagnosis of disease.

1. Given the rapid advances in biotechnology and the challenge of balancing the risks and benefits, WHO, in collaboration with regulatory authorities, should monitor developments and continue to provide clear guidelines on issues relating to quality, safety and efficacy of biotechnology-derived medicinal products, including biocomparability.
Rapid dissemination of this advice is crucial and WHO should strive to improve awareness of available guidance.

2. Regulatory authorities lacking experience in the regulation of biotechnology-derived products should be strengthened through education, training and updating, as appropriate. They should draw upon the knowledge and skills of regulatory authorities already experienced in this area, with the collaboration of WHO. Regulatory authorities should recognize the need to support the participation of officials at scientific and related meetings dealing with the regulation of this fast-developing field.

3. Regulatory authorities with limited experience should identify sources of expertise within their countries, such as in academia, to assist in the review of applications for clinical trials and for marketing authorizations. Where these are lacking, the support of experts from more experienced regulatory authorities should be explored, with the assistance of WHO, as a means of obtaining the necessary skills and knowledge.

4. WHO should continue development of International biological reference materials that can serve as reference standards for new products.

5. Progress should be reported back to the ICDRA.

Regulatory challenges: health sector reform and drug regulatory capacity

Health sector reform, especially in developing countries, has been driven more by financial constraints than by health needs. This is an important challenge for drug regulatory authorities that are confronted with reduction of public funding and the need to develop new mechanisms to finance their activities.

Globalization of economies and intensification of international commerce have created new challenges for drug regulatory authorities. Most authorities, especially the less resourced ones, are confronted with regulatory decisions made elsewhere under diverse circumstances.

1. It is in the paramount interest of public health that drug regulation remains a fundamental responsibility of the public sector, is not left to market forces alone, and is not subordinated to commercial interests.

2. New dimensions should be considered in the regulatory assessment of drug quality, safety, efficacy, and information. This must continue to be based on solid scientific evidence, while taking into account the implications of regulatory decisions on public health goals and on access to medicines by the majority of the population.

3. The resources necessary to ensure full regulatory assessment of pharmaceuticals cannot be available to all countries. In order to contribute to strengthening national regulatory capacity, WHO should study existing experience and undertake research in order to develop models for intensified collaboration and, where appropriate, joint decision-making among national regulatory authorities.

4. Availability of information is a crucial tool to achieve appropriate regulatory decisions. WHO should further support national authorities to introduce or improve data management systems in order to produce and interchange information and to achieve evidence-based decision-making.

5. Progress should be reported back to the ICDRA.

Access to drugs and vaccines I

1. WHO should continue its efforts in strengthening international guidelines for registration of generic drugs.

2. In collaboration with Member States, WHO should continue to focus on activities related to good trade and distribution practices of starting materials to assure the use of high quality materials.

3. WHO should work with other technical partners, within the concept of a global alliance, to improve the quality of products moving in international commerce.

4. WHO should establish a pre-qualification quality assurance system for essential medicines.

5. WHO should continue its prequalification project for procurement of medicines for priority diseases.

6. In collaboration with Member States, WHO should develop additional international guidance on important elements of combination medicines focusing on rational use to maximize the benefit in specific disease treatment.
7. Governments and drug regulatory authorities should encourage the development of therapies for neglected diseases through incentives, co-operative efforts and public/private initiatives.

8. Progress should be reported back to the ICDRA.

Access to drugs and vaccines II

1. Countries should implement programmes aimed at assuring the availability, accessibility, quality and rational use of essential medicines.

2. The Model List of Essential Medicines is a central element of national drug policies. WHO should continue to maintain the Model List and support countries in adapting it to their needs and national context. Selection of essential medicines should be based on safety, quality and efficacy in addition to accessibility.

3. Access to medicines is improved by competition brought about by generic products. Countries should take measures to foster the development of a competitive generic market.

4. Countries and WHO should further develop initiatives aimed at expanding the implementation of the concept of essential medicines to encompass both the public and private sectors.

5. Countries and WHO should intensify efforts aimed at improving access to vital medicines, particularly those used for HIV/AIDS-related care and treatment.

6. Problems of vaccine availability are becoming more frequent. Countries and WHO should intensify their efforts to prevent supply shortages.

7. Countries and WHO should continue to study the impact of international trade agreements on access to medicines and initiatives aimed at promoting essential medicines and rational use.

8. Progress should be reported back to the ICDRA.

Counterfeit pharmaceutical products: panel discussion

1. Governments should adopt WHO guidelines for the development of measures to combat counterfeit drugs.

2. Governments of exporting countries should have a system of control to prevent the export of counterfeit drugs.

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Homoeopathy

1. In collaboration with Member States, WHO should harmonize definitions of homoeopathic products and practices in order to allow classification and identification of homoeopathic products at national level.

2. WHO should cooperate with governmental institutions to establish recommendations for safe degrees of dilutions of homoeopathic preparations.

3. In collaboration with Member States, WHO should promote the exchange of information. A reference list of information resources on homoeo-
pathic medicines, including official pharmacopoeias should be made available. WHO should develop systems to collect and provide information to consumers on the safe use of homoeopathic medicines.

4. WHO should provide guidance to governments and NGOs for training of homoeopathic medicine providers.

5. Progress should be reported back to the ICDRA.

Safety monitoring

There have been major advances in the area of pharmacovigilance and drug monitoring since WHO established its Programme for International Drug Monitoring in 1968 as the global standard for drug safety. These recommendations highlight important issues for action by regulatory authorities and WHO.

1. Regulatory authorities should expand the scope of their activities to include surveillance of medication errors, medical devices, homoeopathic products, herbal medicines, natural health products and identify reports that may point to quality defects or to counterfeit products.

2. Regulatory authorities should improve efforts to evaluate the effectiveness of the various reporting mechanisms in operation in their countries.

3. Regulatory authorities should improve communication of emerging safety concerns. To assist in this and to ensure that confidentiality and security of shared data is maintained, WHO should develop a secure web-based communication system.

4. Regulatory authorities should be encouraged to develop post-marketing risk management strategies for products identified as posing a significant risk.

5. WHO should finalize and distribute its crisis management plan to Member States. This should be tested periodically. WHO should provide professional assistance and resources in crisis management, communications and research to Member States.

6. The WHO adverse reactions database utility should be strengthened by:

- Use of best methods to ensure timely reporting to WHO of case information, and by taking steps to increase national reporting rates.

- Assigning unique case identification codes to avoid duplication to all case-report recipients.

- Opening access to the WHO database to all stakeholders with a genuine public health interest and the ability to evaluate such case information.

7. The current WHO Programme for International Drug Monitoring should be supported by:

- Encouraging all WHO Member States including ICH member countries to participate actively in the WHO Programme, and contribute to its development.

- Periodically and regularly reviewing definitions, tools, and procedures in the light of developments in safety in medicine.

- Strengthening WHO’s role as the mandated global pharmacovigilance system and recognizing WHO definitions, tools and practices for pharmacovigilance and drug monitoring as world standards.

8. WHO should convene an expert group to examine the special needs for assessing the safety and risk of medicines used in the treatment of HIV/AIDS, particularly in developing countries.

9. Progress should be reported back to the ICDRA.

E-Commerce

1. Patient/consumer protection should be the first priority of regulatory authorities in their approach to e-commerce. National authorities should endeavour to ensure that patients have the same level of protection whether they purchase pharmaceuticals through legitimate Internet sites or through the traditional channels.

2. Regulatory authorities should improve the information contents of their websites and establish appropriate programmes, including mass media campaigns, aimed at providing unbiased information and warn the public on the possible risks of unregulated pharmaceutical e-commerce. These programmes must be designed in a way that ensures that they effectively reach health professionals and consumers.
3. National authorities should establish and encourage the use of simple mechanisms for consumers and health professionals to report illegal sites and negative experience they have had with e-commerce.

4. WHO should establish and maintain a list of national focal points and circulate it to all regulatory authorities in order to foster international collaboration in combating illegal pharmaceutical e-commerce.

5. WHO should continue to create opportunities, through international meetings of national regulatory officials, for discussing and foster awareness on the public-health issues related to pharmaceutical e-commerce.

6. Progress should be reported back to the ICDRA.

**Current topics**

1. There should be only one standard of quality, safety and efficacy of medicines, whether these are produced for local consumption or for export only. Member States should regulate drugs for export in accordance with appropriate international standards.

2. WHO should collaborate closely with the PIC/S to enhance capacity building of national inspectorates. This could be undertaken within the concept of the Global Alliance.

3. WHO should continue its efforts towards the development of international specifications and pharmacopoeial requirements and the establishment of international reference standards for drugs responding to major public health needs.

4. In collaboration with Member States, WHO should develop guidelines for the regulation of xenotransplantation.

**The Parenteral Society**

The Parenteral Society is a non-profit organization established to promote and advance the practice and science of parenteral drug therapy in the interests of public health and to preserve and improve the integrity and standards of the parenteral drug industry. It was originally founded in the United Kingdom in 1981 to serve the country's healthcare community but has developed an international membership over the years which now stands at over 1100 members in 29 countries.

The Parenteral Society has been developed by and for those active in the field of injectable and implantable drugs and devices. The Society has members active in academia, hospitals, industry, health ministries and other areas. Members’ interests cover research and development, manufacturing, quality control, engineering, medicine, nursing care and related activities. The Parenteral Society is a founder member of the European Sterile Products Confederation (ESPC).

A key service provided to its members is the provision of information concerning all aspects of parenteral technology and parenteral administration from basic concepts to current advanced science and technology. It encourages a spirit of friendly cooperation among members and promotes favourable relations with the health care professions. The Society is committed to cultivating and maintaining cooperative relations with governments and agencies, medical, pharmaceutical and related health organizations, the academic community, compendial bodies, manufacturers, suppliers to the industry and related organizations. It also initiates and participates in cooperative ventures and undertakings.

The Parenteral Society is active in the education and training of personnel in parenteral drug technology and parenteral administration. Seminars, meetings, workshops, tutorials, round table discussions and conferences are held regularly in the United Kingdom and Ireland, taking various forms and covering a range of subjects. In addition, a five day course “Training for Pharmaceutical Process Operators” is held at Bath University, United Kingdom, in June and September each year.

Six specialized working groups are currently active, providing for interchange of current information and ideas, leading to publication of monographs on specialized topics. The Parenteral Society Contact Scheme enables members to be placed in contact with one another for help and advice on aspects of parenteral drug technology. This has resulted in creation of an extensive database of valuable knowledge and experience.

The Society additionally has an active publications programme. It produces the quarterly *European Journal of Parenteral Sciences* in association with
other members of ESPC. A quarterly newsletter is also published and the Society issues its own reports, a series of technical monographs and of tutorial booklets, and other relevant literature. Each year, the Parenteral Society Award is open to practising scientists from all branches of parenteral science, and is designed to encourage the furtherance of knowledge in this field. The award is based on submission of the author’s original completed work.

From its achievements to date, the Society has increased in profile and stature as an influential body by providing a valuable discussion platform for the legislated, legislator, public health and academic communities. The Parenteral Society website provides an introduction, current activities, publications information and news updates on the global regulatory scene relating to parenteral drug products plus details of how to obtain membership. Further information is available from: http://www.parenteral.org.uk or: The Parenteral Society, Tel: +44 (0) 1793 824254 Fax: +44 (0) 1793 832551 e-mail: secretary@parenteral.demon.co.uk.
Adverse reactions to natural health products

Over 50% of Canadians now use natural health products in the form of traditional herbal products, vitamin and mineral supplements, traditional Chinese, Ayurvedic and other medicines and homeopathic preparations. However, there seems to be an overall misconception that these agents are naturally safe because they come from 'natural' plants (1, 2). The use of herbal products, a type of natural health product, can be associated with adverse effects attributable to factors such as inadequate or excessive dosing, low-quality herbs or supplements, misidentified plant species, variability of constituents, contamination with heavy metals, adulteration with prescription drugs, interactions with prescription drugs and allergic reactions (1). Also, some herbal ingredients are intrinsically toxic (2). A number of reported suspected reactions to natural health products have been described (3–9). These factors along with the practice of using health products with multiple ingredients, make the evaluation of adverse effects complex.

With the opportunity for self-selection and the wide availability of natural health products, the public needs to be aware of the possible risks associated with these products as well as their benefits. Many products contain multiple ingredients that may prove challenging to consumers in allowing informed choices. Furthermore, consumers are sometimes misinformed by promotional information about some herbs or ingredients that may either obscure the risks associated with their use or exaggerate efficacy. Some examples include the presence of ephedra in products used as diet aids or energy boosters, and Ginkgo biloba in products promoted as dietary supplements that enhance memory.

Health care professionals need to know whether their patients are using various health products, including natural health products, certain foods, and prescription and nonprescription drugs, in order to evaluate their overall therapy. Patients may be reluctant to discuss the use of natural health products (1) and may be less likely to report adverse reactions associated with their use than those associated with conventional over-the-counter medicines (10). Health care professionals should ask their patients if they are using complementary or alternative therapies in order to provide advice and to monitor for possible adverse reactions. As with conventional medicines, specific groups — pregnant and breastfeeding mothers, children, elderly people, patients with cardiovascular disease, patients undergoing surgery and patients using conventional medicines where there is the potential for interactions — may be at increased risk of ARs if using complementary and alternative medicines (2).


References

1. Bielory, L. Adverse reactions to complementary and alternative medicine: ragweed’s cousin, the coneflower (echinacea), is “a problem more than a sneeze”. Annals of Allergy & Asthma Immunology, 88:7–9 (2002).


Leflunomide: haematologic, hepatic and respiratory reactions

Treatment of rheumatoid arthritis has shifted toward earlier and more aggressive therapy with disease-modifying antirheumatic drugs (DMARDs) (1, 2). Leflunomide (Arava®), a newer immunomodulatory DMARD, is indicated for the treatment of active rheumatoid arthritis in adults (3).

Because leflunomide has an active metabolite with a long elimination half-life of about 2 weeks, serious adverse reactions (hepatotoxic, haematotoxic or allergic) may occur even after leflunomide treatment has been stopped (3). Also, recovery from adverse reactions may be prolonged (4).

The European Medicines Evaluation Agency (EMEA) has raised concerns about the safety profile of this drug, especially with regard to hepatotoxicity, pancytopenia and serious skin reactions (5, 6). In Canada, the manufacturer has issued a safety alert regarding severe and serious hepatic reactions (7).

From March 2000, when leflunomide was marketed in Canada, to May 31, 2002, Health Canada received 99 reports of suspected adverse reactions involving the drug, 79 considered to be serious and 4 with a fatal outcome. Three fatal cases were due

<table>
<thead>
<tr>
<th>System</th>
<th>Reaction term†</th>
<th>Total no. of AR reports</th>
<th>No. of reports with use of MTX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haematologic†</td>
<td>Leucopena (5); thrombocytopenia (5); anaemia (4); granulocytopenia (4); pancytopenia (3); leukocytosis (2); anaemia aplastic (1); anaemia haemolytic (1); Coomb's direct test positive (1); eosinophilia (1); epistaxis (1); lymphopenia (1); marrow depression (1); prothrombin prolonged (1); purpura (1)</td>
<td>20</td>
<td>8</td>
</tr>
<tr>
<td>Hepatic and biliary</td>
<td>Alanine aminotransferase increased (8); aspartate aminotransferase increased (7); hepatic function abnormal (3); phosphatase alkaline increased (2); gamma-glutamyl transferase increased (2); hepatic enzymes increased (1); hepatitis viral (1)</td>
<td>11</td>
<td>1</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Dyspnea (5); pulmonary infiltration (4); bronchitis (2); coughing (2); hypoxia (2); pneumonia (1); pneumonia lobar (1); pneumonitis (1); pulmonary fibrosis (1); respiratory disorder (1); respiratory insufficiency (1); upper respiratory tract infection (1)</td>
<td>11</td>
<td>6</td>
</tr>
</tbody>
</table>

Note: MTX = methotrexate.
*These data cannot be used to determine the incidence of ARs because ARs remain under reported and total patient exposure is unknown.
†Several reaction terms may be listed per AR report, therefore, the same case may be counted under more than one system. Reaction terms are based on the “preferred term” of the World Health Organization (WHO) Adverse Reaction Dictionary (WHOART).
‡Includes red blood cell, white blood cell, reticuloendothelial system, platelet, bleeding and clotting disorders.
Concomitant use of leflunomide with DMARDs toxic to liver and bone marrow is not advisable, as such therapy can lead to additive or even synergistic toxicity (3). Strict vigilance in monitoring liver and bone marrow function is recommended for all patients prescribed leflunomide, particularly if used with other medications associated with increased risk of hepatic or haematologic reactions (3).

Recommended monitoring parameters are as follows (3):

- Alanine amino transferase and aspartate amino transferase levels before treatment with leflunomide and at monthly or more frequent intervals during the first 6 months, and every 8 weeks thereafter.

- A complete blood count, including differential white blood cell count and platelet count, before treatment with leflunomide and every 2 weeks for the first 6 months, and every 8 weeks thereafter.

It is important to note that, if a severe undesirable effect occurs during treatment with leflunomide, the washout procedures outlined in the product monograph should be followed in order to clear the active metabolite from the body. These washout procedures should also be followed when changing therapy from leflunomide to another DMARD, since the possibility of additive risks of ARs exists for a long time after switching (3).

Health care professionals are reminded that treatment with leflunomide may have serious hepatic, haematologic and respiratory effects (4) and that these risks may be increased with concomitant methotrexate use.

References


Herbal mixture and palpitations

A 30-year-old man who had taken Aphrodite® tablets (a herbal mixture of dry extracts of Tribulus terrestris (40 mg), Cinnamomum zeylanicum (11 mg), Zingiber officinal (12 mg) and Crocus sativus (3 mg)) for his impotence problem (one tablet every 8 hour for 2 days) complained of rapid heartbeat. On examination, minor systolic hypertension was observed. The patient had no previous history of cardiovascular problems and was not under any other treatment. One day after stopping the use of Aphrodite®, the palpitation was fully cleared.

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All components of Aphrodite® have shown benefit in the treatment of male impotence, however the exact mechanism of this action is not known. T. terrestris as a herbal remedy that has been used in traditional medicine as a tonic with aphrodisiac activity and C. zeylanicum has well-defined aphrodisiac properties in traditional medicine (1). C. sativum has the same properties. Z. officinal has
shown to be cardiotonic/inotropic with peripheral vasodilatory activity added to its aphrodisiac action (2) which may be the main cause of palpitation observed in this patient. It was concluded that Aphrodite® should be used with caution in patients with a history of cardiovascular disease.

Ebrahim Zabihi, Mohammad Abdollahi, Tehran Drug & Poison Information Center, Ministry of Health & Medical Education, Tehran, Iran.

References


Indapamide and hyponatraemia

An article recently published in the Medical Journal of Australia describes hyponatraemia in association with the non-thiazide diuretic, indapamide. Marketed in the mid-1980s in Australia, indapamide is the most commonly reported cause of hyponatraemia with 164 reports. Of these 164 reports, 68 also described hypokalaemia. Over half described accompanying symptoms including confusion, nausea, vomiting, dizziness, anorexia, malaise, fatigue, syncope, somnolence and convulsions. Most patients were 65 years old or over and 82% were female. Many of the reports documented a serum sodium concentration, and in 75 cases the concentration was less than or equal to 120 mmol/L.

Despite the fact that hyponatraemia can complicate treatment with any diuretic medication, the Australian Drug Reactions Advisory Committee, ADRAC, continues to receive reports of the association. In the first 5 months of 2002, there have been 18 reports. It should also be noted that indapamide is present in combination with perindopril. ADRAC recommends that indapamide should be used cautiously and changes in conscious or mental state should prompt measurement of serum sodium concentration.

References


Regulatory and Safety Action

Epoetin alfa: pure red cell aplasia

**United Kingdom** — Epoetin alfa (Eprex®) is indicated for the treatment of anaemia associated with chronic renal failure, cancer chemotherapy, autologous blood donation, and during major elective orthopaedic surgery.

There have been 40 cases of confirmed or suspected pure red cell aplasia reported worldwide in chronic renal failure patients treated with epoetin alfa. The estimated reporting rate of this suspected adverse reaction is less than 1:10 000 patients treated.

Patients typically present with sudden worsening of anaemia that is unresponsive to increasing doses of erythropoietin. Such patients have detectable antibodies to erythropoietin in serum. Many do not respond to alternative erythropoietins and become transfusion dependent.

In patients developing epoetin alfa failure:

- Typical causes of non-response (e.g. iron, folate and B12 deficiency, aluminium intoxication, infection or inflammation, blood loss, and haemolysis) should be investigated.

- If no cause is identified, a bone marrow examination should be considered.

- If pure red cell aplasia is diagnosed, therapy with epoetin alfa must be discontinued and testing for erythropoietin antibodies should be considered.

- Appropriate therapy should be initiated and such patients should not be switched to another erythropoietin.


Australia — Pure red cell aplasia (PRCA) is a rare adverse effect of epoetin alfa which has recently been highlighted in an article and subsequent letter in the literature (1, 2). The condition results from the development of anti-erythropoietin antibodies, resulting in transfusion-dependant anaemia. PRCA has been reported only after chronic use of epoetin in patients with renal failure. In a series of 82 cases reported by the FDA, PRCA developed after the use of epoetin alfa from 1 month to 5 years.

The Australian Adverse Drug Reactions Committee has received 12 reports of PRCA associated with epoetin alfa (Eprex®) use.

Anti-erythropoietin antibodies which develop in this condition cross react with other erythropoietin products, including darbepoetin (Aranesp®). This product has been available in Australia since November 2001, experience is limited and it is not known whether PRCA will develop.

The sponsor of Eprex® has issued a letter recommending intravenous use where feasible. In patients with worsening anaemia, other causes should be excluded. If PRCA is suspected, it should be confirmed with antibody testing and/or bone marrow examination. Epoetin alfa should be discontinued and patients should not be switched to another erythropoietin. PRCA may respond to immunosuppressive therapy (3).

**References**


Ergot-derived dopamine receptor agonists: fibrotic reactions

**United Kingdom** — Pergolide, bromocriptine, cabergoline, and lisuride are ergot-derived dopamine receptor agonists indicated for the management of Parkinson's disease. Fibrotic reactions are recognized adverse events of ergot derivatives.
Suspected fibrotic reactions have been reported in the UK: many at an advanced stage. Some cases required surgery and 3 patients died. Before starting treatment it may be appropriate to perform baseline investigations and a chest X-ray. If possible, lung function tests should be performed. Prescribers of ergot derivatives should remember that various symptoms and signs could arise from fibrotic reactions which may cause unexplained or progressive dyspnoea, pleuritic or pericardial pain, abdominal discomfort or distention, edema and renal insufficiency.

Prognosis of fibrosis can be prevented by early diagnosis and cessation of drug treatment.


Buprenorphine approved for opiate dependence

United States of America — The Food and Drug Administration has approved buprenorphine hydrochloride (Subutex®) and buprenorphine hydrochloride and naloxone hydrochloride (Suboxone®), for the treatment of opiate dependence. These products treat addiction by preventing symptoms of withdrawal from heroin and opiates.

The first product is intended for use at the beginning of treatment for drug abuse, and the second is a formulation used in maintenance treatment of opiate addiction. Naloxone has been added to guard against intravenous abuse of buprenorphine. Both drugs are supplied in 2 mg and 8 mg tablets, to be dissolved under the tongue.

These products have been studied in over 2000 patients and shown to be safe and effective treatments for opiate dependence. Side effects most commonly seen include cold and flu-like symptoms, headaches, sweating, sleeping difficulties, nausea and mood swings. These effects usually peak at the beginning of treatment and may last a number of weeks. Clinical data indicate that the risk of serious diminished breathing may be less with buprenorphine than with other opioids when used in high doses or in overdose situations. Nonetheless, buprenorphine has been associated with deaths due to diminished breathing, especially when used in combination with alcohol or other CNS depressant drugs.

The sponsor, in collaboration with the FDA, has developed a comprehensive risk management programme designed to deter abuse and diversion from legitimate use, including limits on the number of patients individual physicians are allowed to treat and special registration for the use of the drug. The programme also provides surveillance systems to identify if drugs are being abused, including interviews monitoring, data collection and surveillance efforts.


Human tissue recalled

United States of America — The Food and Drug Administration has ordered Cryolife Inc. to recall distributed human tissue processed since 3 October 2001, since the FDA has determined that Cryolife cannot ensure that the tissue is free from fungal and bacterial contaminants.

Tissue has been associated with the death of a patient in November 2001 who received a soft tissue implant during reconstructive knee surgery. During its inspection of the company, FDA found numerous significant violations of regulations and issued a warning letter. The company had also distributed tissue from a donor after the presence of harmful microorganisms in tissue samples from the same donor had been confirmed.

Signs and symptoms of a bacterial or fungal infection following a tissue transplant would usually appear within days to weeks and it is therefore unlikely that patients are at future risk.

Current federal regulations for human tissue require firms to prepare, validate and follow written procedures to prevent infectious disease contamination or cross contamination during processing.


Lepirudin and fatal anaphylactic reactions

European Union — The European Medicines Evaluation Agency (EMEA) has been informed of 7 reports of severe anaphylactic reactions in patients receiving lepirudin (Refludan®). In 6 of these cases, the reaction occurred after re-exposure and 5 cases
were fatal. In several of the cases, Refludan® was prescribed outside the approved therapeutic indication.

Refludan® contains lepirudin, a recombinant hirudin, which acts as a specific direct inhibitor of free- and clot-bound thrombin. It is indicated as an anticoagulant in adult patients suffering from heparin-associated thrombocytopenia type II with thromboembolic disease mandating parenteral antithrombotic treatment. It was authorized in the European Union in 1997 and is currently marketed in Austria, Belgium, Finland, France, Germany, Greece, Ireland, Spain, and United Kingdom. Approximately 35,000 people have been treated.

Physicians treating patients should consider carefully the approved indications and the possibility of allergic reactions.


Valdecoxib: new warnings

United States of America — The Food and Drug Administration, together with the manufacturer of valdecoxib (Bextra®) are advising health care professionals about new warnings and information in the product labelling.

Valdecoxib is a drug approved for treatment of osteoarthritis, rheumatoid arthritis and dysmenorrhea (menstrual pain). The labelling is being updated with new warnings following postmarketing reports of serious adverse effects including life-threatening risks related to skin reactions — including Stevens Johnson Syndrome, and anaphylactoid reactions (serious allergic reactions). In addition, the labelling will state that the drug is contraindicated — not to be used — in patients allergic to sulfa containing products.

In November 2002, the manufacturer of Bextra® sent letters to health care professionals advising them of postmarketing reports and new warnings that will be included in the drug label. Since the firm began marketing the drug in March of 2002, cases of serious skin and hypersensitivity reactions have been reported. These included cases of Stevens Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis and erythema multiforme. Although these adverse events are rare, some of these patients required hospitalization. Based on these reports, FDA has approved labelling changes that include a warning for serious skin reactions. As these reactions can be life threatening, people who experience a rash should discontinue the drug immediately.


Parecoxib/valdecoxib: serious hypersensitivity reactions

European Union — The European Medicines Evaluation Agency (EMEA) has received information on reports of serious hypersensitivity reactions (anaphylaxis and angio-oedema) and serious skin reactions (Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme and exfoliative dermatitis) in patients treated with valdecoxib (Bextra®, Valdyne®, Valdecoxib Pfizer and Kudeq®, Valdecoxib Pharmacia Europe®) a selective COX-2 inhibitor. Some of these reactions have occurred in patients with a history of allergic-type reactions to sulfonamides.

Valdecoxib is the active metabolite of parecoxib sodium (Dynastat®, Rayzon® and Xapit®) and it is therefore possible that such reactions may also occur with this substance.

As an urgent measure, prescribing and patient information have been modified.


Mefloquine labelling strengthened

United States of America — Healthcare professionals have been notified that mefloquine hydrochloride (Lariam®) tablets are contraindicated in patients with known hypersensitivity to mefloquine or related compounds. It should not be prescribed for prophylaxis in patients with active depression, a recent history of depression, generalized anxiety disorder, psychosis, schizophrenia or other major psychiatric disorders or with a history of convulsions.

Mefloquine is indicated for the treatment of mild to moderate acute malaria caused by mefloquine-susceptible strains of *Plasmodium Falciparum* or *P. vivax*.
During prophylactic use, if psychiatric symptoms such as acute anxiety, depression, restlessness or confusion occur, these may be considered prodromal to a more serious event. In these cases, the drug must be discontinued and an alternative medication substituted.

References

2. Communication from Roche Laboratories Inc., USA. September 2002

Glucowatch for diabetes

United States of America — The Food and Drug Administration (FDA) has approved a wrist-watch-like glucose monitoring device for use by children and adolescents with diabetes. The device, which was approved for adult use in March 2001, provides information that can be used to detect trends and track patterns in glucose levels.

The GlucoWatch G2 Biographer®, extracts fluid through the skin and then measures the glucose in the fluid. Once the device has been warmed up and calibrated through the use of a finger stick blood glucose test, it is capable of providing up to six painless glucose measurements per hour for 13 hours. The device sounds an alarm if the glucose reaches dangerous levels, alerting patients to a potential problem.

Although it is not a replacement for standard finger stick blood tests, this device can help improve the quality of life of children with diabetes. These types of products may one day completely eliminate the need for daily finger-prick blood tests. Currently the GlucoWatch measurements must be used along with finger stick blood tests to ensure accurate results.

Approval of the GlucoWatch® was based on results of a study that evaluated use in 66 Type-I diabetics between ages 7 and 17. The study was conducted at a clinic in a home-simulated environment where the participants could go about various normal daily activities. The study showed that the product was safe and effective for detecting trends and tracking patterns in glucose levels in children and adolescents.

Although measurements are generally consistent with those of traditional finger-stick blood glucose tests, results can differ significantly. Because these variations are unpredictable, individual GlucoWatch® readings should never be used to make changes in insulin dose. Instead, results should be interpreted with several sequential readings over time and then confirmed with a finger stick test. Diabetes is a chronic disease that affects the body’s ability to produce or respond to insulin. This can cause wide fluctuations in blood glucose levels, from extremely high to extremely low.

More than 150,000 children in the United States have diabetes. While there is no known cure, studies have shown that patients who regularly monitor and regulate their blood glucose levels have a lower incidence of complications from the disease. Uncontrolled, diabetes can result in such serious outcomes as blindness, serious infection, amputation of limbs, coma, and death.


Generic omeprazole approved

United States of America — The Food and Drug Administration has approved 10 and 20 mg omeprazole delayed-release capsules for the treatment of certain gastro-intestinal conditions. The generic drug is identical to the brand name drug in dosage form, strength, route of administration and most labelled uses.

Although generic drugs are chemically identical to their branded counterparts, they are typically sold at substantial discounts from the branded price. To gain FDA approval, a generic drug must:

• contain the same active ingredients as the innovator drug (inactive ingredients may vary)
• be identical in strength, dosage form, and route of administration
• have some of the same use indications
• be bioequivalent (Generic drugs use the same active ingredients and are shown to work the same way in the body. Therefore they have the same risk-benefit profile as their brand-name counterparts.)
• meet the same batch requirements for identity, strength, purity, and quality

• be manufactured under the same strict standards of FDA’s good manufacturing practice regulations required for innovator products


Oxaliplatin for colorectal cancer

United States of America — The Food and Drug Administration has approved oxaliplatin injection (Eloxatin®) for use in combination with infusional 5-fluorouracil and leucovorin for the treatment of patients with colorectal cancer whose disease has recurred or become worse following initial therapy with a combination of irinotecan with bolus 5-fluorouracil and leucovorin. The combination including oxaliplatin was shown to shrink tumours in some patients and delay resumed tumour growth. There are as yet no data on the effects of the combination on survival.

The FDA review took just seven weeks to complete under the "rolling review" procedures of fast track approval. Fast track is used for drugs in development having the potential to be an advance in treatment for a serious illness and the rolling review procedure allows for some components of an application to be presented before the remaining sections are completed. Completion of all sections took place in June 2002.

Oxaliplatin is intended for use by physicians experienced in the use of cancer agents and a black box warning details this use together with information on possible anaphylactic reactions. Oxaliplatin can have a toxic effect on nerve endings that may result in either an acute or cumulative pattern of side effects. Other common side effects include vomiting, diarrhoea, anaemia, increased risk of bleeding or infection, or allergic reaction. Women should be advised to avoid becoming pregnant.


Ergotamine and ischaemia

United States of America — Recent changes have been announced to the prescribing information for ergotamine tartrate and caffeine (Cafergot®) suppositories and tablets, which include a new warning on interactions with potent CYP 3A4 inhibitors.

Co-administration of ergotamine with potent CYP 3A4 inhibitors (ritonavir, nelfinavir, indinavir, erythromycin, clarithromycin, and troleandomycin) has been associated with acute ergot toxicity (ergotism) characterized by vasospasm and ischemia of the extremities, with some cases resulting in amputation. There have been rare reports of cerebral ischemia in patients on protease inhibitor therapy when ergotamine tartrate and caffeine was co-administered, with at least one case resulting in death. Because of the increased risk for ergotism and other serious vasospastic adverse events, ergotamine use is contraindicated with these drugs and other potent inhibitors of CYP 3A4 (e.g., ketoconazole, itraconazole).


Acetylsalicylic acid and Reye's syndrome

United Kingdom — Reye's syndrome is a very rare but often fatal disease characterized by encephalopathy and fatty degeneration of the liver. It has mostly affected children aged less than 5 years but also occurs in older children and teenagers. The causes of Reye's syndrome are incompletely understood, but an association with use of acetylsalicylic acid in the presence of a viral infection has been implicated in many cases.

Sporadic cases continue to be reported and the Committee on Safety of Medicine now advises that acetylsalicylic acid (Aspirin®) should not be given to children under 16 years of age unless specifically medically advised.

References


Sertraline interactions

United States of America — A change in the prescribing information for sertraline hydrochloride tablets and oral concentrate (Zoloft®) has been announced by the manufacturer. This change was made at the request of the Food and Drug Administration and articulates a pimozide-sertraline interaction demonstrated by a phase I study. The prescribing information now states that concomitant use in patients taking monoamine oxidase inhibitors (MAOIs) or pimozide is contraindicated.

The study compared the disposition of intravenously administered diazepam before and after 21 days of dosing with either Zoloft® (50 to 200 mg/day escalating dose) or placebo. There was a 32% decrease relative to baseline in diazepam clearance for the ZOLOFT group compared to a 19% decrease relative to baseline for the placebo group (p<0.03). There was a 23% increase in Tmax for desmethyldiazepam in the Zoloft® group compared to a 20% decrease in the placebo group (p<0.03). The clinical significance of these changes is unknown.

In a placebo-controlled trial in normal volunteers, the administration of two doses of Zoloft® did not significantly alter steady-state lithium levels or the renal clearance of lithium. Nonetheless, at this time, it is recommended that plasma lithium levels be monitored following initiation of therapy with appropriate adjustments to the lithium dose.

In a controlled study of a single dose (2 mg) of pimozide, 200 mg sertraline (q.d.) co-administration to steady state was associated with a mean increase in pimozide AUC and Cmax of about 40%, but was not associated with any changes in EKG. Since the highest recommended pimozide dose (10 mg) has not been evaluated in combination with sertraline, the effect on QT interval and PK parameters at doses higher than 2 mg at this time are not known. While the mechanism of this interaction is unknown due to the narrow therapeutic index of pimozide and due to the interaction noted at a low dose of pimozide, concomitant administration of sertraline hydrochloride and pimozide should be contraindicated.

The risk of using sertraline hydrochloride in combination with other CNS active drugs has not been systematically evaluated. Consequently, caution is advised if concomitant administration with such drugs is required.

Inhaled corticosteroids and adrenal suppression

United Kingdom — The Committee on Safety of Medicines (CSM) has reminded prescribers that adrenal suppression is a well-established adverse reaction of all inhaled corticosteroids. There have been rare reports of adrenal suppression leading to adrenal crisis. Symptoms and signs may be under-recognized, particularly in children receiving higher than licensed doses of inhaled corticosteroids. The CSM has recently reviewed evidence, including spontaneously reported adverse drug reactions and a recent national survey of adrenal crisis due to inhaled corticosteroids.

Presenting symptoms of adrenal suppression and crisis are non-specific and include anorexia, abdominal pain, weight loss, tiredness, headache, nausea, vomiting, decreased level of consciousness, hypoglycaemia and seizures. Situations which may trigger acute adrenal crisis include...
infection, trauma, surgery or any rapid reduction in dosage. These are dose related class effects, and prescribers are strongly advised that the licensed dosages of all inhaled corticosteroids should not be exceeded in paediatric patients.


Re-introduction of urokinase

United States of America — The Food and Drug Administration recently approved the re-introduction of urokinase (Abbokinase®) onto the market. Urokinase has been used for more than 20 years by an estimated four million patients.

As a result of a review of previous use, the product is now indicated solely for the treatment of pulmonary embolism; lysis of massive pulmonary emboli and pulmonary emboli accompanied by unstable haemodynamics.

Information has been added to the labelling regarding post-marketing reports of anaphylaxis and other infusion reactions, as well as class information regarding the potential for cholesterol embolization.


Ezetimibe approved for cholesterol-lowering

United States of America — The Food and Drug Administration has approved ezetimibe (Zetia®), a new class of lipid-lowering compounds that selectively inhibits the intestinal absorption of cholesterol and related phytosterols.

Ezetimibe is effective in reducing total-C, LDL-C, Apo B and TG and increases HDL-C in patients with hypercholesterolaemia when administered with an HMG-CoA reductase inhibitor. It reduces blood cholesterol by inhibiting the absorption of cholesterol by the small intestine. Compared to placebo, ezetimibe had no clinically meaningful effect on plasma concentrations of the fat soluble vitamins A, D and E and did not impair adrenocortical steroid hormone production.

Ezetimibe is contraindicated in patients with active liver disease or unexplained persistent elevations in serum transaminases. All HMG-CoA reductase inhibitors are contraindicated in pregnancy.

WHO Collaborating Centre for Drug Statistics Methodology: Proceedings of the twentieth anniversary symposium:

In March 2002, the WHO Collaborating Centre for Drug Statistics Methodology celebrated its Twentieth anniversary in Oslo, Norway. The celebration was organized around a scientific symposium in parallel with the Eleventh meeting of the WHO International Working Group for Drug Statistics Methodology. Presentations were made by members of the Working Group, the World Health Organization, Ministry of Health, Norway, and the Norwegian Institute of Public health. An important aim of the symposium was to applaud the work and achievements of the WHO Collaborating Centre in drug utilization research and rational use of drugs.

A historical overview of the ATC/DDD methodology

Marit Rønning, WHO Collaborating Centre for Drug Statistics Methodology, Norway

Drug utilization research has attracted increased attention since its early beginnings in the 1960s. A breakthrough study on drug consumption during the period 1966–1967, pioneered by the WHO Regional Office for Europe, pointed to the differences in drug utilization between population groups in six European countries (1). In 1969, a WHO symposium declared the need for an internationally acceptable classification system. It was at this time that the Drug Utilization Research Group (DURG) was established and entrusted with development of drug utilization research methods. Inspired by this interest, a system named the Anatomical Therapeutic Chemical (ATC) classification was developed in Norway as a modification and extension of the European Pharmaceutical Market Research Association (EPhMRA) classification system.

In order to measure drug use, it is essential to have both a classification system and a unit of measurement. To deal with the drawbacks of traditional units of measurement, a technical unit of measurement called the Defined Daily Dose (DDD) was developed for use in drug utilization studies. This unit was defined as the assumed average maintenance dose per day for a drug when used for its main indication in adults.

The ATC/DDD system rapidly expanded to include most drugs on the Nordic market. The Nordic Statistics on Medicines was published using the ATC/DDD methodology for the first time in 1976. Meanwhile, international interest in the ATC/DDD system for drug utilization research was expanding beyond the Nordic countries, largely through activity of the DURG.

In 1981, the WHO Regional Office for Europe formally recognized the ATC/DDD system for drug utilization studies and, in 1982, the WHO Collaborating Centre for Drug Statistics Methodology at the Norwegian Medicinal Depot (NMD) was designated by WHO and financed by the Norwegian Government. In 1996, WHO recognized the need to strengthen the ATC/DDD system as an international standard and responsibility for the Centre was transferred to WHO Headquarters in Geneva. This was seen as an important step in the link between international drug utilization studies and WHO’s initiatives to promote access to essential drugs and the rational use of drugs. Provision of independent, validated information on drug use is essential to identify problems and needs for educational or other interventions and before monitoring of drug utilization patterns can take place.

In January 2002, the Centre was relocated to the Norwegian Institute of Public Health. According to the agreement between WHO and the Norwegian government, the Centre’s main responsibilities are focused around development and maintenance of the ATC/DDD system, including:
• To classify drugs according to the ATC system.
• To establish DDDs for drugs which have been assigned an ATC code.
• To review and revise as necessary the ATC classification system and DDDs.
• To stimulate and influence the practical use of the ATC system by cooperating with researchers in drug utilization.

In order to make the ATC/DDD system more internationally applicable, WHO established the WHO International Working Group for Drug Statistics Methodology. This working group consists of twelve WHO-appointed experts in clinical pharmacology, drug utilization, drug regulation, drug evaluation, statistics and medicine representing different users of the ATC/DDD system within the six WHO regions.

The main terms of reference of the working group are:
• To continue the scientific development of the ATC/DDD system.
• To discuss and approve all new ATC codes, DDD assignments and alterations to existing ATC codes and DDDs.
• To develop further the use of the ATC/DDD system as an international standard for drug utilization studies.
• To revise as necessary the guidelines for assignment and change of ATC codes and DDDs.
• To revise as necessary the procedures for applications for assignment of and changes to ATC codes and DDDs to ensure they are consistent and transparent.
• To assess the sources and availability of statistics on drug use internationally, and to encourage the systematic collection of comprehensive drug use statistics in all countries and regions using the ATC/DDD system as the international standard.
• To develop methods, manuals and guidelines for the practical application and appropriate use of the ATC/DDD system in drug utilization studies in a variety of settings, particularly those applicable to developing countries.
• To work with groups involved in rational drug use initiatives to integrate methods for measurement of drug use in assessing needs and outcomes of interventions with the aim of improving drug use.

A drug classification system represents a common language for describing the drugs available in a country or region and is a prerequisite for national and international comparisons of drug use data. The purpose of the ATC/DDD system is to serve as a tool for drug utilization research in order to improve the quality of drug use. One component of this is the presentation and comparison of drug consumption statistics.

A major aim of the Centre and Working Group is to maintain stable ATC codes and DDDs over time to allow trends in drug consumption to be studied without the complication of frequent changes to the system. There is a strong reluctance to make changes to classifications or DDDs where such changes are requested for reasons not directly related to drug consumption studies. For this reason the ATC/DDD system by itself is not suitable for guiding decisions about reimbursement, pricing and therapeutic substitution. The classification of a substance in the ATC/DDD system is not a recommendation for use, nor does it imply any judgments about efficacy or relative efficacy of drugs and groups of drugs.

After nearly 30 years of experience with ATC/DDD, the methodology has demonstrated its suitability in drug use research. The rapid increase in the number of users is a good indicator of the usefulness of the system. The main challenge in coming years will be to educate users worldwide on how to use the methodology properly.

References

2. Further information about the WHO Collaborating Centre for Drug Statistics Methodology and the ATC/DDD system: http://www.whocc.no
Drug utilization statistics and health policy

Anne Kari Lande Hasle, Secretary General, Norwegian Ministry of Health

Drug utilization statistics are an indispensable tool to fulfil goals outlined in health policy. Pharmaceuticals are recognized as playing a major role in maintaining health. In meeting health needs, medicinal drug policies need to be part of health policies and use of drugs in a community should thus be consonant with overall health goals. Achieving quality use of drugs is a priority in both developing and developed countries.

It should be underlined that drug utilization statistics are an important tool in the planning, monitoring and assessment of national drug policies. Drugs are one of the most frequently used treatments for a majority of diseases and complaints. As an example, an average 60% of all general practitioner consultations within Norway result in delivery of a prescription.

Availability of national data on drug use represents the first step in improving the quality of drug use in the population. In order to measure drug use, it is important to have a classification system and a unit of measurement. To meet this need, the Anatomical Therapeutic Chemical (ATC) classification system and the Defined Daily Dose (DDD) were developed in Norway in the early 1970s.

Norway has a long tradition of accurate wholesale statistics on drugs and was the first country to produce public drug statistics. Since 1977, these statistics have been published annually. This annual report contains complete information about drug sales in Norway and offers a rough estimate of what percentage of the population is receiving a certain drug treatment. Overall sales statistics are a valuable source of time trends and regional variations in drug consumption, both within the country and in comparison with others. Staff of the WHO Collaborating Centre in Oslo have also been responsible for drug use statistics at the national level. The centre is therefore a user of the methodology that it is responsible for maintaining and developing at the international level.

Although highly useful, the figures based on drug sales from wholesalers to pharmacies and hospitals have certain limitations for our use in Norway. The data do not reveal facts about the users or the prescribers. Thus, we still need information on:

- How many people in the population are using drugs.
- Which age and gender.
- For how long, and in which doses, they use drugs.

There is, therefore, a further need to establish a more comprehensive statistical base which will give deeper insight into prescribing and utilization of drugs in Norwegian society. To regulate and subsequently evaluate the impact of a country’s national drug policy for a more rational use of drugs, it is vital that the system designed to collect medicine consumption data is set up at the level of individual patients. However, studies of how drugs are actually being used, and identification of determinants for change in patterns of use, can only be made after the drug has been launched on the market.

Therefore, the Norwegian Ministry of Health is considering the establishment of a new national register based on computerized prescriptions from all pharmacies in Norway. The initiative to seek more detailed drug statistics came partly in response to changes in the infrastructure of the Norwegian drug market, when Norway became a member of The European Economic Association (EEA) in 1995.

In the future, importance will focus on analysis of the use of medications from a public health perspective and an evaluation of other aspects of public health in relation to drug expenditure. The recommended prescription register in Norway will cover the entire population of 4.5 million inhabitants, and will clearly offer unique possibilities for research and a better knowledge base for national decision-making in drug utilization.

The work of the WHO Centre represents an important basis for all types of drug utilization statistics. From January 2002, the Centre has been formally located at the Norwegian Institute of Public Health. This location will hopefully provide positive synergy between the Centre and the new Institute. The Ministry of Health in Norway considers it important to secure optimal continuation of the good work of the Centre, particularly with regard to its independent status.
Trends in drug utilization research in developing countries
Hans V. Hogerzeil, Policy, Access and Rational Use, Department of Essential Drugs and Medicines Policy, World Health Organization

The price of essential medicines is growing. For example, gonorrhoea is increasingly resistant to penicillin: the new-generation antibiotics now needed to cure the disease are 50 to 90 times more expensive. New arthemether-based combination medicines against malaria are 25 times as expensive as chloroquine, the standard malaria treatment, even at the preferential rate for developing countries negotiated by WHO. Other malaria combination therapies can cost up to 200 times as much as chloroquine. Six months of DOTS treatment for uncomplicated tuberculosis now costs less than $10 per person; but treatment for multidrug-resistant tuberculosis may be 100 times as expensive.

Thirty-eight countries have an annual medicines budget of less than $2 per person. But many of these countries are heavily hit by HIV/AIDS, for which antiretroviral treatment costs several hundred dollars per year. In view of these huge costs, the careful selection of a treatment of choice for public supply systems or reimbursement purposes remains extremely important, both medically and economically.

Within WHO, the selection of essential medicines is moving away from experience-based towards evidence-based selection, or, as some like to call it, “from eminence-based to evidence-based”. At the same time, considerations of efficacy of the drug are balanced by cost-effectiveness of the treatment as a whole and, if possible, by marginal cost-effectiveness (comparing the additional benefit in effectiveness or safety against the additional cost).

An example of this approach is the recent review by WHO and UNAIDS health economists of the cost-effectiveness of the various interventions in the prevention and treatment of HIV/AIDS (1). For example, the targeted distribution of condoms is very cost-effective — at less than one dollar per life year gained. Certain methods to ensure safe blood transfusion, the treatment of tuberculosis and the prevention of mother-to-child transmission of HIV with nevirapine cost less than $100 per life year gained. On the other hand, the treatment of some HIV opportunistic infections and combination treatment with antiretroviral medicines may cost several hundreds of dollars per life year gained.

Early drug utilization studies, as practised in Nordic countries for example, were usually based on aggregated drug use data from national or provincial sales reports or prescription data. These studies tended to be purely descriptive which limited their utility and were not always easy to translate into action. In the early 1990s, WHO and the International Network for the Rational Use of Drugs (INRUD) developed and published a simple sampling method and a standard set of indicators to describe core aspects of prescribing and dispensing (2). These indicators have proved extremely useful in screening the quality of care, identifying problem areas, making comparisons between countries and over time, and in measuring the impact of interventions. The indicators are also descriptive but they can be targeted to certain populations, they cover other aspects of the quality of care and they add quantitative measures. They describe WHAT and HOW MUCH. For example, what proportion of prescriptions in a given province or hospital contain one or more antibiotics.

Before one can hope to change a certain pattern of irrational drug use it is essential to know why a certain type of behaviour is occurring. This could be through lack of knowledge, workload, patient demand, commercial pressure, financial incentives or any other reason. In order to know this, qualitative studies are needed, usually based on observations, structured interviews, peer group discussion or other techniques. They describe the WHY of drug utilization. For example, why do doctors prescribe so many antibiotics?

When it is known why a certain prescribing behaviour occurs, a targeted intervention may be started. But does it change anything? To know this, a drug use intervention study will be needed. Most of such studies use the WHO indicators mentioned above which adequately cover most aspects of irrational drug use: polypharmacy, overuse of antibiotics and injections, lack of generic prescribing and non-adherence to national or institutional essential medicines lists. These studies measure the effectiveness of the intervention and answer the question DOES IT WORK? Did the intervention actually reduce the percentage of prescription with one or more antibiotics? And did the effect last? Did the effect occur in the control group which was not subject to the intervention?

And even that is not enough. A small-scale intervention in a research setting may be effective; but that may be due to intensive planning and supervi-
sion, for example. So management studies are needed with a focus on the question is the intervention reproducible and is the intervention cost effective? The selection of policy decisions and management interventions is increasingly based on evidence of effectiveness and, preferably, cost-effectiveness. Probably the best study in this regard was published by Guiscafré (3) in which he proved that scaling up of an educational intervention in the treatment of diarrhoea and respiratory infection in Mexico was very cost-effective (savings amounted to 4.4 and 21.6 times the cost of the intervention, respectively).

The first International Conference on Improving the Use of Medicines (ICIUM) held in Chiang-Mai (Thailand) in 1997, systematically reviewed the interventions in developing countries. Considerable gaps in research were identified, especially in the field of improving drug use in hospital settings, in the private sector and in the community; on interventions to improve the use of antibiotics and antimalarial drugs; and the impact of drugs and therapeutic committees and of financial incentives. It is hoped that ICIUM-2, which will again be held in Chiang Mai, in April 2004, will identify more effective interventions in these areas. The research methods are available.

References


Drug utilization data constraints in developing countries

Tariq Iqbal Bhutta, Professor of Paediatrics, Nishtar Medical College, Pakistan

Private expenditure on pharmaceuticals in developing countries typically accounts for 50–90% of all spending on drugs. Even for rural populations and the urban poor, the most common source of drugs is out-of-pocket purchase from the private market. On the other hand, sometimes as much as 50% of the health budget of developing countries is used for buying drugs. Beyond these figures, very little data is available on how drugs are utilized.

Drug provision and distribution usually rely on a mix of public and private services to ensure the regular supply of essential drugs. Although drugs are available through both the public and private health systems, data on their use is either unavailable or totally inadequate in most developing countries. In addition, it is known that up to 80% of the population in developing countries also use traditional medicine to help meet health care needs.

In developing countries, public health is afforded little interest or priority by the authorities and there exists a further divide between urban and rural areas. Although much of the population lives in the rural areas, most of the health care budget is spent in the urban areas with the result that rural populations lack access to the most basic services and to qualified medical practitioners. The doctor-patient ratio in rural areas is extremely low, with the result that the majority of the population will seek care from traditional health practitioners.

A large number of factors influence drug utilization in these countries. Firstly, much depends upon the priority that the health sector receives in the budget. It will also depend upon the medical needs and demands of the population. For example, if there is a high incidence of HIV/AIDS, malaria, and tuberculosis, this will reflect in the demand for drugs to treat these diseases. None the less, introduction of new drugs on the market and their sometimes aggressive marketing can significantly increase their use irrespective of actual need.

Drug utilization also responds to regulatory efforts and national drug policies, registration policies and — at a local level — by the existence of local drug committees. In most developing countries, the public sector’s role in providing health care to the population is shrinking and that of the private sector is expanding. This is particularly true for the least developed countries of Africa as well as emerging market economies like India, Pakistan, and China. A decreasing government role in drug control is known to have a marked influence on drug utilization.

Health professionals and their preferences are also playing an ever-increasing role in determining what drugs are prescribed, marketed and even registered. To a certain extent, cultural preferences may
also influence drug utilization, such as the popularity of injections in certain countries like Pakistan and Middle East countries due to the perception that injectable drugs are more potent and effective compared to oral formulations.

In many developing countries, drugs are supplied without any record being kept. They are usually available without prescription and can also be dispensed by pharmacists, traditional practitioners and drug vendors. Even in those situations where drugs are introduced through the government or private sector there is total absence of monitoring — and substandard or counterfeit drugs may also compound the problem. Where drugs are in short supply or expensive, drug smuggling is also practised.

Drug utilization data is therefore difficult to obtain and almost nonexistent in most of the developing world. Neither is data on imported drugs available within the ministry of health — responsible for prescribing — but usually with other ministries like commerce and industry responsible for importation. Even in those countries where drugs are being manufactured locally, the data on quantities supplied is not available or reliable. Finally, in large hospitals in the public sector, records of drug supply or dispensing are incomplete since many drugs are bought directly by the patients on the market.

The Working Group has two members from each of the six WHO regions. Its terms of reference require it to approve all new and altered ATC classifications and DDD assignments, to revise the policies and guidelines as appropriate, and to stimulate the application of the system to improve drug use particularly in relation to developing countries.

Most developing and, indeed, developed countries do not have comprehensive data on drug use at a national level. Drug utilization data is essential to:

- follow trends in drug consumption and cost;
- benchmark against similar countries or regions;
- audit use against practice guidelines;
- measure the impact of interventions against misuse;
- increase awareness in stakeholders including governments; and
- assess the access to and the quality and cost effectiveness of care.

An example of the need for drug utilization data is demonstrated by antibiotic resistance surveillance. Antibiotic utilization data are needed to:

- Relate resistance development to antibiotic exposure
- Target prevention and control measures.
- Identify and provide early warning of problems relating to changes in exposure and utilization.
- Monitor the outcomes of interventions aimed at changing exposure.
- Assess quality of care against practice guidelines.
- Inform policy.
- Raise awareness in health professionals, consumers and policy makers.

Very little information on drug consumption is available in most developing countries. Information is often lacking on even the broadest measures of drug use such as the overall volume of use and total spending on drugs. Additionally, the actual use within various drug groups is needed to assess the

The future of ATC/DDD and drug utilization research

D. J. Birkett, Professor and Head, Department of Clinical Pharmacology, Flinders University and Flinders Medical Centre, Adelaide, Australia and Chair, WHO International Working Group for Drug Statistics Methodology

The ATC/DDD drug classification and measurement system has been central to the development of drug utilization research. The system was initially developed in the Scandinavian countries and was then administered through the WHO Regional Office for Europe by a European Advisory Group, and inevitably had a European ‘flavour’. In 1996, WHO accepted the system as its official international standard, and established the WHO Collaborating Centre for Drug Statistics Methodology in Oslo and an expert group — The WHO International Working Group for Drug Statistics Methodology — to maintain and further develop the system.
profile of use against, for example, the national essential drug list or local health needs. At a finer level, drug utilization data is needed to address issues such as the proportion of overall use represented by generics, the use of irrational combination products, the routes of administration (oral versus injected antibiotics for example) and the profiles of drug use in regions, hospitals or health facilities. Once such information is available, the profiles of drug use can be compared with those in other countries to benchmark practice and to develop hypotheses about the reasons for variation in use.

The International Working Group has identified the following priorities at international level:

• Availability of valid and comprehensive drug utilization data should be an integral component of national drug policies.

• There is a need to establish the availability, sources and types of data available and accessible in a variety of settings, particularly in developing countries. These might include import data, wholesale sales data, claims data and so on. It is anticipated that some useful data would be available in most countries but access to it will need to be developed and the data validated.

• Use of the ATC/DDD system needs to be encouraged at an international level to allow valid international comparisons of drug use. This does not preclude the use of local coding, classification and measurement systems as these can easily be mapped to the ATC/DDD system.

• Drug utilization measures need to be applied as process and outcome indicators to inform drug policy and enhance quality use of medicines at national and international levels. These indicators need to be simple, practicable, robust, tested and validated.

• Information on prescribed daily doses (PDDs) is needed from a variety of settings and ethnic groups. Detailed interpretation of DDD data in a particular setting requires knowledge of the relationship of the PDD to the DDD. Information provided to the International Working Group indicates that the PDDs for some drug groups differ substantially between different countries — as much as three- to fourfold. Interestingly, these variations in PDDs do not seem to be reflected by the dosing recommendations in the local approved product information documents.

• Finally, regional training courses are needed on the methods and applications of drug utilization research and on the use of the ATC/DDD system.

Some of these needs are being addressed. The International Working Group has established several pilot projects to investigate at a practical level the types of data that could be available in developing and developed countries. The utilization of antibiotics and antihypertensives are being looked at in the first instance. A project is also being developed to look at whether a consistent stream of data on PDDs in various countries could be available to inform the setting of and changes to DDDs.

A manual, *Introduction to Drug Utilization Research*, has been produced by the International Working Group and is being used in training workshops that are to be held in each of the WHO regions.

The primary purpose of the ATC/DDD system is to serve as a tool for drug utilization research, and to follow and compare profiles and trends in drug consumption. This demands a stable system as possible and militates against frequent changes in classification or DDD values. The DDD is set initially, usually at the time of marketing, on the basis of dose recommendations in the product information and information from clinical trials. This is reviewed after three years or on request from users of the system. However, in the interest of maintaining a stable system, changes of less than 50% are usually only considered at the three-year review. DDDs may be changed due to changes in the main indication, or changes in the prescribed daily doses post marketing.

Some governments are using ATC classification groups as a basis for reference group pricing, and DDDs to establish "therapeutically equivalent doses" for pricing purposes. Pharmaceutical manufacturers also do not hesitate to use the system for marketing or in price negotiations when it suits their purposes. This results in considerable pressure from the industry on the International Working Group to change ATC classifications and to make frequent small changes to DDDs to achieve advantage for companies in pricing negotiations or marketing.

This conflicts with the primary goal of the Oslo Collaborating Centre and the International Working Group – to maintain a stable drug classification.
system and utilization metric for use in studies of drug consumption. The system may be an acceptable starting point for drug reimbursement decisions but because it is established and maintained for a different purpose, it is not suitable as the sole basis for such decisions. Regulatory and reimbursement decisions, even if using the ATC/DDD system as a starting point, have to be made at a local level based on local regulatory and reimbursement policies and practices, and include considerations of local patterns and cultures of drug use. Maintenance of the ATC/DDD system raises complex scientific and sensitive commercial issues. The end result is not perfect, as it is inevitably a compromise between scientific accuracy, a stable system and (unfortunately) commercial pressures. Nonetheless, it works well in practice, there is long experience with its use, and it is endorsed by WHO as the international standard. Such an international system is necessary to allow valid international comparisons of drug use patterns and trends to support quality use of medicines and better health outcomes. To achieve this, the challenge now is to develop and validate sources of drug use information in a variety of settings at the international level.
Recent Publications and Sources of Information

International Ethical Guidelines for Biomedical Research Involving Human Subjects

This is the third in the series of international ethical guidelines for biomedical research involving human subjects issued by the Council for International Organizations of Medical Sciences (CIOMS) since 1982. Its scope and preparation reflect the transformation that has occurred in the field of research ethics and the changes to the Helsinki Declaration, upon which the guidelines are based. They particularly reflect the conditions and needs of biomedical research within all countries and the implications for international research of both different cultures and universal ethical standards.

The mere formulation of ethical guidelines for biomedical research will hardly resolve the doubts that can arise in the application of all research, but the guidelines attempt to draw the attention of sponsors, investigators and ethical review committees to the need to consider carefully the ethical implications of research protocols and the conduct of clinical trials. In this way, the highest possible scientific and ethical standards may be achieved.

International Ethical Guidelines for Biomedical Research Involving Human Subjects. Available from: Council for International Organizations of Medical Sciences (CIOMS), World Health Organization, Geneva. e-mail: gallagherj@who.ch

Surveying and Evaluating Ethical Review Practices

Ethical review provides essential guidance on conducting research and protection of trial subjects. The purpose of Surveying and Evaluating Ethical Review Practices is to facilitate and support procedures for quality and transparency in ethical review. The guideline is complementary to the earlier Operational Guidelines for Ethical Committees that Review Biomedical Research, published in 2001 by the Tropical Disease Research Programme (TDR) at the World Health Organization.

Monitoring and evaluation of ethical review practices will contribute to strengthening of public confidence in research and clinical trial management by facilitating procedures for quality and transparency and promoting good practices. Ethical standards underpinning such practices have been established in international guidelines, including the Helsinki Declaration and the CIOMS International Ethical Guidelines for Biomedical Research Involving Human Subjects.

There is growing national and international interest in ensuring that ethical review achieves the highest standards in protecting individuals and communities alike and internal review of the ethical committee’s operations, such as self assessment checklists, also provides measures to evaluate performance.

Surveying and Evaluating Ethical Review Practices. Available from: Product Research and Development, TDR/CDS, World Health Organization, Geneva. e-mail: karbwangj@who.ch

The Importance of Pharmacovigilance

This document sets out to present the case for the importance of pharmacovigilance, to record its growth and potential as a discipline within medical science, and to describe its impact on patient welfare and public health. It presents a critical examination of the strengths and weaknesses of present systems of safety monitoring.

Pharmacovigilance — the detection, assessment, understanding and prevention of adverse drug reactions — involves the rapid transmission of information on adverse drug reactions detected by monitoring systems collecting international and national data.

In order to meet the challenges of drug safety needs for the coming ten years, increase the impact of pharmacovigilance systems, and ensure that these deliver their benefits, an appraisal needs to be made and collaboration and communication at local, regional and international levels strengthened.
As the scope of pharmacovigilance extends beyond that of drugs to include herals, blood products, biologicals, vaccines, and medical devices, new safety concerns need to be reconciled. These changes are compounded by illegal sale of medicines, substandard and counterfeit products, self medication, drug interactions, and sale of products over the Internet.

The document offers an overview of the challenges facing pharmacovigilance in the future. Increasing public expectations of safety add another dimension of pressure for change and increased need for collaboration. National monitoring centres are in a limited position to address safety concerns, but are particularly able to detect and anticipate impact.

Major challenges outlined in the document include globalization, e-commerce, automated signal detection, and changing patterns of drug use.

The Importance of Pharmacovigilance. Safety Monitoring of Medicinal Products. Available from: Essential Drugs and Medicines Policy, World Health Organization, Geneva e-mail couperm@who.ch

Effective drug regulation

Drugs play a crucial role in saving lives, restoring health and preventing diseases and epidemics. But they also need to be safe, efficacious, of good quality and used rationally. Their production, import/export, storage, supply and distribution should be subject to government control through prescribed regulations and an effective system. Substandard and counterfeit drugs proliferate primarily in an environment where drug regulation has proved ineffective. If regulatory objectives are to be achieved, governments need strong national drug regulatory authorities with a sound structure and the legal power to carry out their duties.

Effective drug regulation: a multicountry study presents a synthesis of studies carried out in ten countries (5% of WHO Member States): Australia, Cuba, Cyprus, Estonia, Malaysia, the Netherlands, Tunisia, Uganda, Venezuela and Zimbabwe in 1998–1999. It gives an overview of development of drug regulation in these countries as well as an indication of the resources available and the strategies applied to implement drug regulation. A guide for data collection to assess drug regulatory performance is also provided as an annex.


Dialogue in pharmacovigilance

In 1997, the Verona Initiative aimed to improve communication of drug safety information to the benefit of patients, health professionals, drug regulators, the pharmaceutical industry, educators, researchers, the media and legal profession.

The main outcomes of the meeting were to allow information providers and recipients to be equal partners in a win/win position and to achieve understanding, openness, and empowerment through initiatives in education and appropriate communication. A general model was proposed and the present document provides guidance on principles of good communication, the role of the parties in providing education and information, and crisis management.

Dialogue in Pharmacovigilance. More Effective Communication is available from: The Uppsala Monitoring Centre, http://www.who-umc.org or e-mail: info@who-umc.org

Good storage practices

The Guide to Good Storage Practices for Pharmaceuticals was approved at the Thirty-seventh meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations held on 22–26 October 2001 in Geneva. The guide is intended for those involved in the storage, transportation and distribution of pharmaceutical products. It supplements earlier documents on related subjects.

Instructions are given covering personnel, premises and facilities, storage conditions and requirements, receipt and stock rotation, and product recall.

International Nonproprietary Names for Pharmaceutical Substances (INN)

RECOMMENDED International Nonproprietary Names (Rec. INN): List 48

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. Wild 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 (1–85) and Recommended (1–45) International Nonproprietary Names can be found in Cumulative List No. 10, 2002 (available in CD-ROM only).

Dénominations communes internationales des Substances pharmaceutiques (DCI)

Dénominations communes internationales RECOMMANDÉES (DCI Rec): Liste 48


Denominaciones Comunes Internacionales para las Sustancias Farmacéuticas (DCI)

Denominaciones Comunes Internacionales RECOMENDADAS (DCI Rec.): Lista 48

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.

<table>
<thead>
<tr>
<th>Latin, English, French, Spanish:</th>
<th>Recommended INN</th>
<th>Chemical name or description; Molecular formula; Graphic formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>DCI Recommandée</td>
<td>Nom chimique ou description; Formule brute; Formule développée</td>
<td></td>
</tr>
<tr>
<td>DCI Recomendada</td>
<td>Nombre químico o descripción; Fórmula empírica; Fórmula desarrollada</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>acolbifenum</th>
<th>(+)-(2S)-3-(4-hydroxyphenyl)-4-methyl-2-[4-[2-(piperidin-1-yl)ethoxy]phenyl]-2H-1-benzopyran-7-ol</th>
</tr>
</thead>
<tbody>
<tr>
<td>acol bifene</td>
<td>(+)-(2S)-3-(4-hydroxyphényl)-4-méthyl-2-[4-[2-(pipéridin-1-yl)éthoxy]phényl]-2H-1-benzopyran-7-ol</td>
</tr>
<tr>
<td>acol bifène</td>
<td>(+)-(2S)-3-(4-hidroxyfenil)-4-metil-2-[4-[2-(piperidin-1-il)etoxi]fenil]-2H-1-benzopiran-7-ol</td>
</tr>
</tbody>
</table>

\[
\text{acolbifeno} \quad \text{(+)-(2S)-3-(4-hidroxi fenil)-4-metil-2-[4-[2-(piperidin-1-il)etoxi]fenil]-2H-1-benzopiran-7-ol}
\]

\[
C_{29}H_{31}NO_4
\]

\[
\text{acolbifeno} \quad \text{(+)-(2S)-3-(4-hidroxi fenil)-4-metil-2-[4-[2-(piperidin-1-il)etoxi]fenil]-2H-1-benzopiran-7-ol}
\]

\[
C_{29}H_{31}NO_4
\]

<table>
<thead>
<tr>
<th>asprinsnilum</th>
<th>11β-[4-[(E)-(hydroximino)methyl]phenyl]-17β-methoxy-17-(methoxymethyl)estra-4,9-dien-3-one</th>
</tr>
</thead>
<tbody>
<tr>
<td>asprinsnil</td>
<td>11β-[4-[(E)-(hydroximino)méthyl]phényl]-17β-méthoxy-17-(méthoxyméthyl)estra-4,9-dién-3-one</td>
</tr>
<tr>
<td>asprinsnilo</td>
<td>11β-[4-[(E)-(hidroxiimino)metil]fenil]-17β-metoxi-17-(metoximetil)estra-4,9-dien-3-ona</td>
</tr>
</tbody>
</table>

\[
\text{asprinsnilo} \quad \text{11β-[4-[(E)-(hidroxiimino)metil]fenil]-17β-metoxi-17-(metoximetil)estra-4,9-dien-3-ona}
\]

\[
C_{28}H_{35}NO_4
\]
**atomoxetinum**  
atomoxetine  
(-)-(3R)-N-methyl-3-(2-methylphenoxy)-3-phenylpropan-1-amine

**atomoxétine**  
atomoxétine  
(-)-(3R)-N-méthyl-3-(2-méthylphénoxy)-3-phénylpropan-1-amine

**atomoxetina**  
atomoxetina  
(-)(3R)-3-fenil-N-metil-3-(2-metilfenoxi)propan-1-amina  

\[C_{17}H_{21}NO\]

\[
\begin{array}{c}
\text{O} \\
\text{H} \\
\text{N} \\
\text{CH}_3 \\
\end{array}
\]

**bazedoxifenum**  
bazedoxifene  
1-[4-[2-(hexahydro-1H-azepin-1-yl)ethoxy]benzyl]-2-(4-hydroxyphenyl)-3-methyl-1H-indol-5-ol

**bazédoxifène**  
bazedoxifene  
1-[4-[2-(hexahydro-1H-azépin-1-yl)éthoxy]benzyl]-2-(4-hydroxyphényl)-3-méthyl-1H-indol-5-ol

**bazedoxifeno**  
bazedoxifeno  
1-[4-[2-(hexahidro-1H-azepin-1-il)etoxi]bencil]-2-(4-hidroxifenil)-3-metil-1H-indol-5-ol  

\[C_{30}H_{34}N_2O_3\]

\[
\begin{array}{c}
\text{O} \\
\text{N} \\
\text{CH}_3 \\
\text{OH} \\
\text{O} \\
\text{N} \\
\end{array}
\]

**bifarceptum**  
bifarcept  
interferon α/β receptor (human isoform p40 precursor)

**bifarcept**  
bifarcept  
précurseur de la partie soluble de la chaîne 2 du récepteur humain de type I de l’interféron α et β

**bifarcepto**  
bifarcepto  
precursor de la fracción soluble de la cadena 2 del receptor humano de tipo I del interferón α y β
Recommended INN: List 48

**coluracetamum**

*coluracetam*  
\[N-(2,3\text{-dimethyl-5,6,7,8-tetrahydrofuro}[2,3-b]quinolin-4-yl)-2-(2-oxopyrroloidin-1-yl)acetamide\]

*coluracétam*  
\[N-(2,3\text{-diméthyl-5,6,7,8-tétrahydrofuro}[2,3-b]quinoléin-4-yl)-2-(2-oxopyrroloidin-1-yl)acétamide\]

*coluracetam*  
\[N-(2,3\text{-dimetil-5,6,7,8-tetrahidrofuro}[2,3-b]quinolin-4-il)-2-(2-oxopirroloidin-1-il)acetamida\]

\[\text{C}_{19}\text{H}_{23}\text{N}_{3}\text{O}_{3}\]

\[
\begin{array}{c}
\text{N} \\
\text{O} \\
\text{H} \\
\text{O} \\
\text{CH} \_3 \\
\end{array}
\]

**dapivirinum**

*dapivirine*  
\[4\text{-}[4\text{-}[2,4,6\text{-trimethyl phenyl}]amino]pyrimidin-2-yl]amino]benzonitrile\]

*dapivirine*  
\[4\text{-}[4\text{-}[2,4,6\text{-triméthyl phényl}]amino]pyrimidin-2-yl]amino]benzonitrile\]

*dapivirina*  
\[4\text{-}[4\text{-}[2,4,6\text{-trimetilfenil}]amino]pirimidin-2-il]amino]benzonitrilo\]

\[\text{C}_{30}\text{H}_{31}\text{N}_{5}\]

\[
\begin{array}{c}
\text{H} \_3 \\
\text{N} \\
\text{H} \\
\text{N} \\
\text{CN} \\
\text{CH} \_3 \\
\text{CH} \_3 \\
\text{H} \_3 \\
\text{CH} \_3 \\
\end{array}
\]
**deferasiroxum**
deferasirox 4-[3,5-bis(2-hydroxyphenyl)-1H-1,2,4-triazol-1-yl]benzoic acid
déférasirox acide 4-[3,5-bis(2-hydroxyphényl)-1H-1,2,4-triazol-1-yl]benzoïque
deferasirox ácido 4-[3,5-bis(2-hidroxifenil)-1H-1,2,4-triazol-1-il]benzoico

\[\text{C}_{21}\text{H}_{15}\text{N}_{3}\text{O}_{4}\]

![Chemical structure of deferasiroxum](image)

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**degarelixum**
degarelix \(N\)-acetyl-3-(naphtalen-2-yl)-\(\delta\)-alanyl-4-chloro-\(\delta\)-phenylalanyl-3-(pyridin-3-yl)-\(\delta\)-alanyl-L-sereryl-4-[\(\{(4\,S\,)-2,6\text{-dioxohexahydropyrimidin-4-yl}\}\text{carbonyl}\text{amino}\}]-\(\delta\)-phenylalanyl-4-(carbamoylamino)-\(\delta\)-phenylalanyl-L-leucyl-\(N^6\)-(1-methylethyl)-L-lysyl-L-prolyl-\(\delta\)-alaninamide
dégarélix acétyl-[3-(naphtalen-2-yl)-\(\delta\)-alanyl]-(4-chloro-\(\delta\)-phénylalanyl)-[3-(pyridin-3-yl)-\(\delta\)-alanyl]-L-séryl-[4-\[\{(4\,S\,)-2,6\text{-dioxohexahydropyrimidin-4-yl}\}\text{carbonyl}\text{amino}\]]-\(\delta\)-phénylalanyl]-[4-(carbamoylamino)-\(\delta\)-phénylalanyl]-L-leucyl-[\(N^6\)-(1-méthyléthyl)-L-lysyl]-L-prolyl-\(\delta\)-alaninamide
degarelix \([N\text{-acétilel}-3-(naftalen-2-Il)-\(\delta\)-alani]-[4-cloro-\(\delta\)-fenilalani]-[3-\{piridin-3-Il\}-\(\delta\)-alani]-L-seri]-[4-\{(4\,S\,)-2,6\text{-dioxohexahidropirimidin-4-Il}\}carbonil]-L-fenilalani]-[4-(carbamoilamino)-\(\delta\)-fenilalani]-L-leucil-[\(N^6\)-(1-metiletil)-L-lisi]-L-proli-\(\delta\)-alaninamida

\[\text{C}_{82}\text{H}_{103}\text{ClN}_{18}\text{O}_{16}\]

![Chemical structure of degarelixum](image)
**dersalazinum**

dersalazine  

**dersalazine**  

**dersalazina**  

\[C_{35}H_{32}N_{6}O_{4}\]

**detiviciclovirum**

detiviclovir  
2-[(2-amino-9H-purin-9-yl)methyl]propane-1,3-diol

détiviclovir  
2-[(2-amino-9H-purin-9-yl)méthyl]propane-1,3-diol

detiviclovir  
2-[(2-amino-9H-purin-9-il)metil]propano-1,3-diol

\[C_{9}H_{13}N_{5}O_{2}\]

**edonentanum**

edonantan  
\[N-\{2'-\{[4,5-dimethylisoxazol-3-yl]sulfamoyl\}-4-(oxazol-2-il)biphenyl-2-yl\}methyl\}N,3,3-trimethylbutanamide\]

édonantan  
\[N-\{2'-\{[4,5-dimethylisoxazol-3-yl]sulfamoyl\}-4-(oxazol-2-il)biphényl-2-yl\}méthyl\}N,3,3-triméthylbutanamide\]

edonentán  
\[N-\{2'-\{[4,5-dimetilisoxazol-3-il]sulfamoil\}-4-(oxazol-2-il)bifenil-2-il\}metil\}N,3,3-trimetilbutanamida\]
**efaproxiralum**

**efaproxiral**

2-[4-[(3,5-dimethylphenyl)amino]-2-oxoethyl]phenoxy]-2-methylpropanoic acid

**édaproxiral**

acide 2-[4-[[3,5-diméthylphényl]amino]-2-oxoéthyl]phénoxy]-2-méthylpropanoïque

**efaproxiral**

ácido 2-[4-[[3,5-dimetilfenil]amino]-2-oxetil]fenoxi]-2-metilpropanoico

\[ C_{28}H_{32}N_{4}O_{5}S \]

![Chemical structure of efaproxiralum](image)

**fadolmidinum**

**fadolmidine**

3-(imidazol-4-ylmethyl)-5-indanol

**fadolmidine**

(3RS)-3-[[1H-imidazol-4-yl)méthyl]-2,3-dihydro-1H-indén-5-ol

**fadolmidina**

3-(imidazol-4-ilmetil)-5-indanol

\[ C_{13}H_{14}N_{2}O \]

![Chemical structure of fadolmidinum](image)
flindokalnerum
flindokalner (3S)-3-(5-chloro-2-methoxyphenyl)-3-fluoro-6-(trifluoromethyl)-1,3-dihydro-2H-indol-2-one

flindokalner (3S)-3-(5-chloro-2-méthoxyphényl)-3-fluoro-6-(trifluorométhyl)-1,3-dihydro-2H-indol-2-one

flindokalner (3S)-3-(5-cloro-2-metoxifenil)-3-fluoro-6-(trifluorometil)-1,3-dihidro-2H-indol-2-ona

\[
C_{16}H_{10}ClF_4NO_2
\]

![Flindokalnerum](image)

gimatiecanum
gimatecan (4S)-11-[(E)-[(1,1-dimethylethoxy)imino]methyl]-4-ethyl-4-hydroxy-1,12-dihydro-14H-pyran[3',4':6,7]indolizino[1,2-b]quinoline-3,14(4H)-dione


gimatecán (4S)-11-[(E)-[(1,1-dimetiletoxi)imino]metil]-4-etil-4-hidroxi-1,12-dihidro-14H-pirano[3',4':6,7]indolizino[1,2-b]quinolina-3,14(4H)-diona

\[
C_{25}H_{25}N_3O_5
\]

![Gimatecanum](image)

icardinum
icaridin 1-methylpropyl 2-(2-hydroxyethyl)piperidine-1-carboxylate

icaridine 2-(2-hydroxyéthyl)pipéridine-1-carboxylate de 1-méthylpropyle

icaridina 2-(2-hidroxietil)piperidina-1-carboxilato de sec-butilo

\[
C_{12}H_{23}NO_3
\]

![Icaridinum](image)
**iguratimodum**

*iguratimod*  
\[N-\{(\text{methylsulfonyl})\text{amino}\}\text{-}4\text{-}\text{oxo}-6\text{-}\text{phenoxy}\text{-}4\text{H}-1\text{-}\text{benzopyran-3-yl}\}\text{formamide}\]

*iguratimod*  
\[N-\{(\text{méthylsulfonyl})\text{amino}\}\text{-}4\text{-}\text{oxo}-6\text{-}\text{phénoxy}\text{-}4\text{H}-1\text{-}\text{benzopyran-3-yl}\}\text{formamide}\]

*iguratimod*  
\[N-\{(\text{metilsulfonil})\text{amino}\}\text{-}4\text{-}\text{oxo}-6\text{-}\text{fenoxi}\text{-}4\text{H}-1\text{-}\text{benzopiran-3-il}\}\text{formamida}\]

\[C_{17}H_{14}N_{2}O_{6}S\]

---

**ilaprazolum**

*ilaprazole*  
\[2\text{-}\{(\text{RS})\text{-}\{(4\text{-methoxy}-3\text{-methylpyridin-2-yl})\text{methyl}\}\text{sulfinyl}\}\text{-}5\text{-}\{(1\text{H}-\text{pyrrol-1-yl})\}\text{-}1\text{H}-\text{benzimidazole}\]

*ilaprazole*  
\[2\text{-}\{(\text{RS})\text{-}\{(4\text{-méthoxy}-3\text{-méthylpyridin-2-yl})\text{méthyl}\}\text{sulfinyl}\}\text{-}5\text{-}\{(1\text{H}-\text{pyrrol-1-yl})\}\text{-}1\text{H}-\text{benzimidazole}\]

*ilaprazol*  
\[2\text{-}\{(\text{RS})\text{-}\{(4\text{-metoxi}-3\text{-metilpiridin-2-il})\text{metil}\}\text{sulfinil}\}\text{-}5\text{-}\{(1\text{H}-\text{pirrol-1-il})\}\text{-}1\text{H}-\text{bencimidazol}\]

\[C_{19}H_{18}N_{4}O_{2}S\]

---

*and enantiomer*  
*ét enantiomère*  
*y enantiómero*
**indiplonum**

**indiplon**  
$N$-methyl-$N$-[3-[3-(thiophen-2-ylcarbonyl)pyrazolo[1,5-a]pyrimidin-7-yl]phenyl]acetamide

**indiplone**  
$N$-méthyl-$N$-[3-[3-(thiophén-2-ylcarbonyl)pyrazolo[1,5-a]pyrimidin-7-yl]phényl]acétamidé

**indiplón**  
$N$-metil-$N$-[3-[3-(tiofen-2-ilcarbonil)pirazolo[1,5-a]pirimidin-7-il]fenil]acetamida

$C_{20}H_{16}N_{4}O_{2}S$

![Indiplon molecule](image)

**indisulamum**

**indisulam**  
$N$-(3-chloro-$1\text{H}$-indol-7-yl)benzene-1,4-disulfonamide

**indisulam**  
$N$-(3-chloro-$1\text{H}$-indol-7-yl)benzène-1,4-disulfonamide

**indisulam**  
$N$-(3-cloro-$1\text{H}$-indol-7-il)benceno-1,4-disulfonamida

$C_{14}H_{12}ClN_{3}O_{4}S_{2}$

![Indisulam molecule](image)

**leconotidum**

**leconotide**  
omega-conopeptide MVIIA

**léconotide**  
conopeptide MVIIA oméga

**leconotida**  
conopéptido MVIIA omega

$C_{107}H_{179}N_{35}O_{36}S_{7}$

H-Cys-Lys-Ser-Lys-Gly-Ala-Lys-Cys-Ser-Lys-  
Leu-Met-Tyr-Asp-Cys-Ser-Gly-Ser-Cys-  
Ser-Gly-Thr-Val-Gly-Arg-Cys-NH$_2$
**Licofelonum**

licofelone  
[6-(4-chlorophenyl)-2,2-dimethyl-7-phenyl-2,3-dihydro-1H-pyrrolizin-5-yl]acetic acid

licofélone  
acide [6-(4-chlorophényl)-2,2-diméthyl-7-phényl-2,3-dihydro-1H-pyrrolizin-5-yl]acétique

licofelona  
ácido [6-(p-clorofenil)-7-fenil-2,2-dimetil-2,3-dihidro-1H-pirrolizin-5-il]acético

C$_{23}$H$_{22}$ClNO$_2$

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**Lonafarnibum**

lonafarnib  

lonafarnib  

lonafarnib  

C$_{27}$H$_{31}$Br$_2$ClN$_4$O$_2$
lubazodonum
lubazodone
(2S)-2-[(7-fluoro-2,3-dihydro-1H-inden-4-yl)oxy]methyl)morpholine

lubazodona
(2S)-2-[(7-fluoro-2,3-dihydro-1H-inden-4-yl)oxi]metil]morfolina

C_{14}H_{18}FNO_{2}

luliconazolum
luliconazole
(-)-(E)-[(4R)-4-(2,4-dichlorophenyl)-1,3-dithiolan-2-ylidene](1H-imidazol-1-yl)acetonitrile

luliconazole
(-)-(E)-[(4R)-4-(2,4-dichlorophényl)-1,3-dithiolan-2-ylidène](1H-imidazol-1-yl)acétonitrile

luliconazol
(-)-(E)-[(4R)-4-(2,4-diclorofenil)-1,3-ditiolan-2-ilideno](1H-imidazol-1-il)acetonitrilo

C_{14}H_{9}Cl_{2}N_{3}S_{2}

meldonium
meldonium
3-(2,2,2-trimethylidazaniumyl)propanoate

meldonium
3-(2,2,2-triméthylidazaniumyl)propanoate

meldonio
3-(2,2,2-trimetildazanioi)propanoato

C_{6}H_{14}N_{2}O_{2}

**metelimumabum**
m
temelimumab

Immunoglobulin G4, anti-(human transforming growth factor β1) (human monoclonal CAT-192 γ4-chain), disulfide with human monoclonal CAT-192 κ-chain, dimer

**métiquelimumab**
m

temétiquelimumab

Immunoglobuline G4, anti-(facteur de croissance transformant humain β1) (chaîne γ4 de l’anticorps monoclonal humain CAT-192), dimère du disulfure avec la chaîne κ de l’anticorps monoclonal humain CAT-192

**metelimumab**
m

Inmunoglobulina G4, anti-(factor de crecimiento transformador humano β1) (cadena γ4 del anticuerpo monoclonal humano CAT-192), dúmero del disulfuro con la cadena κ del anticuerpo monoclonal humano CAT-192

**mitémçinalum**
m

temitémcinal

8,9-didehydro-N-demethyl-9-deoxo-6,11-dideoxy-6,9-epoxy-12-O-methyl-N-(1-methylethyl)-11-oxoerythromycin

**mitémçinal**
m

(2S,4R,5R,8R,9S,10S,11R,12R)-9-[(2,6-dideoxy-3-C-méthyl-3-O-méthyl-α-L-ribo-hexopyranosyl)oxy]-5-éthyl-4-méthoxy-2,4,8,10,12,14-hexaméthyl-11-[[3,4,6-tridésoxy-3-[méthyl(1-méthyléthyl)amino]-β-D-xylo-hexopyranosyl]oxy]-6,15-dioxabicyclo[10.2.1]pentadéc-1(14)-ène-3,7-dione

**mitémçinal**
m

(2S,4R,5R,8R,9S,10S,11R,12R)-9-[(2,6-didesoxi-3-C-metil-3-O-metil-α-L-ribo-hexopiranosil)oxi]-5-etil-4-metoxi-2,4,8,10,12,14-hexametil-11-[[3,4,6-tridesoxi-3-[metil(1-metiletil)amino]-β-D-xifo-hexopiranosiloxi]-6,15-dioxabiciclo[10.2.1]pentadec-1(14)-eno-3,7-diona

\[C_{40}H_{69}NO_{12}\]
naxifyllinum

naxifylline

\[8\cdot(1S,2R,4S,5S,6S)-3\text{-oxatricyclo}[3.2.1.0^{2,4}]\text{oct-6-yl}]\cdot1,3\text{-dipropyl-3,7\text{-dihydro-1H-purine-2,6-dione}}\]

naxifylline

\[8\cdot(1S,2R,4S,5S,6S)-3\text{-oxatricyclo}[3.2.1.0^{2,4}]\text{oct-6-yl}]\cdot1,3\text{-dipropyl-3,7\text{-dihydro-1H-purine-2,6-dione}}\]

naxifilina

\[8\cdot(1S,2R,4S,5S,6S)-3\text{-oxatriciclo}[3.2.1.0^{2,4}]\text{oct-6-il}]\cdot1,3\text{-dipropil-3,7-dihidro-1H-purina-2,6-diona}\]

\[
C_{18}H_{24}N_4O_3
\]

oglufanidum

oglufanide

\(L\cdot\alpha\text{-glutamyl-L-tryptophan}\)

oglufanide

\(L\cdot\alpha\text{-glutamyl-L-tryptophane}\)

oglufanida

\(L\cdot\alpha\text{-glutamil-L-triptófano}\)

\[
C_{16}H_{19}N_3O_5
\]

olcegepantum

olcegepant

\(N\cdot[(1R)\cdot2\cdot[(1S)\cdot5\text{-amino-1-}[4\text{-}(pyridin-4-yl)piperazin-1-yl]carbonyl[pentyl]amino]-1-(3,5\text{-dibromo-4-hydroxybenzyl})-2\text{-oxoethyl}]\cdot4\cdot(2\text{-oxo-1,4\text{-dihydroquinazolin-3(2H)-yl})piperidina-1-carboxamida}\)

olcégépant

\(N\cdot[(1R)\cdot2\cdot[(1S)\cdot5\text{-amino-1-}[4\text{-}(pyridin-4-yl)pipérazin-1-yl]carbonyl[pentyl]amino]-1-(3,5\text{-dibromo-4-hydroxybenzyl})-2\text{-oxothyl}]\cdot4\cdot(2\text{-oxo-1,4\text{-dihydroquinazolin-3(2H)-yl})pipéridine-1-carboxamida}\)

olcegepant

\(N\cdot[(1R)\cdot2\cdot[(1S)\cdot5\text{-amino-1-}[4\text{-}(piridin-4-il)piperazin-1-il]carbonil[pentil]amino]-1-(3,5\text{-dibrho-4-hidroxibencil})-2\text{-oxoetil}]\cdot4\cdot(2\text{-oxo-1,4\text{-dihidroquinazolin-3(2H)-il})piperidina-1-carboxamida}\)
oregovomabum
oregovomab

immunoglobulin G1, anti-(human CA125 (carbohydrate antigen)) (mouse monoclonal B43.13 γ1-chain), disulfide with mouse monoclonal B43.13 κ-chain, dimer

orégovomab

immunoglobuline G1, anti-(antigène osidique humain CA125) (chaîne γ1 de l’anticorps monoclonal de souris B43.13), disulfure avec la chaîne κ de l’anticorps monoclonal de souris B43.13

oregovomab

immunoglobulina G1, anti-(antígeno osídico humano CA125) (cadena γ1 del anticuerpo monoclonal de ratón B43.13), dimero del disulfuro con la cadena κ del anticuerpo monoclonal de ratón B43.13

otamixabanum
otamixaban

methyl (2R,3R)-2-(3-carbamimidoylbenzyl)-3-[[4-(1-oxidopyridin-4-yl)benzoyl]amino]butanoate

otamixaban

(2R,3R)-2-(3-carbamimidoylbenzyl)-3-[[4-(1-oxydopyridin-4-yl)benzoyl]amino]butanoate de méthyle

otamixabán

(2R,3R)-2-(3-carbamimidoibencil)-3-[[4-(1-oxidopiridin-4-il)benzoil]amino]butanoato de metilo

C_{38}H_{47}Br_{2}N_{9}O_{5}
paliferminum

califermin

[23-methionine]-23-163-fibroblast growth factor 7 (human clone 32/49 reduced)

califermine

[23-méthionine]-23-163-facteur 7 de croissance du fibroblaste, protéine réduite produite par le clone humain 32/49

califermina

[23-metionina]-23-163-factor 7 de crecimiento de fibroblastos, proteína reducida producida por el clon humano 32/49

\[ C_{729}H_{1156}N_{204}O_{207}S_{10} \]

\begin{verbatim}
MSYDYMEEGD IRVRLFCRT QWYLRIDKRG KVKGTQEMKN
NYNIMEIRTG AVGIVAIKGV ESEFYLAMNK EGKLYAKKKE
NEDCNFKELI LENHYNTYAS AKWTHNGGEM FVALNQKGIP
VRGKKTKEQ KTAHFLPMAI T
\end{verbatim}

peramivirum

peramivir

(1S,2S,3R,4R)-3-[(1S)-1-(acetylamino)-2-ethylbutyl]-4-(carbamimidoylamino)-2-hydroxycyclopentanecarboxylic acid

péramivir

acide (1S,2S,3R,4R)-3-[(1S)-1-(acétylamino)-2-éthylbutyl]-4-(carbamimidoylamino)-2-hydroxycyclopentanecarboxylique

peramivir

ácido (1S,2S,3R,4R)-3-[(1S)-1-(acetilamino)-2-etilbutil]-4-(carbamimidoilamino)-2-hidroxiciclopentanocarboxílico

\[ C_{15}H_{28}N_{4}O_{4} \]

\[
\begin{array}{c}
\text{HN} = \text{NH}_2 \\
\text{HN} \rightarrow \\
\text{HN} \rightarrow \\
\text{H}_3 \text{C} \\
\text{H}_3 \text{C} \\
\text{O} \\
\text{H} \\
\text{O} \\
\text{CH}_3 \\
\text{CH}_3 \\
\text{CO}_2 \text{H} \\
\end{array}
\]
**talibegronum**

**talibegron**


**talibégron**


**talibégrón**


\[C_{18}H_{21}NO_4\]

![Chemical structure of talibegronum](image)

---

**tariquidarum**

**tariquidar**

\(N\)-[2-[[4-[2-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)ethyl]phenyl]carbamoyl]-4,5-dimethoxyphenyl]quinoline-3-carboxamide

**tariquidar**

\(N\)-[2-[[4-[2-(6,7-diméthoxy-3,4-dihydroisoquinoléin-2(1H)-yl)éthyl]phényl]carbamoyl]-4,5-diméthoxyphényl]quinoléine-3-carboxamide

**tariquidar**

\(N\)-[2-[[4-[2-(6,7-dimetoxi-3,4-dihidroisoquinolin-2(1H)-il)etil]fenil]carbamoil]-4,5-dimetoxifenil]quinolina-3-carboxamida

\[C_{38}H_{38}N_4O_6\]

![Chemical structure of tariquidarum](image)

---

**tebaniclinum**

**tebanicline**

5-[[2R]-azetidin-2-ylmethoxy]-2-chloropyridine

**tébanicline**

5-[[2R]-azétidin-2-ylméthoxy]-2-chloropyridine

**tebaniclina**

5-[[2R]-azetidin-2-ilmetoxi]-2-cloropiridina

\[C_9H_11ClN_2O\]

![Chemical structure of tebaniclinum](image)
**tecastemizolum**

1-(4-fluorobenzyl)-N-(piperidin-4-yl)-1\(H\)-benzimidazol-2-amine

C\(_{19}\)H\(_{21}\)FN\(_4\)

---

**technetium (\(^{99m}\)Tc) fanolesomab**

immunoglobulin M, anti-(human CD15 antigen) (mouse monoclonal RB5 \(\mu\)-chain), disulfide with mouse monoclonal RB5 light chain, pentamer, \([^{99m}\text{Tc}]\)technetium salt

---

**tigecyclinum**

(4S,4aS,5aR,12aS)-4,7-bis(dimethylamino)-9-[[[1,1-dimethyllethyl)amino]acetyl]amino]-3,10,12,12a-tetrahydroxy-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide

---

**tigecycline**

(4S,4aS,5aR,12aS)-4,7-bis(diméthylamino)-9-[[[1,1-diméthyléthyl)amino]acétyl]amino]-3,10,12,12a-tétrahydroxy-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotétracène-2-carboxamide

---

**tigeciclina**

(4S,4aS,5aR,12aS)-4,7-bis(dimetilamino)-9-[[[1,1-dimetiletil)amino]acetil]amino]-3,10,12,12a-tetrahidroxi-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahidrotetraceno-2-carboxamida
**tiviciclovirum**

**tiviciclovir** 2-amino-9-[3-hydroxy-2-(hydroxymethyl)propyl]-1,9-dihydro-6H-purin-6-one

**tiviciclovir** 2-amino-9-[3-hydroxy-2-(hydroxyméthyl)propyl]-1,9-dihydro-6H-purin-6-one

**tiviciclovir** 2-amino-9-[3-hidroxi-2-(hidroximetil)propil]-1,9-dihidro-6H-purin-6-ona

C$_{9}$H$_{13}$N$_{5}$O$_{3}$

---

**tosagestina**

**tosagestin** 17-hydroxy-11-methylene-19-nor-17α-pregna-4,15-dien-20-yn-3-one

**tosagestin** 17-hydroxy-11-méthylène-19-nor-17α-prègna-4,15-dién-20-yn-3-one

**tosagestina** 17-hidroxi-11-metilen-19-nor-17α-pregna-4,15-dien-20-in-3-on

C$_{21}$H$_{24}$O$_{2}$


C_{39}H_{43}N_{3}O_{11}S

Zosuquidarum (zosuquidar) (2R)-1-[4-[(1aR,6r,10bS)-1,1-difluoro-1,1a,6,10b-tetrahydrodibenzo[a,e]cycloheptan-6-yl]piperazin-1-yl]-3-(quinolin-5-yloxy)propan-2-ol

Zosuquidar (2R)-1-[4-[(1aR,6r,10bS)-1,1-difluoro-1,1a,6,10b-tétrahydrodibenzo[a,e]cycloheptén-6-yl]pipérazin-1-yl]-3-(quinoléin-5-yloxy)propan-2-ol

Zosuquidar (2R)-1-[4-[(1aR,6r,10bS)-1,1-difluoro-1,1a,6,10b-tetrahidrohibenzo[a,e]ciclohepten-6-il]piriperazin-1-il]-3-(quinolin-5-iloxi)propan-2-ol

C_{32}H_{31}F_{2}N_{3}O_{2}
AMENDMENTS TO PREVIOUS LISTS
MODIFICATIONS APPORTÉES AUX LISTES ANTÉRIEURES
MODIFICACIONES A LAS LISTAS ANTERIORES

Recommended International Nonproprietary Names (Prop. INN): List 40
Dénominations communes internationales recommandées (DCI Prop.): Liste 40
Denominaciones Comunes Internacionales Recomendadas (DCI Prop.): Lista 40

p. 177  \textit{suprimase} \ efavirenzo  \textit{insértese}  \textit{efavirenz}

p. 187  \textit{suprimase} \ moxifloxacin \textit{insértese}  \textit{moxifloxacino}

p. 200  \textit{technetii} (99mTc) \textit{apcitidum} \ thorntecnio (99mTc) \textit{apcítida}  \textit{sustituyase la descripción por la siguiente:}  
hidrógeno \textit{[N-(mercaptoacetil)-d-riosil-S-(3-aminopropil)-L-cisteinilglicil-L-\alpha-aspartil-L-cisteinilglicilglicil-S-(acetamidometil)-L-cisteinilglicil-S-(acetamidometil)-L-cisteinilglicilglicil-L-cisteinamida (1\rightarrow5)-sulfuro cíclico (5-)-N^11,N^12,N^13,S^13]oxo[99mTc]tecnetato(V) de sodio}

p. 202  \textit{tobicillinum}  \textit{tobicillina}  \textit{sustituyase la descripción por la siguiente:}  
(2S,5R,6R)-3,3-dimetil-7-oxo-6-(2-fenilacetamido)-4-tia-1-azabiciclo[3.2.0]heptano-2-carboxilato de \alpha-hidroxi-m-tolilo, isobutirato (éster)

p. 205  \textit{suprimase} \ clorprotixeno \textit{insértese}  \textit{clorprotixeno}

Recommended International Nonproprietary Names (Prop. INN): List 41
Dénominations communes internationales recommandées (DCI Prop.): Liste 41
Denominaciones Comunes Internacionales Recomendadas (DCI Prop.): Lista 41
(\textit{WHO Drug Information}, Vol. 13, No. 1, 1999)

p. 39  \textit{anatumomabum mafenatoxum} \textit{anatumomab mafenatox}  \textit{sustituyase la descripción por la siguiente:}  
immunoglobulina G1 (cadena \gamma_1 del fragmento Fab del anticuerpo monoclonal humanizado de ratón, clon pMB125, dirigido contra la glicoproteína 72 humana asociada a tumores)-[227-alanina]enterotoxina A (\textit{Staphylococcus aureus}) complejada con la cadena \kappa del anticuerpo monoclonal de ratón clon pMB125

p. 46  \textit{suprimase} \ olamufloxacina \textit{insértese}  \textit{olamufloxacino}
Recommended INN: List 48

Dénominaciones comunes internacionales recomendadas (DCI Prop.): Liste 42

Denominaciones Comunes Internacionales Recomendadas (DCI Prop.): Lista 42

WHO Drug Information, Vol. 16, No. 3, 2002

p. 48 suprimase
estansoporfina

insértese
estansoporfina

p. 48 stannsoporfinum
estansoporfina

sustituyase la descripción por la siguiente:
(OC-6-13)-dicloro[7,12-dietil-3,8,13,17-tetrametilporfirina-2,18-dipropionato(4-)-N²¹,N²²,N²³,N²⁴]estannato(2-) de dihidrógeno

Recommended International Nonproprietary Names (Prop. INN): List 42

p. 190 suprimase
enrasentano

insértese
enrasentán

p. 196 minopafantum
minopafant

sustituyase la descripción por la siguiente:

p. 203 tabimorelinum
tabimorelina

sustituyase la descripción por la siguiente:
(R)-α-[(E)-5-amino-N,5-dimetil-2-hexenamido]-N-metil-N-[(R)-α-(metilcarbamoil)fenetil]-2-naftalenopropionamida

p. 212 sulesomabum
sulesomab

sustituyase la descripción por la siguiente:
inmunoglobulina G1, anti-(antígeno celular NCA-90 de granulocito humano) fragmento Fab' (cadena γ1 del anticuerpo monoclonal de ratón IMMU-MN3), disulfuro con la cadena ligera del anticuerpo monoclonal de ratón IMMU-MN3

p. 212 technetium (⁹⁹mTc) pintumomabum
teceocio (⁹⁹mTc) pintumomab

sustituyase la descripción por la siguiente:
sal de [⁹⁹mTc]tecnecio de la inmunoglobulina G1 anti-(antígeno asociado a los adenocarcinomas humanos) (cadena γ1 del anticuerpo monoclonal de ratón 170), dímero del disulfuro con la cadena κ del anticuerpo monoclonal de ratón 170

p. 214 igovomabum
igovomab

sustituyase la descripción por la siguiente:
inmunoglobulina G1, anti-[([antígeno osídico) CA 125 humano] (fragmento F(ab')2 (cadena γ1 del anticuerpo monoclonal de ratón OC125F(AB')2), dímero del disulfuro con la cadena ligera del anticuerpo monoclonal de ratón OC125F(AB')2
Recommended International Nonproprietary Names (Prop. INN): List 43
Dénominations communes internationales recommandées (DCI Prop.): Liste 43
Denominaciones Comunes Internacionales Recomendadas (DCI Prop.): Lista 43

p. 46  cadrofloxacinau  
replacer la description par la suivante:
(-)-acide 1-cyclopropyl-8-(difluorométhoxy)-6-fluoro-7-[(3S)-3-méthylpipérazin-1-yl]-4-oxo-1,4-dihydroquinoléine-3-carboxylique

p. 53  finrozolum  
replace the description and the graphic formula by the following:
p·[(1RS,2SR)-3-(p-fluorophenyl)-2-hydroxy-1-(1H-1,2,4-triazol-1-yl)propyl]benzonitrile

p. 57  ibritumomabum tiuxetanum  
sustituyase la descripción por la siguiente:
inmunoglobulina G1, anti-(antígeno CD20 humano) (cadena γ1 del anticuerpo monoclonal de ratón IDEC-Y2B8), dímero del disulfuro con la cadena κ del anticuerpo monoclonal de ratón IDEC-Y2B8, conjugada con N-[2-[bis(carboximetil)amino]-3-(4-isotiocianatofenil)propil]-N-[2-[bis(carboximetil)amino]propil]glicina

p. 67  sibrotuzumabum  
sustituyase la descripción por la siguiente:
inmunoglobulina G1, anti-(FAP (proteína de activación de los fibroblastos) humana) (cadena γ1 del anticuerpo monoclonal humanizado de ratón BIBH1), dímero del disulfuro con la cadena κ del anticuerpo monoclonal humanizado de ratón BIBH1

p. 75  lintuzumabum  
sustituyase la descripción por la siguiente:
inmunoglobulina G1, anti-(antígeno CD33 humano) (cadena γ1 del anticuerpo monoclonal humanizado de ratón HuM195), dímero del disulfuro con la cadena κ del anticuerpo monoclonal humanizado de ratón HuM195
Recommended International Nonproprietary Names (Prop. INN): List 44
Dénominations communes internationales recommandées (DCI Prop.): Liste 44
Denominaciones Comunes Internacionales Recomendadas (DCI Prop.): Lista 44

p. 202 prinomastatum
prinomastat

replace the description by the following:
(S)-2,2-dimethyl-4-[[p-(4-pyridyloxy)phenyl]sulfonyl]-3-thiomorpholinecarbohydroxamic acid

p. 202 pumafentrinum
pumafentrina

sustituyase la descripción por la siguiente:
(-)-p-[[4aR*,10bS*]-9-etoxi-1,2,3,4,4a,10b-hexahidro-8-metoxi-2-metilbenzo[c][1,6]naftiridin-6-il]-N,N-diisopropilbenzamida

Recommended International Nonproprietary Names (Prop. INN): List 45
Dénominations communes internationales recommandées (DCI Prop.): Liste 45
Denominaciones Comunes Internacionales Recomendadas (DCI Prop.): Lista 45
(WHO Drug Information, Vol. 15, No. 1, 2001)

p. 54 suprimase
olmesartán medoxmilo

insértense
olmesartán medoxomilo

p. 33 bevacizumab
bevacizumab

sustituyase la descripción por la siguiente:
imunoglobulina G1 anti-(factor de crecimiento del endotelio vascular humano) (cadena γ1 del anticuerpo monoclonal humanizado de ratón rhuMab-VEGF), dímero del disulfuro con la cadena ligera del anticuerpo monoclonal humanizado de ratón rhuMab-VEGF

p. 34 bivatuzumab
bivatuzumab

replace the description by the following:
imunoglobulina G1 human-mouse monoclonal BIWA4 γ1-chain anti-human antigen CD44v6), disulfide with human-mouse monoclonal BIWA4 κ-chain, dimer

bivatuzumab

remplacer la description par la suivante:
immunoglobuline G1 anti (antigène CD44v6 humain) (chaîne γ1 de l’anticorps monoclonal de souris BIWA4 humanisé), dimère du disulfure avec la chaîne κ de l’anticorps monoclonal de souris BIWA4 humanisé

bivatuzumab

sustituyase la descripción por la siguiente:
imunoglobulina G1 anti-(antígeno humano CD44v6) (cadena γ1 del anticuerpo monoclonal humanizado de ratón BIWA4), dímero del disulfuro con la cadena κ del anticuerpo monoclonal humanizado de ratón BIWA4

p. 40 gadofosvesetum
gadofosveset

sustituyase la descripción por la siguiente:

266
p. 47 ozogamicinum
ozogamicina

sustituyase la descripción por la siguiente:

p. 48 pitavastatinum
pitavastatina

sustituyase la descripción por la siguiente:
ácido (3R,5S,6E)-7-[2-ciclopropil-4-(p-fluorofenil)-3-quinolil]-3,5-dihidroxi-6-heptenoico

Recommended International Nonproprietary Names (Prop. INN): List 46
Dénominations communes internationales recommandées (DCI Prop.): Liste 46
Denominaciones Comunes Internacionales Recomendadas (DCI Prop.): Lista 46
( WHO Drug Information, Vol. 15, No. 3-4, 2001)
p. 213 **tipifarnibum**
tipifarnib

sustituyase la descripción por la siguiente:

\( (+)-6-[(R)\text{-amino}(4\text{-clorofenil})(1\text{-metil}-1H\text{-imidazol-5-il})\text{metil}]-4-(3\text{-clorofenil})\text{-1-metilquinolin-2(1H)}\text{-ona} \)

p. 216 **zelandopamum**
zelandopam

sustituyase la descripción por la siguiente:

\( (-)-(S)-4-(3,4\text{-dihidroxifenil})\text{-1,2,3,4-tetrahydro-7,8-isoquinolinadiol} \)

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**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.