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WORLD HEALTH ORGANIZATION • GENEVA
General Policy Issues

WHO roundtable with the International Generic Pharmaceutical Alliance

On 11 February 1999, Dr Gro Harlem Brundtland, the Director-General of WHO, met with some key figures of the generic pharmaceutical industry to explore ways in which access to affordable, innovative and essential drugs can be improved. The roundtable was attended by the Chief-Executive Officers of the principal generic pharmaceutical companies, the Chairman of the European Generic Medicines Association, and the co-Director of the International Generic Pharmaceutical Alliance (IGPA)

The meeting offered an opportunity for both sides to address issues of public health concern including the WHO essential drugs concept, intellectual property issues and ensuring quality control and developing good manufacturing practice within the generics industry. WHO's goal is to build a constructive dialogue with the private sector and collaborate in improving global health.

Global partnerships for health

Gro Harlem Brundtland
Director-General
World Health Organization

We have been awaiting the opportunity to bring together leading representatives of the generic pharmaceutical industry, and I am glad to see that so many people with experience and insight have accepted our invitation to attend the roundtable.

A roundtable, as we apply the term in WHO, is not a single event. It is a method of work. The reason is simple. There are many key players in world health, and those key players need to meet and talk. They need to exchange views, look for common ground and be aware of differences. WHO invites its partners in health whether from among the UN family, industry, or nongovernmental organizations to join in a dialogue on the key issues facing us.

Pharmaceuticals, of course, are critical to any health system. In some parts of the world access to drugs and vaccines is almost routine. But we have seen negative consequences on populations who are denied access even to the most essential drugs. Our objective is to define a clear, transparent and unified policy to guide the WHO clusters, departments and regions in their contacts and relations with the pharmaceutical industry.

The pharmaceutical industry is not a single body — different sectors of this industry have different views and perceptions. Some months ago, I met with representatives of the research-based industry and today I look forward to listening to the views and perceptions of the generic industry.

WHO is one organization, with one policy and one objective in the area of pharmaceuticals: to improve equity of access to essential drugs of assured quality as part of the fundamental right to health care. Equity is a core value. We need to constantly pursue strategies aimed at helping all people to access health services.

We are committed to helping countries establish and sustain national drug policies, as we are committed to the concept of essential drugs and vaccines, and the establishment of norms and standards to obtain quality drugs for patients.

The Essential Drugs and Other Medicines Department is WHO's main instrument in helping governments to implement these policies and to promote the essential drugs concept. Essential drugs are one of the most cost-effective elements in modern health care, and their potential health impact is crucial.

This year alone, there will be over 40 million deaths in developing countries, one-third among children under five. Ten million deaths will be due to acute respiratory infections, diarrhoeal diseases, tuberculosis, and malaria — all are conditions for which safe, inexpensive, essential drugs of assured quality can be life-saving.
Simple folic acid + ferrous salt preparations can reduce maternal and infant mortality arising from anaemia during pregnancy; treatment of sexually-transmitted diseases can reduce transmission of HIV; and treatment of hypertension reduces heart attacks and strokes.

The economic impact of pharmaceuticals is also substantial — especially in developing countries. While spending on pharmaceuticals represents less than one-fifth of total public and private health spending in most developed countries, it represents 15–30% of total health spending in transitional economies and 25–66% in developing countries. In most low-income countries, pharmaceuticals account for the largest public health expenditure after personnel, and the largest household health expenditure.

Furthermore, lack of essential drugs, irrational use of drugs, and poor drug quality remain a serious global health problem. Let me mention some examples:

- Over one-third of the world's population still lacks access to essential drugs.
- In the poorest parts of Africa and Asia, this number climbs to over 50%.
- 50–90% of drugs purchased in developing countries are paid for out-of-pocket.
- The burden falls mainly on the poor who are not adequately protected by health policies.
- Up to 75% of antibiotics are prescribed inappropriately.
- Antimicrobial resistance is growing for most major infectious diseases.
- Worldwide, an average of only 50% of patients take their medicines correctly.
- 10–20% of sampled drugs fail quality control tests in many developing countries.

A lot remains to be done. National policies and procedures can be improved. We need mechanisms which ensure that quality-controlled drugs are made more available to all at the lowest possible price. We know that generic drugs are usually more affordable, and here your activities can complement our goals. WHO is currently working with governments, industry, and other partners to encourage legislation and regulation which supports improved access to essential drugs. This includes, of course, access to generic drugs of assured quality.

WHO has done important work in the area of generic drugs. Earlier this week we had a consultation on "Global comparator drug products for multi-source bioequivalence testing". This is one of several initiatives aimed at making generic drugs of assured quality more available.

We need contributions from both the generic as well as the research-based pharmaceutical industry and we need to create the right incentives for innovation. There have to be constructive ways of recovering investments in research and development. But generally we need to look for the most cost-effective solutions, those which guarantee the users quality drugs at an acceptable price.

WHO remains committed to national drug policies as part of national health policies. The national drug policy process can and should engage the public sector, professional bodies, the private sector, consumers, academics, and other concerned partners. In this way, we can work together to develop new strategies for addressing the problem of drug access. We need to support an environment which allows quality production of drugs to take place also in developing countries.

This roundtable is a point of departure. I am certain that we will find sufficient common ground for a genuine partnership in the future to address critical issues in the area of access to essential drugs.

Role of the international generic pharmaceutical industry in public health

G. Perry, International Generic Pharmaceutical Alliance, Brussels, Belgium

The decision to have a roundtable discussion with representatives of the generic pharmaceutical industry is an important recognition by WHO that there are many players on the pharmaceutical scene. Although in commercial terms globalization of the generic industry is less than ten years old, it has only recently acted at global level as an association.
The existence of the International Generic Pharmaceutical Alliance (IGPA) owes much to WHO. The Organization has encouraged our companies and regional associations to join together at international level. WHO was also extremely helpful in ensuring IGPA participation in the International Conference on Harmonization (ICH) process. During our short existence, the IGPA has already participated in WHO working groups dealing with bioequivalence, registration and issues of counterfeiting.

WHO has stated that generic medicines are critical for ensuring access to pharmaceutical care and has played a significant role in the promotion of generic medicines through its essential drugs policy. However, affordability is only one aspect of generic medicine use. We must stress that off-patent medicines can only be classed as generic if they meet all the required standards of safety, efficacy and quality. We understand that WHO is also sensitive to this point.

In our view, generic medicines offer the following advantages to health systems.

• Good quality therapy which is less expensive.

• Increased accessibility to care.

• Encouragement of innovation through competition.

• Savings made in health care budgets by use of generics enable purchases of high-cost new medicines when relevant.

• Opportunity for less developed countries to develop a local pharmaceutical base.

There are a number of questions which we would like to address. Firstly, why are low-cost essential medicines not more available to people throughout the world? It is unacceptable that so many children suffer each year from illnesses that could be treated by low-cost medicines. We need to address the barriers to availability of these essential products and seek solutions.

Secondly, do medicines meet the quality standards needed to be referred to as generic? Where this is not the case, we have to assess whether the generic industry can help fill the gap and assist in the development of quality products at local level. Similarly, we need to ensure that mechanisms are in place that will prevent the production and trade in counterfeit versions of generic medicines.

Thirdly, what measures are needed to develop and promote a market based on generics? WHO has laid the foundations for this in its “enabling measures” outlined in its document Public–Private Roles in the Pharmaceutical Sector: Implications for Equitable Access and Rational Drug Use (1). WHO has also acknowledged the implications of Trade Related Aspects of Intellectual Property Rights (TRIPS) to world health and we fully support the decision by WHO to produce its report Globalization and Access to Drugs: Perspectives on the WTO/ TRIPS Agreement (2). We wish to stress the importance that a balanced intellectual property law will give to the future of any programme for generics and to WHO’s essential drugs policy. Critical to this is the need for generic manufacturers to undertake the preparatory work necessary to produce a generic product during the patent period of the originator product.

In many areas, we see our objectives overlapping with those of WHO. Indeed, IGPA’s main objective is to ensure that all consumers have access to affordable, quality medicines.

As a matter of basic principle, the IGPA and its member associations:

• Support the development of international and regional policies which seek to ensure access to medicinal care for all consumers.

• Promote balanced and generic-friendly intellectual property rights in the pharmaceutical sector that ensure a timely access to markets of generic medicines.

• Encourage scientific development, professional awareness and general knowledge of generic medicines.

• Promote the global harmonization of regulations relating to generic products.

• Provide guidance to international organizations and national governments in improving the regulatory and legal expertise relating to the registration and marketing of generic medicines.

• Promote uniform and effective good manufacturing practice (GMP) standards and quality controls.
for generic pharmaceuticals and their active ingredients.

- Seek strict and effective controls to prevent the production and trade in counterfeit versions of generic and original brand medicines.

- Support the right of all governments to regulate their own pricing, substitution, prescribing and reimbursement policies.

The IGPA supports the WHO Revised Drug Strategy and WHO’s work in seeking world standards for bioequivalence, GMP, guidelines on registration, improved control on active pharmaceutical ingredient quality, action against counterfeit products and work in relation to health options under TRIPs.

As part of the roundtable, we hope to learn more about the activities of WHO, including the new partnership with the private sector and what is expected of us. Finally, we want to know how we can work with WHO in meeting our common goal of ensuring affordable pharmaceutical care throughout the world.

References
Reports on Individual Drugs

Short-course zidovudine in perinatal HIV transmission: more evidence and debate

The results of two clinical trials in Thailand and in the USA which documented a 50–68% relative efficacy of short-course zidovudine in prevention of perinatal HIV transmission in non-breast-feeding women, were reviewed in the previous issue of this journal (1). The definitive results of the short-course zidovudine trial conducted in Thailand have since been published (2).

Complementary studies from two African trials have now been published (3, 4), including a meta-analysis of 15 studies focusing on the role of elective caesarean section in prevention of HIV transmission (5, 6). The studies, carried out in breast-feeding women in Burkina Faso and Côte d'Ivoire (3, 4) demonstrated a 37–38% relative efficacy in prevention of perinatal HIV transmission with a short-course oral zidovudine regimen given antenatally and similar to the two previous studies (1).

Since the African trials were stopped prematurely following the positive results of the Thailand trial, their power to address definitively the efficacy of zidovudine in breast-feeding women is limited (7). The reduction of transmission in the zidovudine group was statistically significant in newborns. None the less, whether efficacy will decline with continued breastfeeding can only be determined through follow-up of infants enrolled in these studies.

The African trials also demonstrated that even with these simple regimens there were significant logistical difficulties in HIV counselling and testing and drug management during labour (7). For example, only 61% of those who tested positive for HIV returned for their results, and a large proportion of women refused enrolment or did not reach the study clinic to give birth.

It is estimated that some 2.3 million HIV-positive women worldwide give birth each year and a number of maternal, virological, immunological and fetal factors contribute to maternal transmission. Transmission may occur before birth, although 70% of cases of maternal transmission occur during labour and delivery (6). It is therefore crucial to know how zidovudine treatment and avoidance of certain obstetrical factors may assist in the prevention of transmission during delivery.

The meta analysis of data on individual patients carried out in 15 prospective cohort studies in Europe and the USA compared the rate of vertical transmission of HIV associated with elective caesarian section (5). The HIV status was known for all 8533 mother-infant pairs. In the absence of antiretroviral therapy, the rate of transmission was 10.4% with elective caesarean section, as compared with 19% with other modes of delivery. Antiretroviral therapy decreased the transmission rate to only 2% with elective caesarean section as compared to 7.3% with other modes of delivery.

Scientists and clinicians from South Africa have commented on these new findings (8). It is a fact that most African women have little choice other than to breast-feed given the nutritional, immunological and birth-spacing benefits that breastfeeding confer. If short-course antiretrovirals were made available in Africa many children would be saved from HIV infection although many others would remain at risk of acquiring HIV through the breastmilk of infected mothers.

Although South Africa is relatively rich in resources, implementation of a short-course zidovudine regimen would consume a substantial proportion of the health budget. This intervention alone would cost more than most African countries spend per capita on health. Moreover, health care personnel including nurses, counsellors, laboratory technicians and a functioning primary health system is required to implement the therapy rationally, safely and effectively. This kind of costly, vertical programme might also draw financial and human resources away from other health and health-related programmes. Additionally, many women live in remote, rural areas, urban slums or war zones and others deliver outside health services with no access to prenatal care. These circumstances call for simple interventions with moderate costs.
It has been suggested that vaginal lavage with chlorhexidine, development of new topical vaginal virucide preparations, maintenance of sufficient vitamin A levels and proper application of elective caesarean section could play an important role in the prevention of vertical transmission of HIV (7–9). Although formula feeding may not always be a realistic option, it should still be evaluated in certain situations. It is evident that research must continue to identify new effective and affordable antiretroviral agents and feasible interventions for administration to all pregnant women irrespective of their HIV status.

In conclusion, although short-course zidovudine is cheaper than the previously used long course — approximately US $50 compared with US $800 — even this is prohibitive for many developing countries when compared with resources available for health care (7).

References


Low-dose acetylsalicylic acid: risks of intracerebral haemorrhage?

Low-dose acetylsalicylic acid (ASA) is increasingly recommended as an antithrombosis drug for secondary prevention in patients surviving myocardial infarction (1–3). There is also evidence that ASA may be useful in primary prevention as it reduces the risk of a first myocardial infarction in men (3). Moreover, it seems to reduce the risk of recurring transient ischaemic attacks, stroke or death in men who have had single or multiple ischaemic events.

The probability that ASA might increase the risk of intracerebral haemorrhage has been raised in two large primary prevention studies (1, 2) and several large secondary prevention trials among patients with a history of stroke or transient ischaemic attacks (3). The small number of cases, diagnostic imprecision in intracerebral haemorrhage and varying doses of ASA used have made it difficult to draw firm conclusions from these trials as to the extent and nature of the relative risk.

A case-controlled study (4) has examined the association between use of ASA and other nonsteroidal anti-inflammatory drugs and intracerebral haemorrhage. The study included 331 consecutive cases of stroke and 331 age and sex-matched controls. Stroke was verified by computed tomography or post-mortem examination. Any drugs containing ASA or other nonsteroidal anti-inflammatory drugs taken in the preceding two-week period were categorized according to dose. The low dose category included those taking 100–175 mg/day, which is the dose range commonly used for vascular prophylaxis.

There was no increase in risk of intracerebral haemorrhage among ASA users overall or among those who took lower doses of ASA or other nonsteroidal anti-inflammatory drugs. A statistically significant threefold increase in risk was observed among users of moderate to high doses of ASA (over 1225 mg/week) but this finding was regarded as tentative and requiring confirmation.

References

Rotation of antimicrobials: possibilities for success

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Antibiotic resistance is a growing global problem that threatens the successful treatment of many common infections. In addition to the implementation of basic measures, such as re-educating prescribers about principles of prudent antibiotic use, novel strategies are also needed to counteract this threat. The cycling or rotation of antibiotics has been proposed as a worthwhile new strategy.

The aim of rotation is to limit the time during which organisms are exposed to an antibiotic. Thus the development of resistance will be halted or, if some resistance does develop, the resistance will lessen when another antibiotic is substituted. However, despite the potential merits, there is little reported use of this approach.

It is quite clear that reduction in use of some antibiotics will be followed by a reduction in the rate of resistance of some organisms to that antibiotic, but this is not true antibiotic rotation. At present, there is insufficient information available to support a recommendation for widespread adoption of antibiotic rotation. Large, carefully designed and controlled trials will therefore be needed to investigate the value of this approach as a means of preventing antibiotic resistance.

Rotational use of antibiotics

We have conducted an extensive literature search on this subject and noted that little has been published. The majority of articles have reviewed the problem of drug resistance in general while briefly mentioning the role of antibiotic rotation or cycling. This measure has not been adequately studied as a means of controlling drug resistance and further clinical multicentre trials are needed to determine whether this is likely to have any impact on emergence of drug resistance.

Experience with individual drugs or drug classes

Erythromycin

An interesting study on erythromycin-resistant Group A streptococci has been reported in Finland (1). Following an evaluation of drug resistance related to the annual use of erythromycin and other macrolide antibiotics, a national recommendation to reduce the use of erythromycin for the treatment of respiratory and skin infections in outpatients was evaluated. Consumption of macrolide antibiotics decreased from 2.40 defined daily doses (DDD) per 1000 inhabitants per day in 1991 to 1.38 in 1992 and remained near the lower level until 1996.

This was followed by a steady decrease in the frequency of erythromycin resistance among Group A streptococcal isolates from 16.5% in 1992 to 8.2% in 1996. This convincingly illustrates how drug resistance decreased once the use of an antibiotic was reduced. However, it does not examine the issue of drug rotation. The drug of choice for treatment of these infections is penicillin, to which resistance of Group A streptococci has not emerged so far. There would be no good clinical reason to increase use of erythromycin again, so this particular organism/antibiotic combination is not a good one to investigate the role of antibiotic rotation.

Third-generation cefalosporins

Antibiotic resistance to these drugs is now quite common. One of the two main resistance mechanisms is the induction or derepression of chromosomally-mediated beta-lactamases which are harboured by Gram-negative bacilli such as Pseudomonas aeruginosa, Morganella morganii and the Enterobacter, Serratia, Citrobacter and Providencia spp. (2, 3). The second main resistance mechanism is the acquisition of plasmids which code for the production of extended-spectrum beta-lactamases which can hydrolyse these cefalosporins. Initially these were mainly seen in Escherichia coli and Klebsiella spp. strains, but now they have been detected in other Enterobacteriaceae and also in P. aeruginosa (4–6).
Virtually no reports describe rotation of ceftalosporins with other drugs in a hospital or intensive care unit, but quite a few studies show that ceftalosporin resistance decreases when the use of one or all of these drugs is restricted. It seems that if some of these studies had been continued for several years a real antibiotic rotation might have resulted. Thus, an outbreak caused by multiple-resistant *Escherichia cloacae* was described in a neonatal intensive care unit (7). For 11 years the unit had successfully managed neonatal sepsis by using ampicillin plus gentamicin as initial therapy. Then an outbreak of infection due to gentamicin-resistant *Klebsiella pneumoniae* occurred. Cefotaxime was substituted for gentamicin in the initial therapeutic regimen. The outbreak subsided, but 10 weeks later an outbreak of cefotaxime-resistant *E. cloacae* infections began. The gentamicin-resistant *K. pneumoniae* had disappeared from the unit by then and ampicillin plus gentamicin was suitable again as initial therapy for neonatal sepsis. We do not know whether cefotaxime was again “rotated” in the unit and if so with what success.

An outbreak of ceftazidime-resistant strains of *K. pneumoniae* and other *Enterobacteriaceae* at a Massachusetts chronic-care facility has also been described, whereby the prevalence of the resistant strains decreased after the drug was restricted (8). Similarly, a nosocomial outbreak of ceftazidime-resistant *K. pneumoniae* infections and colonizations in a North American hospital were reported which again was controlled by ceftazidime restriction and infection control measures (9). In both of these reports the resistance was caused by extended-spectrum beta-lactamases, but again it is not known whether ceftazidime usage could be increased later when ceftazidime resistance may have fallen to a low level.

In another USA hospital, ceftazidime and other third-generation cephalosporins were used widely during 1995 (control period), but during 1996 (intervention period) an 80.1% reduction in hospital-wide cephalosporin use was achieved. This was accompanied by a 44% reduction in the incidence of ceftazidime-resistant *Klebsiella* infection and colonization throughout the medical centre, a 70.9% reduction within all intensive care units, and an 87.5% reduction within the surgical intensive care unit. But a concomitant 68.7% increase in the incidence of imipenem-resistant *P. aeruginosa* occurred throughout the hospital (10). Again, we do not know how ceftazidime or imipenem were used in the hospital after the second year.

Similarly, the empiric chemotherapy for Gram-negative ventilator-associated pneumonia and nosocomial bacteraemia in patients undergoing cardiac surgery during two six-month periods has been evaluated (11). During the first 6 months, ceftazidime was used for empirical treatment and this was followed by a 6-month period during which ciprofloxacin replaced ceftazidime. The incidence of ventilator-associated pneumonia was significantly decreased in the second period. Thirteen (31.7%) of the Gram-negative isolates associated with infection in the first period were resistant to ceftazidime and five (12.2%) were resistant to ciprofloxacin. Two (10%) of the Gram-negative isolates associated with infection in the after-period were resistant to ceftazidime and two (10%) were resistant to ciprofloxacin. Thus ceftazidime resistance was reduced when it was no longer used. The question now is — can this study be regarded as the beginning of a trial for antibiotic rotation? Obviously, the drug employed during each cycle would always be used for empirical therapy. It may be used for continuation therapy if cultures and sensitivity tests confirm that it is suitable, but if this is not so, therapy should be changed (12).

Other studies raise, but do not answer, important questions about strategies of drug rotation (13). Should one continue a rotated antibiotic until a certain threshold of resistance to the drug is reached, or should the drug be continued for a pre-defined period of time? How many drugs should be included in the rotation cycle? Should the drugs be from the same or different antibiotic classes? Some researchers consider that the cycle should be changed prior to the time that resistance in the current phase of the cycle appears (14). They also consider that if resistance appears, then the time of the phase of use of these drugs in the cycle needs to be shortened when their phase comes around again, and the drugs should be dropped from the cycle until resistance disappears.

The future design of studies to investigate antibiotic rotation will be a challenge. Apart from deciding which drugs to use, for how long, and when to change them, an even more difficult issue will be the identification of an appropriate control group, either in the same or another hospital (12).

### Aminoglycosides

In the mid-eighties, a number of studies investigated replacing the use of gentamicin or tobramycin by amikacin, a new drug at that time. The studies were sponsored by the company which manufactured amikacin and the main aims were to show...
that amikacin was effective clinically for treatment of infections caused by both gentamicin-sensitive and resistant Gram-negative bacteria. This was indeed the case.

However, resistance emerged more slowly to amikacin than to other aminoglycosides which was to be expected as amikacin can be inactivated by a smaller number of aminoglycoside modifying enzymes (15). In some of these studies, once amikacin was substituted for gentamicin or tobramycin, this switching of drugs did lead to a decrease in resistance to the older aminoglycosides (16). There is no reason to cite here the individual studies of this group; no real rotation of drugs was performed and aminoglycosides in developed countries such as Australia and the USA are used differently today.

More recently, independent studies have shown results similar to those found during the introduction of amikacin into clinical medicine. In one US hospital, tobramycin-resistant *Serratia* spp. declined from 42.1% to 2.5% during a 4.5 year period whilst amikacin was used as the principal aminoglycoside (17). In another US hospital, the rates of gentamicin and tobramycin resistance among Gram-negative bacteria also decreased significantly during a 30-month period once amikacin had been introduced as the principal aminoglycoside (18).

A report was received from another US hospital (19) covering 10 years of aminoglycoside usage and resistance monitoring. On two occasions during the 1980s, amikacin was introduced at high level usage and was associated with a significant reduction in resistance to gentamicin and tobramycin among Gram-negative bacilli. Rapid reintroduction of gentamicin usage in 1982 following the first amikacin period was associated with a significant and rapid increase in gentamicin and tobramycin resistance. But in 1986, gentamicin was again reintroduced at an initially modest level and the percentage of usage of this drug was gradually increased over a 15-month period without significant changes in resistance to gentamicin, tobramycin, or amikacin. By 1989, resistance to all drugs was low. Since 1985, the usage of aminoglycosides also declined and this coincided with the introduction of other drugs in clinical use, such as the third-generation cefalosporins, which are effective for the treatment of infections caused by Gram-negative bacilli.

Nowadays, in developed countries like Australia and the USA or in Europe, serious Gram-negative infections such as septicaemia in neutropenic patients or nosocomial septicaemia or pneumonia in intensive-care units, are usually treated by a combination of beta-lactam plus aminoglycoside therapy. The resistance of organisms to gentamicin or amikacin no longer fluctuates. Recent surveys also show that amikacin resistance in the USA and Europe is very infrequent among Gram-negative bacilli. These organisms are now usually susceptible to gentamicin, except in some South European countries (20, 21).

Thus, trials of antibiotic rotation in developed countries cannot readily be performed with aminoglycosides alone, but rotations such as ceftazidime/gentamicin, imipenem/gentamicin, etc. could certainly be done. In developing countries, gentamicin alone is more often used to treat severe sepsis caused by Gram-negative bacilli, and drugs such as ceftazidime are regarded as reserve antimicrobials, to be used only if bacterial resistance to gentamicin is suspected or proved (22). But it is expensive to perform drug trials, and trials of antibiotic rotation are prolonged and likely to be expensive.

**Chloramphenicol**

In 1995, the Royal Melbourne Hospital, Australia, tested 100 consecutive isolates of methicillin-resistant *Staphylococcus aureus* strains (MRSA) for chloramphenicol sensitivity and, surprisingly, they were all sensitive to the drug. Because of the fear of chloramphenicol-induced aplastic anaemia, the drug had not been used in Australian hospitals for some 10 years. The position is much the same in the USA and most other developed countries. MRSA infections and colonizations became very common in hospitals in Australia and the USA and other developed countries in the early eighties, and the strains at that time were also resistant to many unrelated antibiotics, which usually also involved chloramphenicol (23, 24).

It seems that MRSA strains are again sensitive to this drug because during the last 10 years or so chloramphenicol has been virtually “rotated out” of clinical use in developed countries. However, confirmation of this observation still needs to be obtained. In the developed world, chloramphenicol may remain a forgotten antibiotic. But two MRSA strains with intermediate resistance to vancomycin, isolated from patients in the USA, were found to be chloramphenicol sensitive (25). None the less, even if such strains become more widespread and if complete vancomycin resistance in *S. aureus* occurred, the developed world will probably look at new drugs or antibiotics such as quinupristin-
dalofopristin (26, 27), rather than go back to chloramphenicol.

Chloramphenicol remains an important drug in the developing world for its cheapness. It is used for the treatment of severe *Haemophilus influenzae* or meningococcal infections, typhoid fever and other systemic *Salmonella* infections. Chloramphenicol-resistant *H. influenzae* (28), *Neisseria meningitidis* (29) and *Salmonella typhi* (30) have all been reported from developing countries. The interesting question then arises — if in any given country or area the resistance of these serious pathogens to chloramphenicol becomes so high that reserve drugs have to be used anyhow, could chloramphenicol sensitivity be restored if the drug is not used at all in that area for several years? To investigate this possibility, virtually all chloramphenicol use would have to cease. This may be hard to achieve when antibiotics are available over-the-counter in developing countries, or where travellers may reintroduce resistant organisms. But this could be an interesting and useful possibility.

**Evaluation of treatment protocols by mathematical model**

Complex mathematical models have been used to evaluate treatment protocols to prevent antibiotic resistance (31) where cycling of antibiotics (i.e. using only one drug at a time) would always be inferior to treating the patient all the time with combination therapy consisting of at least two antibiotics. The model mainly applies to those bacterial infections such as tuberculosis, gonorrhoea and some diarrheal diseases in which the recovery from the infection coincides with the termination of carriage of the organisms. The model applies less to nosocomial infections in hospitals. It is well known that tuberculosis should be treated by combination chemotherapy.

For treatment of gonorrhoea, The Centers for Disease Control and Prevention currently recommend either single-dose ceftriaxone, ciprofloxacin or ofloxacin (32). Resistance to ceftriaxone and related drugs has not yet emerged, but ciprofloxacin- and ofloxacin-resistant *N. gonorrhoeae* strains are now being encountered (33). This organism has developed resistance to other antimicrobials over the years. So the suggestion of combination chemotherapy may have some merit, but we doubt whether this could be done in view of the cost and inconvenience involved.

However, it is doubtful that mathematical models such as this can contribute much to our knowledge about antibiotic rotation or drug resistance in general.

**References**


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**Current Topics**

**Ninth International Conference of Drug Regulatory Authorities**

The Ninth International Conference of Drug Regulatory Authorities (ICDRA) took place from 26–29 April in Berlin, Germany, where 280 participants were welcomed from over 90 countries. The ICDRA acts as a forum to harmonize collaboration and address matters of mutual interest to regulatory officials. In this way it proposes recommendations to support drug regulatory activities worldwide.

The success of this event was a tribute to the excellent organization by the Federal Institute for Drugs and Medical Devices, headed by Professor A.G. Hildebrandt. The conference programme, which was drafted by a Planning Committee representing the six WHO regions, was highly relevant to the multiple and increasingly complex responsibilities of drug regulatory authorities.

A highlight of the conference was the keynote address by WHO’s Director-General Dr Gro Harlem Brundtland in support of WHO’s Tobacco Free Initiative. This called on drug regulators to support WHO in the implementation of the Framework Convention on Tobacco Control.

The Tenth International Conference of Drug Regulatory Authorities will take place in Hong Kong, Special Administrative Region of China, from 5–8 November 2001.

**Recommendations from the Ninth ICDRA**

**Good Regulatory Practice**

1. WHO should develop guidelines to define good regulatory practice and develop appropriate indicators to measure performance. These guidelines should be made available over the WHO website to enable countries to formulate their own standard operating procedures (SOPs).

2. In order to implement good regulatory practice:

   • The mission and objectives of drug regulation should be stated clearly so that the attainment of perceived objectives can be assessed adequately.

   • Regulatory procedures and outcomes should be transparent to all the stakeholders, including those affected by such regulation, professional bodies, and the public.

   • Drug evaluation reports including the rationale used to reach decisions concerning regulatory action should be accessible to the public, as applicable within national legislation.

   • The deadline required for the assessment of drug applications should be reasonable, without compromising the safety, efficacy and quality of the product.

   • Special considerations should be made to expedite the review of orphan drugs and drugs of special medical or public health value.

   • Regulatory authorities should be accountable to the government, those regulated and the public.

   • Personnel engaged in drug regulation should be appropriately trained, qualified, competent and of high integrity. Merit-based selection criteria of a high standard should be implemented. Human resource development programmes should be in place to improve the knowledge and skills of staff.

   • In the event of dissatisfaction with regulatory decisions, legislative procedures and mechanisms should be in place to allow pharmaceutical companies, consumer groups and the public to lodge official complaints and appeals.

   • Access to the latest scientific and technological information should be provided to drug regulatory authorities in order to facilitate their work.
Regulatory authorities should acknowledge the rights of citizens to receive accurate and relevant information on drugs that are marketed in the country.

Regulatory authorities should establish mechanisms to ensure the quality of the procedures they operate to.

**Good certification practice**

The workshop discussed the general applicability and practical use of certificates, including the WHO Certification Scheme.

- The usefulness of the WHO Certification Scheme was endorsed by participants.
- The practical usefulness of certificates depends on the credibility of certifying authorities, as well as the quality of information provided.
- Certificates cannot be used by importing country authorities as a replacement for the technical assessment and professional judgement contained in application dossiers for marketing authorization.
- The value of certificates is diminished if products are not authorized for marketing in the certifying country.

The following recommendations were made:

1. WHO should continue to promote the use of the Certification Scheme with a view to assuring its global application.

2. National authorities should insist that manufacturers, traders and other companies comply with the WHO Certification Scheme, and should refuse other certificates.

3. WHO should trigger feedback information on the practical utility of the Scheme, including the certification needs of importing countries, ways to prevent falsification of certificates, and how to improve the effectiveness of the Scheme.

4. WHO should work with national authorities to develop appropriate, safe and reliable mechanisms to permit exchange of verifiable product certificates and information on the Internet.

5. Exporting countries should ensure that maximum information concerning all the manufacturers involved in production — and at least information on the manufacturer responsible for batch release — is provided on certificates.

6. WHO should foster further development of the Certification Scheme to: (a) include provisions for additional information on manufacturers, and (b) address the case of products with no marketing authorization in the certifying country. A declaration by the company's authorized person before the certifying country authority, including information on product development, stability testing, and prior marketing should be given.

7. Member States are requested to ensure that a WHO product certificate with an original signature is provided.

**Counterfeit drugs:**

**Challenges and solutions**

1. Political will to combat counterfeiting at national and international levels should be encouraged.

2. The WHO definition of counterfeit pharmaceutical products should be considered for adoption by all countries.

3. Member States should make every effort to collect and verify more accurate data on counterfeiting within their countries and submit these data to WHO or Interpol, as appropriate, to facilitate international collaboration.

4. Liaison officers of the WHO anti-counterfeit drugs network should be utilized for information exchange and investigation of counterfeit drugs. The draft WHO guidelines for the development of measures to combat counterfeit drugs are useful instruments and will be made available on the WHO website.

5. A national legislative framework should be in place with appropriate penalties and enforcement. National regulatory authorities should be strengthened to implement appropriate measures. In addition, customs services and the police should become integral partners in implementation. Fraudulent activities by members of the responsible authorities should not be tolerated.

6. At national level there is a need to encourage more reporting of counterfeit drugs. The introduction of innovative national approaches to this problem should be considered such as the Brazilian initiative to introduce toll free telephone lines for anonymous reporting of counterfeit drug trafficking.
7. At national and international level, industry should be more closely engaged with the regulatory authority by assisting in the identification of possible counterfeit medicines and in finding ways to address the counterfeiting problem. Action should be focused on the domestic, export and import markets and should cover raw materials and the final product.

8. International cooperation should be strengthened and involve international agencies such as WHO, UNICEF and Interpol. WHO and Interpol should develop initiatives to improve the exchange of information. International agencies should give specific consideration to the conflict between the need for regulatory authorities to know of the circulation of counterfeit products and the need for confidentiality when criminal investigations are under way.

9. Specific recommendations made by Interpol.
   • Manufacturers should be legally required to report to regulatory authorities any information brought to their attention concerning a product which has been or may be counterfeited.
   • Regulatory authorities should be informed of offers of drugs at prices substantially below the official price.
   • Extradition treaties should be expanded to include the crime of drug counterfeiting.

10. The high cost of medicines in developing countries makes them unaffordable to large sectors of the population and increases the risk of counterfeiting. This should be addressed by the manufacturing companies who may need to consider lowering the price of drugs in poor countries most at risk of counterfeiting.

**Current issues in regulation and quality**

WHO should:

1. Continue to serve as a platform for the exchange of information on important regulatory decisions of worldwide implication.

2. Take measures to reinforce the collaboration between drug regulatory and criminal investigation authorities internationally, in particular Interpol and the World Customs Organization, to deal with criminal activities involving pharmaceutical products and materials.

3. Implement recommendations on safe trade and control of starting materials as set out in document WHO/PHARM/98.605, including risk assessment of starting materials.

4. Develop safe trading practices in close collaboration with brokers, traders and other international organizations and institutions.

5. Support training of assessors for new drug applications and good manufacturing practice (GMP) inspectors in countries with limited resources, in collaboration with national health authorities.

Countries should:

6. Establish a structure to facilitate close collaboration between the regulatory authority granting marketing authorizations for pharmaceuticals and inspection bodies.

7. Develop a plan for implementation of drug regulation, and monitor progress

8. Implement quality systems for pharmaceuticals that are also appropriate to starting materials intended for export.

**ICH: Implementation and implications**

1. Globalization of International Conference on Harmonization (ICH) guidelines should be further pursued as appropriate for Member States. WHO should continue to play an important role by taking into account the implications for non-ICH members.

2. WHO should explore the feasibility of integrating ICH products and WHO guidelines into a comprehensive set of guidelines.

3. Countries should take into consideration local factors in applying ICH guidelines.

4. ICH should give greater consideration to developing country needs through WHO particularly as this relates to the quality of all medical products including generic and over-the-counter (OTC) drugs. Mechanisms should be established to increase the balanced participation of developing countries in the consultative process of ICH. Non-ICH countries should actively seek opportunities to participate by reviewing documents under development and submitting comments early in the process, as appropriate.
5. ICH guidelines may be utilized by interested parties as a source of education and training.

6. Since ICH guidelines cover new products and many countries manufacture, register and use generic drugs, WHO is encouraged to continue work on guidelines on requirements for registration of generic drugs.

7. ICH updates should remain a subject for future ICDRAs and related WHO-sponsored regional meetings.

**Drug utilization studies**

Drug utilization studies are an important tool for drug regulators particularly in improving rational drug use and providing data for cost/benefit considerations. WHO should assist drug regulatory authorities by:

1. Encouraging studies of actual use and consumption of drugs by relating pharmacotherapy to the actual disease.

2. Promoting quality of the data by ensuring that the source of the data is accurate and establishing a system of data collection.

3. Raising awareness of how Anatomic-Therapeutic-Chemical (ATC) and Defined Daily Doses (DDDs) are developed through educational programmes in order to prevent misinterpretation and misuse of ATC/DDD.

4. Adopting or adapting manuals for use of the ATC/DDD classification at local level with reference to the manuals prepared by the WHO Collaborating Centre on Drug Statistics Methodology in Oslo, Norway.

5. Promoting greater awareness of changes in the ATC/DDD classification system and establishing conditions for the regular updating of national classification systems.

**Global and national efforts to reduce tobacco use**

1. National drug regulatory authorities should:

• Collaborate with other relevant national authorities, regulatory authorities of other Member States and WHO in identifying the science base for the appropriate regulation of tobacco products and medicines that could reduce the harm from tobacco products.

• Review regulations on medicines for the treatment of nicotine dependence, taking into account the need to increase accessibility to these medicines in order to achieve public health goals.

• Support the development of WHO's Framework Convention on Tobacco Control to ensure that regulatory aspects are properly addressed.

2. WHO should ensure that information about tobacco regulation, including lessons learned by Member States, is disseminated to drug regulatory authorities.

3. The next ICDRA should include tobacco as an agenda item.

**Electronic communication in the regulatory process**

1. WHO should set up an electronic communication system to permit effective, prompt and secure information exchange among drug regulatory authorities.

2. WHO should further promote the implementation of computer-assisted drug registration in order to contribute to effective drug regulation.

3. National authorities should look into their electronic communication needs and on that basis identify requirements and resources.

**Transparency in monitoring the safety of medicines**

1. Countries setting up systems for drug safety monitoring should make use of existing experience, including that from WHO and other countries. In this way, scientific resources can be harnessed.

2. Networks for electronic exchange of drug information, in particular relating to safety and which allow for rapid communication, should be established. WHO should take the lead in this endeavour.

3. Regulators should be prepared for crises and guidelines should be available on how to manage a crisis situation involving drug safety.
4. Plans for post-marketing surveillance should be made during drug development.

5. All relevant stakeholders need to be involved in drug safety issues identified by drug monitoring.

6. New drug safety monitoring programmes can be instrumental in the detection of counterfeit drugs, unexpected “lack of efficacy” should be considered and managed as an adverse drug reaction.

7. Authorities should cooperate with other regional authorities when important signals are detected in order to ensure the earliest possible awareness.

8. Principles of good communication should be developed by WHO with input from WHO Member States and regional authorities.

**Pharmaceutical products for use in special groups**

Guidelines for use of pharmaceutical products in special groups, such as pregnant women, children, elderly and ethnic minorities are important and needed. The only guidelines currently available are ICH Guidelines for the Elderly.

1. WHO, in collaboration with the ICH, should actively disseminate existing guidelines and integrate them into regional educational and training activities.

2. Existing guidelines should be revised and modified according to individual medical practice, health care systems and other local factors, including use in drug monitoring systems, studies in HIV-infected populations, etc.

**Bioequivalence**

1. WHO should develop common definitions and guidelines indicating when in vivo equivalence studies are needed.

2. WHO should coordinate the development of model guidelines for harmonization purposes to determine when in-vitro studies are acceptable.

3. WHO should make the list of international comparator products widely available, including advice on how it can be used by drug regulatory authorities within their national context.

**Antimicrobial resistance**

As part of WHO’s global strategy for the containment of resistance to antimicrobial drugs, and in collaboration with Member States, WHO is invited to:

1. Bring together national authorities for human and veterinary drug regulation to exchange information and to consider joint action.

2. Provide guidance on the clinical development of antimicrobial drugs, in particular to optimize efficacy while minimizing the risk of resistance.

3. Establish a common format for product information and patient information leaflets, specifically addressing antimicrobial resistance issues such as specifications for medicines, susceptibility of common pathogens and measures to prevent resistance. Special attention should be given to improving the communicative potential of the information provided. This information should be regularly updated in the light of prevailing resistance patterns.

4. Continue efforts, as set out in WHO resolution WHA 51.17, to make antimicrobial drugs available on a prescription-only basis.

5. Stimulate drug regulatory authorities to share all relevant information on clinical trials involving antimicrobial drugs, with public health authorities.

**Safety issues of plasma-derived medicinal products**

1. WHO should collaborate with Member States to strengthen the technical expertise of national control authorities in the regulation of plasma products, especially those countries with plasma fractionation activities or facilities to assure adequate quality, safety and efficacy of plasma products. This includes special emphasis on viral testing, viral inactivation procedures, and surveillance for viral and other transfusion transmitted diseases.
2. WHO should promote the regulation of blood bank facilities by National Control Authorities in order to ensure compliance with GMP principles.

3. WHO should facilitate the development of educational programs and training opportunities for National Control Authorities involved in regulation and control of blood products. WHO should promote regional cooperation and training.

4. WHO should assist Member States in the development of appropriate guidelines for plasma fractionation contract activities.

5. WHO should provide guidelines on information to be included in batch release certificates in order to facilitate acceptance of imported plasma products by national control authorities.

Herbal medicines

1. Member States should formulate national policies on traditional medicines taking into particular consideration the traditional processing of herbal preparations and raw materials within local communities. Emphasis should be placed on the development or updating of national legislation for registration and licensing of industrially-prepared herbal medicines, as well as for the regulation of traditional medical practice as an integral component of the national health system.

2. WHO should continue to co-operate with governmental institutions in developing and updating guidelines on the assessment of the quality, safety and efficacy of herbal medicines.

3. WHO should update quality control methods for medicinal materials including the introduction of new technical methods, e.g. capillary electrophoresis to replace solvent extraction and solvent-mixture TLC or HPLC techniques.

4. WHO should continue to compile knowledge on the safety and efficacy of herbal medicines, including development of WHO monographs on selected medicinal plants.

5. WHO should consult on a definition for the terms "traditional" or "herbal" medicine and "drugs" and how these should be delineated from the terms "food" and "dietary supplements".

6. WHO should collaborate with Member States to strengthen the safety monitoring of herbal medicines.

7. WHO and Regional Offices should work together to organise training courses for national authorities and traditional medicine practitioners on assuring the quality, safety and efficacy of herbal medicines.

8. WHO should continue to disseminate information and assure fast and wide availability of all relevant documents via electronic media and the internet.

Recommendations on other traditional medicines and homoeopathy:

9. WHO should continue to prepare similar guidelines in related fields of traditional medicine, especially on the quality and safety of homoeopathic products.

Regulation and access to essential drugs

In recognition of the challenges faced by Member States to achieve availability and accessibility of essential drugs and the complexities involved, the following recommendations are made:

1. Experience from countries facing economic crises demonstrate that the following basic principles should be adopted in an integrated manner, focusing on population groups most in need.

   - Essential drugs and generic drug policies should already be in place and implemented.
   - A decentralized drug management system for recording and reporting should be supported by appropriate guidelines.

2. Procurement for the most needed essential drugs should be pooled and followed by monitored distribution. National essential drug programmes should be made sustainable through mechanisms such as revolving funds, cost-sharing and cost-containment.

3. In order to ensure availability and accessibility to essential drugs at primary levels of health care:

   - Essential drugs lists should be formulated for different levels of health care.
   - Diagnosis and standard treatment guidelines should be developed and adopted for each level of health care.
   - An enabling environment should be created for prescribers and other health care providers to
improve availability of essential drugs within their scope of practice.

4. In order to improve drug donation practices:

• WHO should be proactive in promoting the WHO guidelines for drug donations.

• All donor and recipient countries should adopt and comply with these guidelines.

• There should be close collaboration between regulatory authorities in donor and recipient countries.

• Mechanisms should be established for the timely exchange of regulatory information between donor agencies and regulatory authorities.

• Countries should develop administrative procedures for accepting drug donations and disseminate them to all relevant agencies.

5. In order to improve access to essential drugs, drug regulators should:

• Ensure timely availability of essential drugs through expedited review and approval processes without compromising drug quality, efficacy and safety.

• Facilitate authorization of medicines considered to be major therapeutic advances through information exchange between regulators.

• Harmonize regulatory requirements and promote closer cooperation among regulatory authorities.

6. In order to make drugs affordable, drug regulatory authorities should:

• Establish legislation for generic substitution.

• Ensure timely authorization of generics.

• Establish mechanisms to facilitate introduction of generics promptly after patent expiry.

6. WHO should assist Member States in the implementation of the above recommendations as appropriate, and seek support from bilateral and multilateral agencies to ensure sustainable drug supply at peripheral levels of health care.

ICH and the common technical document (CTD)

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The International Conference on Harmonization (ICH) was established to function as a forum to harmonize technical requirements for registration of new innovative pharmaceuticals. The members of the ICH are drug regulatory authorities and the pharmaceutical industry within the countries of the European Union, Japan and the USA. WHO’s role in the ICH has been one of observer and its function has been to serve as a bridge between the ICH and non-ICH countries. In this way, WHO has promoted understanding of the global applicability of ICH products when this is appropriate.

Since 1990, the ICH has developed some 38 tripartite guidelines dealing with numerous principles of quality, safety and efficacy of pharmaceuticals. Based on existing ICH guidelines, a common technical document (CTD) is now under preparation which will define part of the documentation for the content and format of a new drug application.

The concept of a common technical document

Due to existing practices, traditions and regulations, many administrative requirements and aspects of product labelling vary between International Conference on Harmonization (ICH) countries. Because of this, the proposed common technical document (CTD) will cover only part of the conventional documentation required in a new drug application for marketing authorization (MAA). There are also differences in the overview summaries for scientific documentation, the need for individual clinical case reports, and the data to document findings made in animal studies (1). These and other special local requirements form a substantive portion of an MAA and remain, in principle, outside the current CTD concept. In figure 1 on page 79, the highlighted box indicates that part of the documentation to be harmonized as the CTD.

In the early phase of ICH discussions, the terms “global dossier”, “global technical document” and “global technical data file” were often used when referring to the CTD. However, these terms are not relevant. Firstly, because the CTD does not cover
the MAA as a whole and, secondly, because the term is misleading as understood in a geographical context. ICH is not a worldwide, global institution and has no designated mandate to harmonize outside of the 17 tripartite countries. The only intergovernmental health organization with a worldwide constitutional mandate and responsibility for harmonization in health-related issues is the World Health Organization (2).

**CTD feasibility study**

Before initiating the CTD, a survey was carried out between eight international pharmaceutical companies. The survey showed that it took an average of 3 to 4 months to convert an MAA prepared for the US FDA into an MAA valid for the European Union, or vice versa (1). The survey was useful in demonstrating how the CTD would deliver real savings by decreasing the time and resources required within companies for preparing submissions to regulatory agencies having different MAA requirements and at the same time avoid duplication. It also demonstrated that the CTD would facilitate simultaneous submission of applications to various countries. A follow-up study compared the format and content requirements of the MAA among ICH countries to evaluate existing harmonization and that remaining to be accomplished. It also aimed to analyze any divergencies in MAAs.

![Figure 1. The highlighted box identifies that part of the documentation for marketing authorization applications that will be harmonized by the ICH as the common technical document (CTD).](image-url)
CTD and the non-ICH countries
It is understandable that multinational pharmaceutical companies would also like to use the CTD outside ICH countries. To achieve more extended understanding and acceptance of the CTD, WHO has offered assistance to the ICH through its international consultative mechanisms and by involving non-ICH countries in discussions on CTD harmonization. Thus, pharmaceutical advisers from each of the six regions of WHO have participated in CTD expert working groups since 1998. Their role will be to assist in distributing relevant working documents to drug regulatory authorities within their own region for comment. Success of the CTD will hinge on recognition and adoption by drug regulatory authorities and, unless this is achieved, implementation will remain limited to tripartite countries and will lead to increased regulatory disharmony worldwide (3, 4).

CTD: limitations and obstacles
In principle, ICH guidelines target specific identified areas for harmonization. Although guidelines cover many subtopics there are, as yet, no complete ICH guidelines covering the totality of requirements for quality, safety and efficacy. This means that gaps in guidance must be replaced by national regulations that often vary between tripartite countries. Furthermore, ICH guidelines focus on innovative drug development and address only new drug substances and products, excluding the widely used, well established substances and the multisource (generic) products (5).

GMP and quality requirements for starting materials, excipients, and active pharmaceutical ingredients have proven to be difficult and complicated areas for harmonization within the CTD. ICH started work on GMP for active pharmaceutical ingredients in 1998, but this still needs to be finalized. ICH quality (stability) guidelines cover conditions in climatic zones I and II (ICH climatic zones) but not critical zones III and IV, i.e. those which are hot and dry or hot and moist, and which are found in many developing and tropical countries. Yet pharmaceutical products from ICH countries moving in international commerce claim to be appropriate for use in countries of climatic zones III and IV.

In view of the fact that regulators in these countries are unable to use the ICH criteria, WHO has developed and published a comprehensive stability guideline applicable in all climatic zones which includes generic pharmaceutical products. In 1998, the ICH initiated a revision of their stability guideline, but generic products and climatic zones III and IV are still not highlighted. Equally, specifications for packaging materials, complicated drug substances, bioequivalence studies and many pharmacopoeial requirements — which have been addressed by WHO — currently remain outside the ICH harmonization plan.

Although it is possible to establish a CTD to cover quality and experimental safety documentation, this may not be feasible for efficacy. The question of how to harmonize efficacy requirements and clinical trials for products dealing with a variety of specific diseases and how to predict these in advance for totally new innovative treatments and drugs needs to be addressed. Moreover, clinical trials required for documentation of efficacy and safety in children, the elderly, and during pregnancy or lactation are still under consideration within the ICH. Finally, the complexity of clinical trials is increasing with the need to address long term efficiency in chronic diseases, including unclear endpoints, quality of life issues, health economics, sub-population analysis and, in the near future, an additional parameter for genetic information.

Variations in current contents and structures of MAAs and their review practices should be harmonized to maximize the benefit of CTD, but this may require changes in existing regulations (6). Many research-based pharmaceutical companies within ICH fear that CTD may harmonize requirements upwards (i.e incorporate all current local regulatory features) rather than establish common requirements (1, 6). This could result in excessive costs and delays in development. Furthermore, ICH work has not considered generic products and did not involve the generic industry, “local industries” or the self medication (OTC) industry. Although these partners have now been invited to work on CTD, many issues in the current ICH guidelines will complicate collaboration.

The benefits of CTD
None the less, several potential benefits of CTD can be appreciated. A single format for an important part of the MAA would facilitate communication and exchange of information between regulators and industry. Applications made by electronic submission would be easier, and the resources needed within industry to compile applications in different formats would be minimized. The application of a more logical order of documentation within the CTD would follow, and allow a better development process for new pharmaceutical products.
It is also evident that a CTD could facilitate the evaluation process carried out by regulators, since the MAA would be more structured, consistent and user friendly (1, 6). As these benefits relate currently to tripartite countries alone, they should ideally be extended to regulators and industries worldwide.

**International review of ICH**
During the Ninth International Conference of Drug Regulatory Authorities (ICDRA) some 280 drug regulatory officials from over 90 countries analysed the progress made in ICH and, specifically, on the CTD. Their recommendations are set out on page 74.

**Conclusions**
Harmonization activities such as the ICH and the CTD aim to eliminate unnecessary or duplicative technical and regulatory requirements. This will accelerate new drug development — which is in the interests of public health and patients worldwide — as long as harmonization does not compromise the safety and efficacy of products.

It must be admitted, however, that not all regulatory requirements and procedures can be harmonized. Each country has its own established legislation, regulations and regulatory practices and traditions for pharmaceuticals. It may be sufficient for these to be more consonant and similar regionally as in the European Union.

Above all, a broad consultation is vital in order to render the harmonization process widely transparent and to allow all countries — both in the developed and developing world — to become involved and regard themselves as true partners in an exercise of mutual interest. It is therefore important to succeed in global use of the CTD if progress is to be made in harmonization.

In conclusion, complete harmonization probably remains beyond present-day capabilities and it is unlikely that there will ultimately be a single uniform set of standards for development, assessment and approval, at least in the immediate future. However, when, and if, this happens it will doubtless lead to the establishment of a single regulatory assessment or even to the creation of one global regulatory authority.

**References**


**Good clinical practice: application in tropical disease endemic countries**

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A major objective of WHO’s Special Programme for Research and Training in Tropical Diseases is the discovery and development of affordable drugs, vaccines and diagnostics for the prevention and treatment of tropical diseases. An important component of this activity is the development to registration of quality products and their subsequent marketing approval.

Clinical trials carried out to determine the safety, efficacy and tolerability of candidate products must be planned and conducted to reliable standards according to good clinical practice (GCP) in order to meet the stringent regulatory requirements of
marketing approval. However, those populations most in need of products for tropical diseases are found in developing countries facing problems of poverty, illiteracy and inequality. Conducting clinical trials in these countries under the concepts of GCP has proven to be a major challenge.

In the application of its public health and research mandate, it is TDR’s wish to extend respect for human rights without prejudice to local variations in attitudes and beliefs. Although WHO-supported studies aim to fulfill public health needs, TDR has great difficulty in achieving ethical conformity in line with fundamental international guidelines. Undoubtedly, the most difficult task in the conduct of clinical trials in these countries is the implementation of standard ethical considerations of justification and consent, and the most frequent problems involve implementation of the informed consent procedure according to GCP. Some requirements or criteria, particularly concerning the manner in which informed consent should be elicited, may not be correctly applied due to differences in cultural understanding and acceptance. For example, permission to participate in a study is often sought from the community leaders or from a household member rather than the individual taking part in the trial.

The amount of information to be provided during the informed consent procedure is another area for debate. How much information should a subject receive and what is the subject’s capacity to understand the implications of such information when agreeing to participate in a trial? Here, there are many differences in points of view due to beliefs, attitudes and practices. The understanding of ethics as used in some parts of the world might not be the same as that in others. Ethical principles may be seen as what is acceptable at a particular moment in time and place, but subject to change as society develops. On the other hand, the force of customs, laws or local practices and beliefs should not be used to justify abuse of fundamental rights or the right of self-determination.

Knowledge and understanding obviously vary between different subjects participating in trials and individuals from different regions and countries but, above all, there are huge differences in physician-patient relationships. Patients or volunteers in developing countries almost always leave treatment decisions to a physician. A subject gives informed consent for participating in a trial as part of the process of establishing a fiduciary relationship with their physician. Most subjects hold the belief that whatever the physician does will benefit them and they will consent to whatever a trusted physician asks of them. On the other hand, refusing to participate in a study would jeopardize the patient-physician relationship and future treatment. Since very few subjects or patients can fully understand the implications or be acquainted with all the facts relating to a particular study in which they have been asked to participate, responsibility for the subject’s wellbeing relies very heavily on the physician or study investigator. In practice, there is little evidence to support the claim that informed consent alone can provide protection against the exploitation of subjects or patients in research.

Given this situation, protection of human subjects is assured most effectively by the careful oversight and scrutiny of research proposals presented before a properly constituted national ethical review committee or institutional review board (IRB). The ethical review committee does not need to replace the informed consent procedure, but should complement and oversee it. Ethical review is an important task and the committee should be fully supported by national authorities. In developing countries in particular, the ethical review committee should take full responsibility for examining the experimental design, the procedures to be employed, the expertise of the investigators and any other points that are deemed to be relevant in protecting subjects and local interests. The committee may also decide on the way in which consent is to be obtained — the degree and breadth of the explanation to be given to the patient, and mechanisms to ensure that the explanation can and will be understood.

Unfortunately, as things stand, ethical review committees in disease endemic countries rarely satisfy the requirements of GCP guidelines. The variability in the composition of the committee and methods of working of ethical review committees in these countries is enormous. In many cases, institutional committees may not be able to function in a truly independent manner because members work together within the institute carrying out the research and are appointed by the head of that institute. Often there is a potential conflict of interest and members may not wish to displease colleagues. Equally, if the project belongs to the head of the institute or the institute is dependent on funding related to the study in question, the members may feel compelled to act in one way or another.
Wherever subjects are located in the world, they should be allowed the same basic human rights and their welfare should be a priority for researchers. It is becoming increasingly evident that we must pay much more attention to strengthening ethical review committees and IRBs, including those in developing countries. We can no longer hope that all subjects participating in trials are protected by local mechanisms and that informed consent is sufficient. We also need to realize that, currently, there is no existing procedure to monitor the ethical application of trials once they are under way.

In the meantime, we must ensure that studies are justified and that subjects’ basic rights of informed consent are protected. We believe that this can be achieved through effective ethical review which acknowledges the differences in local practice but fulfils the principles of human rights.

References


Biomedicines and Vaccines

Biomedicines: meeting the challenges

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Over the past two decades, the pace of development of biomedicines has accelerated. With concurrent political and socioeconomic changes, this has put a great strain on international systems of standardization and on the underpinning institutions. However, the public health importance of biomedicines and vaccines makes the continued operational viability and wellbeing of these systems a major international challenge. The commitment of governments, the public, industry and international institutions is pivotal to the successful resolution of the public policy issues concerning the production of biomedicines.

Because of current changes in the social and scientific framework, systems of standardization and control are subject to a powerful combination of forces. Privatization and reduced public spending have resulted in a squeeze on resources, targeting those laboratories on which the international system relies for the sustained operation of standard-setting, reference materials and expertise. This restructuring and streamlining requires that national institutions focus on immediate operational priorities rather than longer term scientific issues.

Conversely, it is evident that national authorities and the international systems they support are unable to keep up with the present upsurge in the number and complexity of biomedicines. Decisive action on priority setting and delegation of responsibilities within the stakeholder group will need to be taken. In order to resolve the disparity, industry may need to assume a greater share of responsibility through self regulation, and worksharing and harmonization will be a primary consideration. In addition, growing public scepticism over new scientific interventions and the social and ethical issues attached to use of diagnostics and treatments based on genetics and xenotransplants will require a broadening of the decision-making process to involve more key players. As the developing world opens up to manufacture and marketing of biomedicines, the demand for international standards and quality control measures will increase even further.

New partnerships
In reviewing the options, it is clear that new partnerships will play key roles. The advances in process control through the use of biotechnological methods provide sound justification for greater responsibility testing by the manufacturer. This, together with the availability of physicochemical methods of analysis, make more precise in-house monitoring feasible. This situation has already been endorsed through amendments to the regulatory mechanisms in the European Union and the United States. In addition, risk-assessment techniques can be used to relate regulatory requirements to potential hazards.

By adopting these mechanisms, the resources of national control authorities will be more effectively utilized. A survey conducted in 1996 by the National Biological Standards Board in the United Kingdom indicated that this change would be supported by industry and major control authorities. Making this happen in an orderly fashion will be a challenge for policy-makers within and outside the biomedicines community since it will be their responsibility to demonstrate that such changes are in the public interest. For the same reason, regulatory and advisory bodies must be careful in structuring a closer partnership with industry and issues such as conflict of interest will need to be addressed.

Another increasingly important partnership is with the public. Today's better-informed and more articulate public wants its views to be heard. New demands from society make biological products more accessible as witnessed by the availability of home tests kits for diagnosis and screening. One challenge here is to develop the right machinery for public input, and some national authorities have already set into motion impressive consultative systems. Evidence is now needed to evaluate how well these work and whether they are appropriate for other countries and regions. Finding the answers will be important for public confidence worldwide.
Rethinking the process
A very relevant comment raised during the National Biologicals Standards Board (NBSB) survey was that governments and people in developing countries would not be able to afford some of the dramatic new advances that are likely to appear in the biologicals sector. It is therefore important to arrange for a more representative input to priority setting at international level before agreeing which products should take precedence for international standard-setting and guidelines. Debate may need to take place at national level on whether compromise or reconsideration of national priorities is called for to achieve equitable global policies.

Other aspects of process also demand attention. Spurred by growth in volume and the complexity of biomedicines, initiatives are already in progress for harmonization of regulation. The present national-based systems of biological standardization, coordinated centrally by WHO, mean that countries may enforce different requirements and that different bodies are duplicating each others' work. Neither is it a question of harmonization being advantageous only to industry, which bears the brunt of varying requirements. National control authorities have equally serious problems of workload. This increasing volume of work highlights the desperate need of both developed and developing countries to develop a system of mutual recognition and acceptance of marketing approvals worldwide.

There is, moreover, a public health interest in avoiding unnecessary delays in bringing safe and effective new drugs onto the market. We should not forget the success of AIDS activists in bringing about accelerated approval of HIV therapy.

However, as the European Union experience demonstrates, the difficulties of mutual recognition should not be underestimated. Although WHO is important as a coordinating agency, its guidance does not yet have comprehensive coverage nor global acceptance. Ideally, it could do more in bringing together national and international organizations for serious discussions — but does it have the resources? There is thus a need for government commitment which may need the same kind of approach as the problem of biodiversity.

A sustainable future
Although it is acknowledged that a strong scientific basis is needed to deal with unpredictable safety concerns such as that experienced in the United Kingdom with bovine spongiform encephalitis, a current climate of financial stringency, public participation and a more consultative process could dilute the science of the biologicals world. Will this affect the long-term sustainability of scientific input to regulation? The national institutions which have nurtured this specialization and maintained research programmes may no longer be able to carry out this work. Some institutions have already reduced or abandoned their long-term research, such as the Statens Serum Institute in Denmark which has pulled out of reference standards manufacture. New institutions have been suggested as the solution. Given the daunting array of new scientific and technical products, the challenge of designing sustainable cross-sectoral and international research institutions may be one that policy makers cannot ignore.

Although WHO has the status to lead such an international programme, it does not control the required resources. This is not necessarily a bad arrangement since cooperative agreements based on local control of finances can be less bureaucratic and more effective. But the evolution of the present international system has led to imbalance. For example, almost 95% of new and the vast majority of existing international standards emanate from a single national establishment. This could lead to problems concerning continuity of supply. It would seem wise to bring in more partners and to agree on funding of an international system.

An essential part of the international programme for standardization and quality control of biologicals is the establishment and strengthening of national or regional authorities in developing countries. However, policy needs to be clear on how to provide funding and training. Can developed countries be persuaded to contribute and can they provide sufficient capacity in their agencies to provide training facilities.

Facing the social issues
There are some areas where a separate advisory mechanism may be needed to explore ethical and social issues linked, for example, to gene therapy. Questions are thus raised concerning the legal status of research, and medical and public health issues including health insurance coverage and accessibility. In the future, the pace of progress of bringing some new biomedicines to market will almost certainly depend on these rather than scientific issues.
Another issue centres around the concept of "one worldwide standard". It is clear that reference standards must be developed for global application. However, where quality control is concerned a host of silent reservations are present. The notion that poorer countries should have lower standards of quality for biomedicines is offensive and tends to suppress discussion of whether the current developed country standards are appropriately pitched. These issues need to be addressed and now is the time to clarify the scope for flexibility within the system.

Already, national control authorities can gain acceptance for their own requirements as equivalent to those of WHO. A growing number of national control authorities rely on risk assessment to determine the stringency of quality control required for their particular circumstances. Thus, the single-standard principle is good, but still needs to be evaluated from time to time with regard to current practices and the appropriateness of quality control measures to specific environments.

A further issue is that the area of biomedicines, biologicals, vaccines and diagnostics is still ill-defined. Boundaries may need to be enlarged to include new kinds of product such as organs for transplant or cloning or even whole transgenic donor animals. Biotechnology enables modification of food and cosmetics to perform quasi-medical functions so these too could be candidates for regulation as biologicals. Thus, matters of what to regulate are likely to constitute some of the more difficult policy issues to be addressed.

The future public policy agenda thus includes many international challenges of this kind.

- To support training for quality control strengthening in developing countries and the long-term maintenance of expertise and programmes for research.

I hope there will be those in the biologicals community who are committed to addressing these challenges and who may have the influence to create the conditions for international discussion.

### Progress in biological standardization

The WHO Expert Committee on Biological Standardization (ECBS) held its 49th meeting in October 1998. The ECBS is responsible for setting global standards for biological substances used in medicine, including vaccines, blood products, biological therapeutics and diagnostic procedures.

Many of the items on the agenda of the meeting reflect the increasing complexity of biotechnology as well as the development of new approaches to in-process testing procedures using, for example, molecular based techniques in place of, or in addition to traditional testing in animals.

#### Hib vaccine recommendations

At the meeting, revised recommendations (formerly requirements) for production and control of *Haemophilus influenzae* type b (Hib) conjugate vaccine were agreed. Prior to publication, these will be circulated for further comment to interested parties. *H. influenzae* type b causes several diseases in humans, the most common and serious being meningitis and pneumonia in children under 5 years of age. The capsular polysaccharide of *H. Influenzae* type b plays an important role in virulence, and conjugate vaccines derived from the type b polysaccharide covalently linked to a protein carrier are a safe and effective means of protecting against such infections. Requirements for *H. Influenzae* type b conjugate vaccine were first published in 1991 and, although valuable, needed updating to

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1 The Expert Committee included members from Belgium, Canada, China, Mexico, the Netherlands, Russia, United Kingdom and the USA. Temporary advisers were invited from Japan, the Netherlands, South Africa, Switzerland, the United Kingdom and USA, with representatives of the Council of Europe, European Association of the Plasma Products Industry, Pharmaceutical Manufacturers Associations, the International Society of Blood Transfusion, the International Society on Thrombosis and Haemostasis, and the International Association for Biologicals.
reflect recent vaccine control strategies. In particular, the biological assay of potency recommended in 1991 was shown not to correlate with the efficacy of the vaccine in infants nor to provide a sensitive indicator of vaccine quality. The ECBS therefore agreed that whilst immunogenicity testing in animals is necessary during vaccine development, an animal immunogenicity test need not be used for routine batch (lot) release. Instead, batch release testing should focus on physicochemical tests to monitor consistency of production of the polysaccharide, the protein carrier, and the bulk conjugate.

**Acellular pertussis vaccine**

WHO Guidelines for the Production and Control of the Acellular Pertussis Component of Monovalent or Combined Vaccines are concerned with vaccines shown to be safe and effective in well-controlled clinical studies (1). However, the language of the Guidelines appears to exclude from the international market some vaccines in routine use in Japan. Acellular pertussis vaccines were introduced rapidly into the Japanese national vaccination programme as a result of concerns about the whole-cell pertussis vaccines, and without the benefit of a classical double-blind clinical efficacy study.

The ECBS emphasized that it was not its intention to exclude effective vaccines of this kind from use and agreed that in such cases the results of product-specific postmarketing surveillance and epidemiological data could be used to demonstrate efficacy. The Committee also confirmed the acceptance of the modified intracerebral assay as an alternative to an immunogenicity test for vaccine potency estimation but not to reflect clinical efficacy.

However, the ECBS expressed concern that considerable confusion could occur if the potency of acellular pertussis vaccines estimated in the modified intracerebral challenge test is expressed in the International Units assigned to the International Standard for whole-cell pertussis vaccine. These International Units are accepted as indicative of protection by whole-cell pertussis vaccine but the ECBS recommended that they should not be used to reflect the protective immunity induced by acellular pertussis vaccines.

**Oral poliovirus vaccine (OPV)**

An addendum containing several additions to the requirements for oral polio vaccine (OPV) was also adopted by the ECBS. Important progress has been made towards the global eradication of poliomyelitis (2) and laboratory stocks may soon be the only source of wild poliovirus. The ECBS made additions to the existing requirements to ensure increased laboratory containment levels for wild polioviruses (3), which are used as controls in one test (the rct40 assay) of OPV.

Progress has also been made in understanding the molecular mechanisms and genetic determinants of virulence attenuation and reversion of the Sabin poliovirus strains used for manufacture of OPV (4). An addition to the requirements was made introducing the MAPREC (mutant analysis by polymerase chain reaction and restriction enzyme cleavage) assay (5) for quality control of OPV. This is the first of a new generation of tests of the molecular consistency of production of virus vaccines.

Additions to the requirements adopted by the ECBS concerned extra tests for adventitious agents. Tests on cell cultures have effectively excluded live simian virus 40 (SV40) from OPV for over 30 years (6). Newly developed gene amplification tests can additionally detect noninfectious SV40 sequences and although there is no evidence for SV40 sequences in OPV (6), the ECBS agreed to introduce a gene amplification test for SV40 in seed viruses to provide an additional level of security. The final addition to the requirements introduced antibody screening tests for foamy viruses in animals used for sourcing primary monkey kidney cells. This reflects modern quality control practices to thoroughly characterize starting materials to minimize any challenges to the manufacturing process.

**Other matters**

The ECBS established eleven new or replacement International Standards and Reference Materials covering a wide range of products (Table 1). Additionally, several International Standards and Reference Materials that are no longer required were discontinued following a recently introduced consultative process (Table 1). The Committee also proposed to discontinue certain Requirements and International Reference Materials at its next meeting. These are listed in Table 2, on page 89 and are proposed for comment.

A fully revised and complete list of WHO International Standards and Reference Reagents will be published as an Annex to the report of the 49th ECBS and will soon be available on the internet. The Committee noted that transfer of International Reference Materials from the Statens Serum Institute in Copenhagen and the Central Veterinary
Laboratory in Weybridge to the National Institute for Biological Standards and Control (NIBSC) had been accomplished in a safe and timely manner. This had been made necessary by changes in the function of the two former custodian laboratories. Neither the Statens Serum Institute nor the Central Veterinary Laboratory will any longer hold and distribute WHO International Reference Materials. The NIBSC and the Central Laboratory of the Netherlands Red Cross Blood Transfusion Service, Amsterdam are WHO International Laboratories for Biological Standards.

It was noted that the Center for Biologics Evaluation and Research (CBER), Food and Drug Administration, USA, has been established as a new WHO Collaborating Centre for Biological Standardization. The ECBS also endorsed several new projects including new international reference materials for blood group reagents, quality control of virus markers (HBsAg, anti-HCV and anti-HIV) in blood screening, and prion diagnostic tests.

The Committee also considered scientific issues that potentially affect the use of biological medi-

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**Table 1**

| International biological standards and reference reagents established by the 49th WHO Expert Committee on Biological Standardization |
| --- | --- |
| **Antibodies** | Second International Standard  
anti-hepatitis A immunoglobulin, human  
Clostridium perfringens beta antitoxin, equine  
**Antigens** | Second International Reference Preparation  
pertussis vaccine  
**Blood products** | Third International Standard  
factor VII, concentrate  
factor VIII, concentrate  
factor VIII and von Willebrand factor, plasma  
heamoglobincyanide  
heparin, unfractionated  
plasmin  
**Cytokines/endocrinological substance** |  
activin A, human, recombinant  
sex-hormone binding globulin  
**DISCONTINUATIONS** |  
**Antibiotics**  
demeclocycline  
doxycycline  
ygromycin B  
minocycline  
oxetacycline  
tetracycline  
**Antibodies** | First International Standard  
histoplasmin antiserum, rabbit, for H and M immunodiffusion test  
Mycoplasma pneumoniae antiserum, equine  
parainfluenza virus antiserum, equine  
**Miscellaneous** | First International Reference Preparation  
histoplasmin for H and M immunodiffusion test  
hyaluronidase | First Reference Reagent  
First International Standard

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Laboratory in Weybridge to the National Institute for Biological Standards and Control (NIBSC) had been accomplished in a safe and timely manner. This had been made necessary by changes in the function of the two former custodian laboratories. Neither the Statens Serum Institute nor the Central Veterinary Laboratory will any longer hold and distribute WHO International Reference Materials. The NIBSC and the Central Laboratory of the Netherlands Red Cross Blood Transfusion Service, Amsterdam are WHO International Laboratories for Biological Standards.

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The Committee also considered scientific issues that potentially affect the use of biological medi-
TABLE 2

WHO Requirements and International Reference Materials proposed for discontinuation at the next meeting of the WHO Expert Committee on Biological Standardization

Requirements for Cholera Vaccine

Requirements for Smallpox Vaccine

Antibiotics
The First International Reference Preparation for candicidin (1978)
The First International Reference Preparation for nisin (1969)
The First International Reference Preparation for rolitetracycline (1968)

Antibodies
The First International Reference Reagent for subtype specific antisera to hepatitis B surface antigens (1980); anti-HBs/ay(goose), anti-HBs/ad(goose), anti-HBs/ay(guinea pig), anti-HBs/ad(guinea pig), anti-HBs/ar(rabbit)
The First International Standard fluorescein isothiocyanate (FITC)-conjugated sheep anti-human IgG (1976)
The First International Standard FITC-conjugated sheep anti-human IgM (1977)

Blood Products

Endocrinological Substances
The First International Reference Preparation for desmopressin (1980)
The First International Reference Preparation for gonadorelin (1980)
The First International Reference Preparation for parathyroid hormone, bovine, for bioassay (1974)

Comments on proposals should be received before 30 September 1999.
Dr E. Griffiths, Quality Assurance and Safety of Biologicals, World Health Organization, 1211 Geneva 27 Switzerland Fax 41 22 791 4210

Drugs and Vaccines including an update on the presence of low levels of reverse transcriptase in vaccines derived from chicken cells (7,8). The ECBS endorsed the proposed establishment of a Task Force to coordinate collaborative research on characterization, quality control and safety assessment of all cell substrates intended for vaccine production. The Committee emphasized that a valuable activity of WHO was to provide an international forum for discussion of important scientific issues that had potential to affect the use of biological medicines.

References


Pertussis vaccines:

WHO position

Pertussis (whooping cough) is a bacterial disease of the respiratory tract caused by Bordetella pertussis. Worldwide, 90% of the 20–40 million annual cases occur in developing countries, with 200 000 fatalities. Before the worldwide introduction of pertussis vaccine into routine childhood vaccination programmes, pertussis was of considerable public health concern due to its highly contagious nature.

Concern about safety of the whole-cell pertussis (wP) vaccine has made routine pertussis vaccination of infants quite controversial in some countries and has led to the development of a new generation of pertussis vaccines based on selected bacterial components rather than on inactivated whole cells. There are major differences in the content, mode of preparation and efficacy of whole-cell pertussis (wP) and acellular pertussis (aP) vaccines.

However, comprehensive clinical trials have demonstrated that the most efficacious vaccines of either category will protect more than 80% of the recipients from clinical disease. Provided that high and sustained vaccination coverage is achieved, such vaccines will eliminate pertussis as a public health problem. At the same time, recent experience illustrates the importance of ensuring documented high quality of wP vaccines used in national immunization programmes.

No causal link has been identified between wP and aP vaccination and permanent brain damage or death. In terms of redness and swelling at the site of injection, fever, agitation, prolonged crying, febrile seizures and hypotonic-hyporesponsive episodes, aP vaccines show some improvement compared with wP vaccines. Better information on the frequency (if any) of rare, serious reactions will be obtained with widespread aP use and postmarketing surveillance studies.

There is no indication of clinically significant immunological interference between aP and other vaccines simultaneously administered at different sites. However, the reduced immunogenicity of Haemophilus influenzae type b vaccine when combined with some aP vaccines is of concern and needs further elucidation. It is recommended that HIV-infected infants should receive the vaccine.

Regulatory Matters

Losartan and irbesartan: similar in advantage to ACE inhibitors

Australia — The Adverse Drug Reaction Advisory Committee (ADRAC) has reviewed reports associated with the angiotensin II receptor antagonists losartan and irbesartan since their introduction in 1997 for the treatment of hypertension. By November 1998, 230 reports had been received for losartan and 133 reports for irbesartan. Skin reactions such as rash or pruritus, and neuropsychiatric disturbances such as insomnia, depression, confusion, nightmares and agitation, were most common. There were also 37 reports of cough with similar clinical characteristics as those seen with use of angiotensin converting enzyme (ACE) inhibitors. Likewise, angioedema with swelling of the neck, face and tongue were reported as well as hepatic dysfunction and hyperglycaemia.

The findings strongly suggest that patients having experienced these reactions while using ACE inhibitors may not benefit from changing medication to the recently introduced angiotensin II receptor antagonists.


Variations in troglitazone assessments

Japan and United Kingdom — The regulatory status of the diabetes drug, troglitazone (Rezulin®), has been reviewed in previous issues of this journal (1).

Troglitazone continues to be marketed in Japan as well as in 12 other countries (2). In the United Kingdom, it was voluntarily suspended by the company in December 1997 after only two months on the market, as a result of reports of serious hepatic reactions. A licence variation application with new prescribing criteria and advice on monitoring of liver function tests was subsequently submitted to the Medicines Control Agency but was rejected because the drug was not considered to have a favourable risk benefit profile (3).

United States of America — The Food and Drug Administration has estimated that the risk of acute liver failure may be as high as 1 in 758 patients taking troglitazone, and that 1 in 1800 patients may develop acute liver failure when taking the drug for six months. As a result of advice from the Advisory Committee on Endocrinologic and Metabolic Drugs, the FDA has considered four options in dealing with the situation: continue to monitor closely the number of cases of liver failure; shorten the time interval for monitoring of liver enzymes; limit use to patients with normal liver function tests; or eliminate one or more indications, such as monotherapy (4).

The following changes reflect the FDA's subsequent decision concerning the labelling and recommended use of troglitazone:

• Troglitazone is no longer indicated for use as initial single agent therapy.
• Transaminase levels should be tested before treatment and at monthly intervals thereafter.
• Each prescription of troglitazone will be accompanied by an information data sheet to be provided to the patient.
• Troglitazone is indicated for use in combination with a sulfonylurea and metformin in diabetes patients who are not adequately controlled with these two drugs alone. (5)

The case of troglitazone has demonstrated that, although considerable progress has been made in the harmonization of regulatory requirements for ICH (International Conference on Harmonization) countries — practical interpretation still differs when evaluated on a case by case basis.

References

2. Pharma Japan, 164: 3, 1999
Zolpidem and zopiclone: dependence

Germany — The Medicines Commission has issued a warning on the dependence potential of the short-acting benzodiazepine agonist hypnotics zolpidem and zopiclone in patients with a history of dependence to benzodiazepines.

The Medicines Commission and the Federal Institute for Drugs and Medical Devices have together received reports of 572 suspected adverse reactions. These included 28 cases of dependence, 16 of withdrawal symptoms and 9 cases of abuse. Some 41 million defined daily doses (DDDs) of zolpidem have been prescribed annually.

In addition to the German reports, WHO’s International Drug Monitoring Programme in Uppsala has received reports of 13 cases of abuse, 71 cases of dependence and 36 cases of withdrawal syndrome associated with zolpidem. Zopiclone has been associated with 6 reports of abuse, 13 of drug dependence and 9 cases of withdrawal syndrome. Some 22 million defined daily doses (DDDs) of zopiclone were prescribed in 1997 (1). As previously reported in this journal, caution should be exercised when prescribing hypnotics (2).

References
1. Data presented at the Ninth International Conference of Drug Regulatory Authorities (ICDRA), Berlin, April 1999.

Etanercept and sepsis

United States of America — The Food and Drug Administration has advised physicians of reports of serious life-threatening infections, including sepsis, in patients using etanercept. Many of the cases occurred shortly after initiation of treatment although clinical studies did not show an increase in serious infections in patients.

Etanercept is a new genetically-engineered protein first approved in November 1998 for the treatment of moderate to severe rheumatoid arthritis not responding to other treatment. Etanercept inhibits the action of tumour necrosis factor, a component of the body’s natural defence against serious infection.

Because of the new reports, the warning related to sepsis has been extended to include patients with active, chronic or localized infection. It is recommended that patients who develop a new infection while being treated should be monitored closely. Physicians should be cautious in prescribing etanercept to patients with a history of recurring infections, or underlying conditions such as advanced, poorly-controlled diabetes.

The Food and Drug Administration has asked the manufacturer to perform additional studies to assess the risk of serious infection related to etanercept.


Clozapine and gastrointestinal obstruction

United Kingdom — The Medicines Control Agency has received 20 spontaneous adverse reaction reports describing gastrointestinal obstruction associated with clozapine, an antipsychotic used to treat resistant schizophrenia. Three of the reported cases were fatal.

The reaction is thought to be due to the anticholinergic properties of clozapine, in particular when used in conjunction with other medications with anticholinergic effects such as tricyclic antidepressants, antiparkinsonian agents and other antipsychotics. Patients with a history of colonic disease or previous bowel surgery may have a higher risk of this reaction.


Orlistat for obesity

United States of America — The Food and Drug Administration has approved orlistat, a new drug for the treatment of obesity. This is the first in a new class of nonsystemically-acting anti-obesity drugs known as lipase inhibitors. Orlistat acts in the gastrointestinal tract by breaking down dietary fats into smaller molecules that can be absorbed by the body. In this way, absorption of fat is decreased.

During treatment, patients should be on a nutritionally balanced, reduced calorie diet that contains not more than 30% of calories in fat. Orlistat is indicated for patients with a body mass index of 30 or more. Because orlistat reduces the absorption of some fat-soluble vitamins and beta carotene, pa-
Patients should take a supplement that contains fat-soluble vitamins and beta carotene.


**Trofloxacin and alatrofloxacin: CPMP recommends suspension**

*European Union* — Reports of serious hepatic events concerning the recently-approved fluoroquinolone antibiotics, trovafloxacin (Trovan®, Turvel®) and the intravenous formulation, alatrofloxacin (Trovan IV®, Turvel IV®), have led to the suspension of the marketing authorization in member countries of the European Union.

Since February 1998, 152 documented cases of serious hepatic events have been reported, including 9 cases in which patients died or required a liver transplant. A review shows that in 35% of cases the events were accompanied by a hypersensitivity reaction and occurred between 1 and 60 days after initiation of treatment, suggesting that onset and severity of events are unpredictable (1).

The Committee for Proprietary Medicinal Products (CPMP) is of the opinion that Trovan®, Turvel®, Trovan IV® and Turvel IV® can no longer be safely administered in normal clinical usage, and has recommended that the marketing authorizations for trovafloxacin and alatrofloxacin be suspended. Existing supplies are to be withdrawn (2).

Patients are advised to contact their physician immediately, but should not stop taking the product until their treatment regimen has been reviewed.

Physicians are requested not to prescribe trovafloxacin and to review treatment of patients currently taking alatrofloxacin with a view to switching to alternative antibiotics or discontinuing treatment.

Reference:


**Trofloxacin and alatrofloxacin: FDA reports reservations in use**

*United States of America* — Following reports of rare but serious liver injuries leading to cases where patients died or required a liver transplant, the Food and Drug Administration has issued a health advisory to physicians concerning use of the antibiotics, trovafloxacin and alatrofloxacin.

Physicians are informed that trovafloxacin and alatrofloxacin should be reserved for use only in patients meeting the following criteria:

- Patients who have at least one of several specified infections such as nosocomial pneumonia, or complication intra-abdominal infections which are serious or life- or limb-threatening;
- Patients who begin their therapy in inpatient health care facilities;
- Patients for whom the physician believes that, even given the new safety information, the benefit of the product outweighs the potential risks.

Therapy should, in general, not continue beyond 14 days and should be discontinued if the patient experiences any clinical signs of liver dysfunction.

The FDA is taking this action to reduce the potential risk from this product while preserving the clinical option of an effective broad-spectrum antibiotic for serious or life-threatening infections. Revised labelling will be approved shortly.


**Control of misoprostol**

*Brazil* — Following a report in this journal concerning abortifacients on free sale in Brazil (1) the Secretariat of Public Health has provided the following clarification and has informed us that marketing of an illegal abortion kit containing misoprostol and methotrexate has not been reported to the authorities in Brazil.

In 1985, the Brazilian Government approved and registered the drug Cytotec® containing misoprostol as the active ingredient. The product was indicated for the treatment and prevention of gastric and duodenal ulcers and a warning stated that it
should not be used in pregnant women, since it could cause abortion or adverse effects on the fetus.

In 1991, the Government adopted restrictive measures with the objective of prohibiting misuse. Sale was limited to prescription-only through pharmacies.

In 1998, the following restrictive measures were decided:

- Medicinal products containing misoprostol can only be used in authorized hospitals.
- Distribution of free samples of medicines containing misoprostol is prohibited.

Reference:

Paracetamol: further warning

Sweden — The Medical Products Agency has strengthened warnings on the labelling, package inserts and product information of paracetamol preparations in order to avoid severe adverse reactions, including liver damage.

The product information must now indicate that higher than recommended doses carry a risk of severe liver damage. The product should not be used without a medical prescription if the user has alcohol problems or liver disorders, or if taking concomitant medications which also contain paracetamol.


Metamizole sodium withdrawn

Yemen — The Supreme Board of Drugs and Medical Appliances has withdrawn all formulations of metamizole sodium because of the potential to cause anaphylactic shock and agranulocytosis.


Ginkgo biloba suspended

Germany — The Federal Institute for Drugs and Medical Devices has extended the suspension of the marketing authorization for a dry extract of Ginkgo biloba for parenteral infusion because of reports of anaphylactic reactions including shock, fever, leucocytosis and cardiac arrhythmia, which in some cases were life-threatening.


Home test for hepatitis C

United States of America — The Food and Drug Administration has approved the first over-the-counter blood collection kit for testing for antibodies to hepatitis C virus (HCV), the most common blood-borne infection and a major cause of liver damage in the USA. It is spread through contact with infected blood and is responsible for 8000–10 000 deaths annually.

The kit does not require a prescription and can be mailed to a designated laboratory for analysis. Results are available anonymously by telephone. As part of the test, the manufacturer provides a telemedicine service which offers education and counselling about HCV and, if desired, referral to a physician.


Urokinase: possible transmission of infectious agents

United States of America — The Center for Biologics Evaluation and Research has issued a warning letter to all health care providers concerning urokinase (Abbokinase®), a treatment for pulmonary embolism, coronary artery thrombosis and intravenous catheter clearance. This recommends that Abbokinase® be reserved only for those situations where a physician has considered alternative treatment and has determined that the use of Abbokinase is critical to the care of a specific patient in a specific situation.

This action was taken subsequent to inspections of Abbott Laboratories and its supplier of human
neonatal kidney cells. The kidney cells used in the manufacture of this product were harvested post-mortem from human neonates from a population at high risk for a variety of infectious diseases, including tropical diseases. Although some efforts were made by the supplier to screen and test mothers, neonate donors and kidney cells, these measures were not consistently or reliably performed.

Prior to use in the manufacture of Abbokinase®, the human kidney cells were harvested, stored and handled in a manner which may have permitted contamination with infectious agents. Nor has the viral inactivation process used on currently available lots of the product been fully validated for viral inactivation.


**Astemizole voluntarily withdrawn**

United States of America — The Food and Drug Administration has announced that the manufacturer of the antihistamine, astemizole (Hismanal®), has decided to voluntarily withdraw the drug from the market given the overall risk benefit profile of the drug.


**Polygeline: hypotension**

Germany — In collaboration with the manufacturer, The Federal Institute for Drugs and Medical Devices has issued a notification for a batch recall of the plasma expander, polygeline, after an increased number of reports of hypotension were received.

Some of these reports described a rapid fall in blood pressure after administration of polygeline but a definitive relationship has not been established. The manufacturer has initiated a precautionary recall worldwide until the issue is clarified.

Reference: Rapid Alert from the Federal Institute for Drugs and Medical Devices, Berlin, 26 February 1999.

**Northern hemisphere influenza vaccine 1999–2000**

The composition of the vaccine for 1999–2000 (northern hemisphere influenza season) has been published and communicated to vaccine manufacturers by WHO. The vaccine will contain the following three components:

- An A/Sydney/5/97 (H3N2)-like virus
- An A/Beijing/262/95 (H1N1)-like virus
- A B/Beijing/184/93-like virus (the most widely-used vaccine is B/Harbin/7/94) OR A B/Shangdong/7/97-like virus

Decisions on the most appropriate B component should be made by national control authorities on the basis of local epidemiological data.

These three strains were chosen because influenza A(H3N2), A(H1N1) and influenza B viruses continued to circulate widely during the 1998–1999 influenza season.

The specific vaccine viruses used in each country should be approved by the national control authorities. National public health authorities are responsible for recommendations regarding the use of vaccines.
# ATC/DDD Classification (Final)

The following classifications were agreed at a meeting of the WHO International Drug Utilization Working Group which took place on 12–14 October 1998. They came into force on **15 April 1999**. All requests for classification should be forwarded to the WHO Collaborating Centre for Drug Statistics Methodology, P.O. Box 100, Veivet, 0518, Oslo, Norway (telephone: 00 47 22 16 9811, fax: 00 47 22 16 9818, e-mail: whocc@nmd.no). The inclusion of a substance in the lists does not imply any recommendation of use in medicine or pharmacy.

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<td>V09AB03</td>
<td></td>
</tr>
<tr>
<td>lansoprazole, amoxicillin and metronidazole</td>
<td>A02BD03</td>
<td></td>
</tr>
<tr>
<td>lansoprazole, tetracycline and metronidazole</td>
<td>A02BD02</td>
<td></td>
</tr>
<tr>
<td>levacetylmethadol</td>
<td>N02AC06</td>
<td></td>
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<tr>
<td>loperamide, combinations</td>
<td>A07DA53</td>
<td></td>
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<tr>
<td>mannitol</td>
<td>A06AD16</td>
<td></td>
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<tr>
<td>metoprolol, combination packages</td>
<td>C07AB52</td>
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<tr>
<td>nonacog alfa</td>
<td>B02BD09</td>
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### New ATC 5th level codes (continued)

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<thead>
<tr>
<th>INN/common name</th>
<th>ATC code</th>
</tr>
</thead>
<tbody>
<tr>
<td>perindopril and diuretics</td>
<td>C09BA04</td>
</tr>
<tr>
<td>potassium permanganate</td>
<td>D08AX06</td>
</tr>
<tr>
<td>pramocaine</td>
<td>D04AB07</td>
</tr>
<tr>
<td>propentofylline</td>
<td>N06BC02</td>
</tr>
<tr>
<td>raloxifene</td>
<td>G03XC01</td>
</tr>
<tr>
<td>rizatriptan</td>
<td>N02CC04</td>
</tr>
<tr>
<td>sertaconazole</td>
<td>D01AC14</td>
</tr>
<tr>
<td>sevelamer</td>
<td>V03AE02</td>
</tr>
<tr>
<td>sodium hypochlorite</td>
<td>D08AX07</td>
</tr>
<tr>
<td>technetium (99mTc) depreotide</td>
<td>V09IA05</td>
</tr>
<tr>
<td>telmisartan</td>
<td>C09CA07</td>
</tr>
<tr>
<td>temocapril</td>
<td>C09AA14</td>
</tr>
<tr>
<td>tilactase</td>
<td>A09AA04</td>
</tr>
<tr>
<td>tirofiban</td>
<td>B01AC17</td>
</tr>
<tr>
<td>trovafloxacin</td>
<td>J01MA13</td>
</tr>
<tr>
<td>trypsin, combinations</td>
<td>M09AB52</td>
</tr>
<tr>
<td>valsartan and diuretics</td>
<td>C09DA03</td>
</tr>
<tr>
<td>voglibose</td>
<td>A10BF03</td>
</tr>
<tr>
<td>ziprasidone</td>
<td>N05AE04</td>
</tr>
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</table>

### ATC code changes

**Previous:** Ferric ammonium citrate B03AB10*

**New:** Ferric ammonium citrate V08CA07

*Previously temporary ATC code

### Change of level name

**Previous:** COX-2 specific inhibitors**

**New:** Coxibs M01AH

**Previous:** Drugs for treatment of hyperkalemia

**New:** Drugs for treatment of hyperkalemia and hyperphosphatemia V03AE

**Previous:** Imidazole derivatives

**New:** Imidazole and triazole derivatives D01AC

**Previously temporary ATC 4th level name

### New DDDs:

<table>
<thead>
<tr>
<th>INN/common name</th>
<th>DDD</th>
<th>Unit</th>
<th>Route of administration</th>
<th>ATC code</th>
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</thead>
<tbody>
<tr>
<td>balsalazide</td>
<td>6.75</td>
<td>g</td>
<td>O</td>
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<tr>
<td>clopidogrel</td>
<td>75</td>
<td>mg</td>
<td>O</td>
<td>B01AC04</td>
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<tr>
<td>dexketoprofen</td>
<td>75</td>
<td>mg</td>
<td>O</td>
<td>M01AE17</td>
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<tr>
<td>dihydroergotamine</td>
<td>1</td>
<td>mg</td>
<td>N</td>
<td>N02CA01</td>
</tr>
<tr>
<td>dolasetron</td>
<td>0.1</td>
<td>g</td>
<td>P</td>
<td>A04AA04</td>
</tr>
<tr>
<td>INN/common name</td>
<td>DDD</td>
<td>Unit</td>
<td>Route of administration</td>
<td>ATC code</td>
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<td>------------------</td>
<td>------</td>
<td>--------------</td>
<td>--------------------------</td>
<td>----------</td>
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<tr>
<td>fenofibrate</td>
<td>0.2</td>
<td>g (micronized)</td>
<td>O</td>
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<td>finasteride</td>
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<td>O</td>
<td>D11AX10</td>
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<td>follitropin beta</td>
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<td>P</td>
<td>G03GA06</td>
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<td>fosphenytoin</td>
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<td>g</td>
<td>P</td>
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<tr>
<td>mometasone</td>
<td>0.2</td>
<td>mg</td>
<td>N</td>
<td>R01AD09</td>
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<tr>
<td>ondansetron</td>
<td>16</td>
<td>mg</td>
<td>R</td>
<td>A04AA01</td>
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<td>orlistat</td>
<td>0.36</td>
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<td>O</td>
<td>A08AB01</td>
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<tr>
<td>pantoprazole</td>
<td>40</td>
<td>mg</td>
<td>P</td>
<td>A02BC02</td>
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<tr>
<td>propiverine</td>
<td>30</td>
<td>mg</td>
<td>O</td>
<td>G04BD06</td>
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<tr>
<td>quetiapine</td>
<td>0.4</td>
<td>g</td>
<td>O</td>
<td>N05AH04</td>
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<td>raloxifene</td>
<td>60</td>
<td>mg</td>
<td>O</td>
<td>G03XC01</td>
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<td>riluzole</td>
<td>0.1</td>
<td>g</td>
<td>O</td>
<td>N07XX02</td>
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<td>rivastigmine</td>
<td>9</td>
<td>mg</td>
<td>N0DA03***</td>
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<tr>
<td>rizatriptan</td>
<td>10</td>
<td>mg</td>
<td>O</td>
<td>N02CC04</td>
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<tr>
<td>temocapril</td>
<td>10</td>
<td>mg</td>
<td>O</td>
<td>C09AA14</td>
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<tr>
<td>triamcinolone</td>
<td>0.22</td>
<td>mg</td>
<td>N</td>
<td>R01AD11</td>
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<tr>
<td>trovafloxacin</td>
<td>0.2</td>
<td>g</td>
<td>O,P</td>
<td>J01MA13</td>
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<tr>
<td>ziprasidone</td>
<td>80</td>
<td>mg</td>
<td>O</td>
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</table>

***New temporary ATC code

**Change of DDDs:**

dalteparin sodium | 2.5  | TU (antiXa)  | P  | B01AB04  |
danaparoid sodium | 1.5  | TU (antiXa)  | P  | B01AB09  |
dexibuprofen      | 0.8  | g            | O  | N01AE14  |
enoxaparin sodium | 2.0  | TU (antiXa)  | P  | B01AB05  |
fluticasone       | 0.2  | mg           | N  | R01AD08  |
nadroparin sodium | 2.85 | TU (antiXa)  | P  | B01AB06  |
parnaparin sodium | 3.2  | TU (antiXa)  | P  | B01AB07  |
reviparin sodium  | 1.43 | TU (antiXa)  | P  | B01AB08  |
tinzaparin sodium | 3.5  | TU (antiXa)  | P  | B01AB10  |
The following temporary classifications were agreed at a meeting of the WHO International Working Group for Drug Statistics Methodology which took place on 13 and 14 May 1999. Comments on or objections to the classification should be forwarded to the WHO Collaborating Centre for Drug Statistics Methodology, P.O. Box 100, Veivet, 0518, Oslo, Norway (telephone: 00 47 22 16 9811, fax: 00 47 22 16 9818, e-mail: whocc@nmd.no) before **15 September 1999**. If no objections are received before this date, the new ATC codes and DDDs will be considered final and be included in the January 2000 issue of the ATC index. The inclusion of a substance in the lists does not imply any recommendation of use in medicine or pharmacy.

### New ATC level codes (other than 5th levels):

<table>
<thead>
<tr>
<th>Cholinesterase inhibitors</th>
<th>N06DA</th>
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<tr>
<td>Anti-dementia drugs</td>
<td>N06D</td>
</tr>
<tr>
<td>Antigonadotropin-releasing hormones</td>
<td>H01CC</td>
</tr>
<tr>
<td>Monoclonal antibodies</td>
<td>L01XC</td>
</tr>
<tr>
<td>Neuraminidase inhibitors</td>
<td>J05AH</td>
</tr>
<tr>
<td>Other anti-dementia drugs</td>
<td>N06DX</td>
</tr>
<tr>
<td>other specific antirheumatic agents</td>
<td>M01CX</td>
</tr>
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### New ATC 5th level codes:

<table>
<thead>
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<th>INN/common name</th>
<th>ATC code</th>
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<tr>
<td>alitretinoin</td>
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<td>amprenavir</td>
<td>J05AE05</td>
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<tr>
<td>androstanolone</td>
<td>G03BB02</td>
</tr>
<tr>
<td>betamethasone and antiinfectives</td>
<td>S03CA06</td>
</tr>
<tr>
<td>brinzolamide</td>
<td>S01EC04</td>
</tr>
<tr>
<td>bufexamac</td>
<td>M01AB17</td>
</tr>
<tr>
<td>cetrimonium bromide</td>
<td>R02AA17</td>
</tr>
<tr>
<td>cetreorelix</td>
<td>H01CC02</td>
</tr>
<tr>
<td>chloramphenicol</td>
<td>S03AA08</td>
</tr>
<tr>
<td>cinnarizine, combinations</td>
<td>N07CA52</td>
</tr>
<tr>
<td>ciprofloxacin</td>
<td>S03AA07</td>
</tr>
<tr>
<td>diphtheria, hepatitis B, tetanus</td>
<td>J07CA07</td>
</tr>
<tr>
<td>etanercept</td>
<td>L04AA11</td>
</tr>
<tr>
<td>flutrimazole</td>
<td>D01AC16</td>
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<td>framycetin</td>
<td>R01AX08</td>
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<tr>
<td>gadobenic acid</td>
<td>V08CA07</td>
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<td>galantamine</td>
<td>N06DA04</td>
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<tr>
<td>ganciclovir</td>
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<td>ganirelix</td>
<td>H01CC01</td>
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<tr>
<td>glyceryl trinitrate</td>
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<tr>
<td>hexamidine</td>
<td>R02AA18</td>
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<tr>
<td>infliximab</td>
<td>L04AA12</td>
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<tr>
<td>irbesartan and diuretics</td>
<td>C09DA04</td>
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<td>isosorbide dinitrate</td>
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## ATC level

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<td>R05DB27</td>
<td>levodropropizine</td>
</tr>
<tr>
<td>N06DX01</td>
<td>memantine</td>
</tr>
<tr>
<td>D01AC52</td>
<td>miconazole, combinations</td>
</tr>
<tr>
<td>J01MA14</td>
<td>moxifloxacin</td>
</tr>
<tr>
<td>C09BA13</td>
<td>moexipril and diuretics</td>
</tr>
<tr>
<td>G03FA13</td>
<td>norgestimate and estrogen</td>
</tr>
<tr>
<td>S01GX09</td>
<td>olopatadine</td>
</tr>
<tr>
<td>J05AH02</td>
<td>oseltamivir</td>
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<tr>
<td>M01AX24</td>
<td>oxaceprol</td>
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<tr>
<td>A02BD04</td>
<td>pantoprazole, amoxicillin and clarithromycin</td>
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<tr>
<td>P03AC54</td>
<td>permethrin, combinations</td>
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<tr>
<td>A10BG03</td>
<td>pioglitazone</td>
</tr>
<tr>
<td>C10AX08</td>
<td>policosanol</td>
</tr>
<tr>
<td>R01AD52</td>
<td>prednisolone, combinations</td>
</tr>
<tr>
<td>A02BC04</td>
<td>rabeprazole</td>
</tr>
<tr>
<td>A10BX02</td>
<td>repaglinide</td>
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<tr>
<td>A10BG02</td>
<td>rosiglitazone</td>
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<tr>
<td>L04AA10</td>
<td>sirolimus</td>
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<tr>
<td>V03AF06</td>
<td>sodium folinate</td>
</tr>
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<td>A06AD17</td>
<td>sodium phosphate</td>
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<tr>
<td>V09IA06</td>
<td>technetium ((^{99}\text{Tc})) arcitumomab</td>
</tr>
<tr>
<td>J01BA52</td>
<td>thiamphenicol, combinations</td>
</tr>
<tr>
<td>A03DA07</td>
<td>tiemonium iodide and analgesics</td>
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<tr>
<td>L01XC03</td>
<td>trastuzumab</td>
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<tr>
<td>R03BA06</td>
<td>triamcinolone</td>
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<td>C05CX01</td>
<td>tribenoside</td>
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<td>J05AH01</td>
<td>zanamivir</td>
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<td>C09AA15</td>
<td>zofenopril</td>
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</table>

### New ATC 5th level codes (continued)

- donepezil: N07AA05, N06DA02
- edrecolomab: L03AX06, L01XC01
- *Ginkgo biloba*: N06BX19, N06DX02
- rituximab: L01XX21, L01XC02
- rivastigmine: N07AA06, N06DA03
- tacrine: N07AA04, N06DA01

### ATC code changes

### Change of level name:

**Previous:**
Progestogens and estrogens, fixed combinations

**New:**
Progestogens and estrogens, combinations G03FA
### New DDDs

<table>
<thead>
<tr>
<th>INN/common name</th>
<th>DDD</th>
<th>Unit</th>
<th>Route of administration</th>
<th>ATC code</th>
</tr>
</thead>
<tbody>
<tr>
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<td>mg</td>
<td>urethral</td>
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<td>anchestim</td>
<td>1.4</td>
<td>mg</td>
<td>P</td>
<td>L03AA12</td>
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<tr>
<td>basilixim</td>
<td>40</td>
<td>mg</td>
<td>P (course dose)</td>
<td>L04AA09</td>
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<tr>
<td>BCG vaccine</td>
<td>1.8</td>
<td>mg</td>
<td>intra-vesicular</td>
<td>L03AX03</td>
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<tr>
<td>celecoxib</td>
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<td>g</td>
<td>O</td>
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</tr>
<tr>
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<td>g</td>
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<td>g</td>
<td>O</td>
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<td>U</td>
<td>P</td>
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<td>fosfomycin</td>
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<td>g</td>
<td>O</td>
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<td>immunocyanin</td>
<td>3</td>
<td>mg</td>
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<tr>
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<td>P</td>
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<td>U</td>
<td>P</td>
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<td>P</td>
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<td>U</td>
<td>P</td>
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<td>P</td>
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<td>P</td>
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<td>mg</td>
<td>O, P</td>
<td>L03AX01</td>
</tr>
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<td>lepirudin</td>
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<td>g</td>
<td>P</td>
<td>B01AX03</td>
</tr>
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<td>molgramostim</td>
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<td>P</td>
<td>L03AA03</td>
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<td>g</td>
<td>O</td>
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</tr>
<tr>
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<td>g</td>
<td>O</td>
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<td>O</td>
<td>J05AG01</td>
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<td>oprelvekin</td>
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<td>O</td>
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<td>pramipexole</td>
<td>1.8</td>
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<td>O</td>
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<tr>
<td>quinapril</td>
<td>15</td>
<td>mg</td>
<td>P</td>
<td>C09AA06</td>
</tr>
<tr>
<td>rabeprazole</td>
<td>20</td>
<td>mg</td>
<td>O</td>
<td>A02BC04*</td>
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<td>repaglinide</td>
<td>6</td>
<td>mg</td>
<td>O</td>
<td>A10BX02*</td>
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<td>P</td>
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<td>mg</td>
<td>O</td>
<td>G04BE03</td>
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<tr>
<td>sodium phosphate</td>
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<td>g</td>
<td>O</td>
<td>A06AD17*</td>
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<td>O</td>
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*Temporary ATC codes*
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<th>Route of administration</th>
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Anti-allergics and drugs used in anaphylaxis

Although there are three types of histamine receptors $H_1$, $H_2$ and $H_3$, it is the $H_1$ receptor antagonists which are generally referred to as antihistamines. They are responsible for inhibiting the wheal, pruritus, sneezing and mucous secretion responses that are characteristic of allergy. $H_1$ receptor antagonists thus relieve the symptoms of allergic reactions, such as urticaria, angioedema, allergic rhinitis, and allergic conjunctivitis. They are also used to treat drug allergies, food allergies and insect stings and some of the symptoms of anaphylaxis. Antihistamines also control the pruritus in skin disorders, such as eczema. However, they are ineffective in the treatment of acute asthmatic attacks.

Drowsiness and sedation are particular disadvantages of the early antihistamines and the patient should be warned against driving or operating any type of machinery. Other central nervous depressants, including alcohol, barbiturates, hypnotics, opioid analgesics, anxiolytic sedatives and neuroleptics may enhance the sedative effects of antihistamines. Since they interfere with skin tests for allergy, therapy should be stopped at least one week before conducting a skin test. Rashes and photosensitivity reactions, palpitations and arrhythmias have also been reported.

Chlorphenamine is considered the prototype for antihistamine $H_1$ antagonists. This class includes drugs with less sedative action than the traditional antihistamines or with different therapeutic potencies. In practice, all antihistamines are equally effective in relieving the symptoms of allergic reactions and differ mainly in the intensity of sedative and anticholinergic effects. Selection of drugs in this class should thus be based on the intended therapeutic uses, the adverse reaction profile and the cost.

Corticosteroids, such as dexamethasone, hydrocortisone, or prednisolone suppress or prevent almost all symptoms of inflammation associated with allergy. The route of administration should depend on the particular type of allergic condition. For example, in the case of a mild allergic skin reaction, the best therapy may be to apply a glucocorticoid ointment or cream. If the skin reaction does not respond to topical corticosteroid therapy, it may be necessary to give corticosteroids orally. Allergic diseases of limited duration and with mild reactions, such as urticaria or allergic rhinitis, usually require no treatment. If, on the other hand, symptoms become persistent, antihistamines constitute the mainstay of treatment.

Corticosteroids should be considered as supplements to primary therapy and used to reduce inflammation. Oral corticosteroids may be required for a few days in an acute attack of urticaria. Oral corticosteroids are also used to relieve severe exacerbations in chronic urticaria, but long-term use of oral corticosteroids should be avoided. Corticosteroids may be used topically to reduce inflammation in allergic rhinitis but should not be used orally or parenterally for this condition.

The adverse effects of corticosteroids include inhibition of growth in children, disturbances of the electrolyte balance leading to oedema and hypertension and to potassium loss, production of osteoporosis and spontaneous fractures, skin thinning, increased susceptibility to infection, mental disturbances and diabetes.
Allergic emergencies

Anaphylactic shock is a medical emergency that can result in cardiovascular collapse and death. It requires prompt treatment of possible laryngeal oedema, bronchospasm or hypotension. Atopic individuals are particularly susceptible. Insect bites and certain foods including eggs, fish, peanuts and nuts are also a risk for sensitized persons. Drugs particularly associated with anaphylaxis include blood products, vaccines, antibiotics (especially penicillins), iron injections, heparin and neuromuscular blocking agents. Acetylsalicylic acid and other nonsteroidal anti-inflammatory drugs (NSAIDs) may cause bronchoconstriction in leukotriene-sensitive patients. In the case of drug allergy, anaphylaxis is more likely to occur after parenteral administration. Resuscitation facilities should always be available if injection of a drug is associated with a certain risk.

First-line treatment includes administering epinephrine, keeping the airway open (assisted respiration may be necessary) and restoring blood pressure. Epinephrine should immediately be given by deep intramuscular or subcutaneous injection to produce vasoconstriction and bronchodilatation and injections should be repeated every ten minutes until blood pressure and pulse have stabilized. If there is complete cardiovascular shock, epinephrine must be given by slow intravenous injection.

Further treatment of anaphylaxis often includes intravenous corticosteroids such as hydrocortisone, intravenous antihistamines, such as chlorphenamine, and may include intravenous fluids, oxygen, an intravenous vasopressor agent, such as dopamine, intravenous aminophylline, and an injected or nebulized bronchodilator, such as salbutamol. Chlorphenamine is a useful adjunctive treatment given after epinephrine injection and continued for 24 to 48 hours to reduce the severity and duration of symptoms and to prevent relapse. An intravenous corticosteroid such as hydrocortisone has an onset of action that is delayed several hours, but should be given to help prevent later deterioration in severely affected patients.

**Steps in anaphylactic shock management**

1. **Epinephrine:**
   - 0.1 ml/10 kg (strength 1:1000, 1 mg/ml) by deep intramuscular injection; the dose can be repeated 10–30 minutes later.
   - If the patient is in shock:
     - *Adults*: 1–3 ml (strength 1:10 000, 0.1 mg/ml) by slow intravenous infusion.
     - *Children*: 0.1–0.5 ml (strength 1:10 000, 0.1 mg/ml) by slow intravenous infusion.

2. **Vital functions**: maintain an open airway; give oxygen by mask.

3. **Corticosteroids–hydrocortisone**
   - *Adult*: 250–500 mg intravenously
   - *Child*: 10 mg/kg intravenously.

4. **Intravenous fluids**: start infusion with sodium chloride (500–1000 ml during the first hour).

5. **If the patient has asthma-like symptoms**, give aminophylline: 5 mg/kg by slow intravenous injection.

6. **Antihistamine orally**.

**CHLORPHENAMINE**

*Tablet*: 4 mg (hydrogen maleate)
*Injection*: 10 mg (hydrogen maleate) in 1-ml ampoule

**Uses**: Symptomatic relief of allergy, hay fever, allergic rhinitis and conjunctivitis, urticaria, insect stings, pruritus of allergic origin and angioedema. Adjunct in the emergency treatment of anaphylactic shock or in the emergency treatment of severe angioedema.

**Dosage**

- **Adults**: 4 mg every 4–6 hours, maximum 24 mg daily.
- **Children**: 1–2 years: 1 mg twice daily. 2–5 years: 1 mg every 4–6 hours (maximum 6 mg daily). 6–12 years: 2 mg every 4–6 hours (maximum 12 mg daily).

**Emergencies**: by subcutaneous or intramuscular injection or slow intravenous injection

**Contraindications**: Patients with prostate enlargement since chlorphenamine may cause urinary retention. Patients with ileus or pyloric stenosis. Glaucoma. Children under one year.
Precautions: Use with caution in patients with epilepsy, hepatic disease and severe cardiovascular disorders. Ability to drive or operate machinery may be impaired.

Adverse effects: Drowsiness, hypotension, headache, palpitations, psychomotor impairment, urinary retention, dry mouth, blurred vision and gastrointestinal disturbances. Other adverse effects include rash and photosensitivity reactions, sweating and tremor. Injections may be irritant and may cause paradoxical central nervous system stimulation and hypotension.

Drug Interactions: Effects of alcohol and other central nervous system (CNS) depressants may be additive. Other drug interactions will appear in tabulated form in the appendix of the published edition of the WHO Model Formulary.

DEXAMETHASONE
Tablet: 0.5 mg, 4 mg
Injection: 4 mg dexamethasone phosphate (as disodium) in 1-ml ampoule
Uses: Adjunct in the emergency treatment of anaphylaxis. Short-term suppression of inflammation in allergic disorders.

Dosage:
Orally: usual range 0.5–10 mg daily.

By intramuscular injection or slow intravenous injection or infusion:
Adults: 2–5 mg/kg daily.
Children: 200–500 µg/kg daily.

Contraindications, precautions and adverse effects: Because rare instances of anaphylactoid reactions such as bronchospasm have occurred in patients receiving parenteral corticosteroid treatment, appropriate precautionary measures should be taken prior to administration, especially when the patient has a history of allergy to drugs.

EPINEPHRINE (ADRENALINE)
Injection: 1 mg (as hydrochloride or hydrogen tartrate) in 1-ml ampoule
Uses: Severe anaphylactic reaction or severe angioedema.

Dosage:
Caution: Different dilutions of epinephrine solution are used for different routes of administration. Use 1:1000 epinephrine solution for intramuscular or subcutaneous injection.

Anaphylaxis

<table>
<thead>
<tr>
<th>Age</th>
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</thead>
<tbody>
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</tr>
<tr>
<td>1 year</td>
<td>0.1 ml</td>
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<tr>
<td>2 years</td>
<td>0.2 ml</td>
</tr>
<tr>
<td>3–4 years</td>
<td>0.3 ml</td>
</tr>
<tr>
<td>5 years</td>
<td>0.4 ml</td>
</tr>
<tr>
<td>6–12 years</td>
<td>0.5 ml</td>
</tr>
<tr>
<td>Adult</td>
<td>0.5–1.0 ml</td>
</tr>
</tbody>
</table>

Repeat the dose every 10 minutes as necessary, according to blood pressure and pulse, until improvement occurs.

Use 1:10 000 epinephrine solution for slow intravenous injection.

This route should be reserved for severely ill patients when there is doubt about the adequacy of circulation and absorption from the intramuscular site.

Adults: 500 µg (0.5 mg), i.e., 5 ml of a dilute 1:10 000 epinephrine injection solution, given at an injection rate of 100 µg (1 ml)/minute stopping once a response is obtained.

Children: 10 µg/kg (0.1 ml/kg of a dilute 1:10 000 epinephrine injection solution) given over several minutes.

Contraindications: Hyperthyroidism, hypertension, diabetes mellitus, ischaemic heart disease, hypertension and closed angle glaucoma. Chronic bronchial asthma and substantial emphysema. Elderly patients.

Adverse effects: Tachycardia and arrhythmias, hypertension, tremor, anxiety, sweating, nausea, vomiting, weakness, dizziness and pulmonary oedema have all been reported. Headache is common.

Drug Interactions: These will appear in tabulated form in the appendix of the published edition of the WHO Model Formulary.
HYDROCORTISONE

Powder for injection: 100 mg (as sodium succinate) in vial

Uses: Adjunct in the emergency treatment of anaphylaxis.

Dosage:
Anaphylactic emergency/by slow intravenous injection:
Adult: 100–300 mg three to four times in 24 hours as required.
Children: < 1 year, 25 mg; 1–5 years, 50 mg; 6–12 years, 100 mg three to four times in 24 hours as required.

Contraindications, precautions and adverse effects: Because rare instances of anaphylactoid reactions such as bronchospasm have occurred in patients receiving parenteral corticosteroid therapy, appropriate precautionary measures should be taken prior to administration, especially when the patient has a history of allergy to drugs.

Drug interactions: These will appear in tabulated form in the appendix of the published edition of the WHO Model Formulary.

PREDNISOLONE

Tablet: 5 mg

Uses: Short-term suppression of inflammation in allergic disorders.

Dosage: Initial dose up to 10–20 mg daily. Severe allergy may require up to 60 mg daily. The maintenance dose is 2.5–15 mg daily. Higher doses may be necessary.

Contraindications: Known hypersensitivity to any corticosteroid. Active bacterial, viral or fungal infection. Unless the benefits outweigh the risks, systemic administration of corticosteroids is contraindicated in patients with peptic ulcer, osteoporosis, psychoses or severe psychoneuroses, congestive heart failure, hypertension, diabetes mellitus, epilepsy, glaucoma, ocular herpes simplex, chronic renal failure or uraemia.

Precautions: Children on corticosteroid therapy should be treated with immunoglobulin if they are exposed to a childhood viral infection to which they have no acquired immunity. They should not receive live-virus vaccines.

Adverse effects: Infections contracted during therapy can be fatal in the absence of effective treatment.

Drug interactions: These will appear in tabulated form in the appendix of the published edition of the WHO Model Formulary.
International Nonproprietary Names for Pharmaceutical Substances (INN)

Notice is hereby given that, in accordance with article 3 of the Procedure for the Selection of Recommended International Nonproprietary Names for Pharmaceutical Substances, the names given in the list on the following pages are under consideration by the World Health Organization as Proposed International Nonproprietary Names. The inclusion of a name in the lists of Proposed International Nonproprietary Names does not imply any recommendation of the use of the substance in medicine or pharmacy.

Lists of Proposed (1–73) and Recommended (1–35) International Nonproprietary Names can be found in Cumulative List No. 9, 1996. The statements indicating action and use are based largely on information supplied by the manufacturer. This information is merely meant to provide an indication of the potential use of new substances at the time they are accorded Proposed International Nonproprietary Names. WHO is not in a position either to uphold these statements or to comment on the efficacy of the action claimed. Because of their provisional nature, these descriptors will neither be revised nor included in the Cumulative Lists of INNs.

Dénominations communes internationales des Substances pharmaceutiques (DCI)

Il est notifié que, conformément aux dispositions de l'article 3 de la Procédure à suivre en vue du choix de Dénominations communes internationales recommandées pour les Substances pharmaceutiques les dénominations ci-dessous sont mises à l'étude par l'Organisation mondiale de la Santé en tant que dénominations communes internationales proposées. L'inclusion d'une dénomination dans les listes de DCI proposées n'implique aucune recommandation en vue de l'utilisation de la substance correspondante en médecine ou en pharmacie.

On trouvera d'autres listes de Dénominations communes internationales proposées (1–73) et recommandées (1–35) dans la Liste récapitulative No. 9, 1996. Les mentions indiquant les propriétés et les indications des substances sont fondées sur les renseignements communiqués par le fabricant. Elles ne visent qu'à donner une idée de l'utilisation potentielle des nouvelles substances au moment où elles sont l'objet de propositions de DCI. L'OMS n'est pas en mesure de confirmer ces déclarations ni de faire de commentaires sur l'efficacité du mode d'action ainsi décrit. En raison de leur caractère provisoire, ces informations ne figureront pas dans les listes récapitulatives de DCI.

Denominaciones Comunes Internacionales para las Sustancias Farmacéuticas (DCI)

De conformidad con lo que dispone el párrafo 3 del “Procedimiento de Selección de Denominaciones Comunes Internacionales Recomendadas para las Sustancias Farmacéuticas”, se comunica por el presente anuncio que las denominaciones detalladas en las páginas siguientes están sometidas a estudio por la Organización Mundial de La Salud como Denominaciones Comunes Internacionales Propuestas. La inclusión de una denominación en las listas de las DCI Propuestas no supone recomendación alguna en favor del empleo de la sustancia respectiva en medicina o en farmacia.

Las listas de Denominaciones Comunes Internacionales Propuestas (1–73) y Recomendadas (1–35) se encuentran reunidas en Cumulative List No. 9, 1996. Las indicaciones sobre acción y uso que aparecen se basan principalmente en la información facilitada por los fabricantes. Esta información únicamente tiene por objeto dar una idea de las posibilidades de aplicación de las nuevas sustancias a las que se asigna una DCI Propuesta. La OMS no está facultada para respaldar esas indicaciones ni para formular comentarios sobre la eficacia de la acción que se atribuye al producto. Debido a su carácter provisional, esos datos descriptivos no deben incluirse en las listas acumulativas de DCI.
Proposed International Nonproprietary Names: List 81

Comments on, or formal objections to, the proposed names may be forwarded by any person to the INN Programme of the World Health Organization within four months of the date of their publication in WHO Drug Information, i.e., for List 81 Proposed INN not later than 15 December 1999.

Dénominations communes internationales proposées: Liste 81

Des observations ou des objections formelles à l’égard des dénominations proposées peuvent être adressées par toute personne au Programme des Dénominations communes internationales de l’Organisation mondiale de la Santé dans un délai de quatre mois à compter de la date de leur publication dans WHO Drug Information, c’est à dire pour la Liste 81 de DCI Proposées le 15 décembre 1999 au plus tard.

Denominaciones Comunes Internacionales Propuestas: Lista 81

Cualquier persona puede dirigir observaciones u objeciones respecto de las denominaciones propuestas, al Programa de Denominaciones Comunes Internacionales de la Organización Mundial de la Salud, en un plazo de cuatro meses, contados desde la fecha de su publicación en WHO Drug Information, es decir, para la Lista 81 de DCI Propuestas el 15 de diciembre de 1999 como fecha limite.

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<td>Nombre químico o descripción: Acción y uso: Fórmula empírica</td>
<td>Número de registro del CAS: Fórmula desarrollada</td>
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<table>
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<th>abetimus</th>
<th>abétimus</th>
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**acidum caloxeticum**

caloxyetic acid

trihydrogen \([N-(2S)-2-[bis(carboxymethyl)amino]-3-(p-ethoxyphenyl)propyl]-N-[2-[bis(carboxymethyl)amino]ethyl]glycinato(5-)]calciate(3-)

*pharmaceutical aid*

**acide caloxétique**

trihydrogénio\([N-(2S)-2-[bis(carboxyméthyl)amino]-3-(4-éthoxyphényl)propyl]-N-[2-[bis(carboxyméthyl)amino]éthyl]glycinato(5-)]calciate(3-)

*auxiliaire pharmaceutique*

**ácido caloxético**

\([N-(2S)-2-[bis(carboximetil)amino]-3-(p-etoxifenil)propil]-N-[2-[bis(carboximetil)amino]etil]glicinato(5-)]calciato(3-) de trihidrógénio

*excipiente*

\(C_{23}H_{31}CaN_3O_{11}\) 135306-78-4
anidulafunginum

anidulafungin

(4R,5R)-4,5-dihydroxy-N²-[4''-(pentyloxy)-p-terphenyl-4-yl]carbonyl-L-ornithyl-L-threonyl-trans-4-hydroxy-L-prolyl-(S)-4-hydroxy-4-(p-hydroxyphenyl)-L-threonyl-L-threonyl-(3S,4S)-3-hydroxy-4-methyl-L-proline cyclic (6→1)-peptide

antifungal

anidulafungine

N²-[2R,6S,9S,11R,12R,14aS,15S,16S,20S,23S,25aS]-23-[(1S,2S)-1,2-dihydroxy-2-(4-hydroxyphényl)éthyl]-2,11,12,15-tétrahydroxy-6,20-bis[(1R)-1-hydroxyéthyl]-16-méthyl-5,8,14,19,22,25-hexaoxotétracosahydro-1H-dipyrrolo[2,1-c:2',1'-l][1,4,7,10,13,16]hexaazacyclohénicosén-9-yl]-4''-(pentiloxi)-1,1':4',1''-terphényle-4-carboxamide

antifongique

anidulafungina

péptido (6→1)-cíclico (4R,5R)-4,5-dihidroxy-N²-[4''-(pentiloxi)-p-terfenil-4-il]carbonil]-L-ornitil-L-treonil-trans-4-hidroxi-L-profil-(S)-4-hidroxi-4-(p-hidroxifenil)-L-treonil-L-treonil-(3S,4S)-3-hidroxi-4-metil-L-proлина

antifúngico

C₅₈H₇₃N₇O₁₇  166663-25-8

artenimolum

artenimol

(3R,5aS,6R,8aS,9R,10S,12R,12aR)-decahydro-3,6,9-trimethyl-3,12-époxy-12H-pyrano[4,3-j]-1,2-benzodioxépin-10-ol

antimalarial

arténimol

(3R,5aS,6R,8aS,9R,10S,12R,12aR)-3,6,9-triméthyldecahydro-3,12-époxyprano[4,3-j]-1,2-benzodioxépin-10-ol

antipaludique

arténimol

(3R,5aS,6R,8aS,9R,10S,12R,12aR)-decahidro-3,6,9-trimetil-3,12-epoxi-12H-pirano[4,3-j]-1,2-benzodioxepín-10-ol

antipalúdico
bexlosteridum
bexlosteride  (4aR,10bR)-8-chloro-1,4,4a,5,6,10b-hexahydro-4-methylbenzo[f]quinolin-3(2H)-one
antineoplastic

bexlostéride  (4aR,10bR)-8-chloro-4-méthyl-1,4,4a,5,6,10b-hexahydrobenzo[f]quinoléin-3(2H)-one
antinéoplastique

bexlosterida  (4aR,10bR)-8-cloro-1,4,4a,5,6,10b-hexahidro-4-metilbenzo[f]quinolina-3(2H)-ona
antineoplásico

C_{15}H_{24}O_{5}  81496-81-3

C_{14}H_{16}ClNO  148905-78-6

cadrofloxacimum

cadrofloxacin  (-)-1-cyclopropyl-8-(difluoromethoxy)-6-fluoro-1,4-dihydro-7-[(S)-3-methyl-1-piperazinyl]-4-oxo-3-quinolinecarboxylic acid
antibacterial

cadrofloxaciné  (-)-acide 1-cyclopropyl-8-(difluorométhoxy)-6-fluoro-7-[(3S)-3-méthylpipérazin-1-yl]-4-oxo-1,4-dihydroquinoléine-3-carboxylique
antibactérien

cadrofloxacino  ácido (-)-1-ciclopropil-8-(difluorometoxi)-6-fluoro-1,4-dihidro-7-[(S)-3-metil-1-piperazinil]-4-oxo-3-quinolinacarboxílico
antibacteriano

C_{19}H_{20}F_{3}N_{3}O_{4}  153808-85-6
**cefmatilenum**

cefmatilen

(-)-(6R,7R)-7-[2-(2-amino-4-thiazolyl)glyoxylamido]-8-oxo-3-[(v-triazol-4-ythio)methyl]thio]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7′-(Z)-oxime

*antibiotic*

**cefmatilène**

(-)-acide (6R,7R)-7-[[Z]-2-(2-aminothiazol-4-yl)-2-(hydroxyimino)acétyl]=amino]-8-oxo-3-[[((1H-1,2,3-triazol-4-yl)sulfanyl]methyl]sulfanyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ène-2-carboxylique

*antibiotique*

**cefmatileno**

7′-(Z)-oxima del ácido (-)-(6R,7R)-7-[2-(2-amino-4-tiazolil)gloxilamido]-8-oxo-3-[[v-triazol-4-iltio]metil]thio]-5-tia-1-azabiciclo[4.2.0]oct-2-eno-2-carboxílico

*antibiótico*

C_{15}H_{14}N_{8}O_{5}S_{4}  
140128-74-1

**cilengitidum**

cilengitide
cyclo(-arginylglycyl-\text{L-}\alpha-aspartyl-d-phenylalanily-N-methyl-L-valily)

*angiogenesis inhibitor*

cilengitide
cyclo[-arginylglycyl-\text{L-}\alpha-aspartyl-d-phénylalanily-(N-méthyl-L-valily)]

*inhibiteur de l'angiogénèse*

cilengitida
ciclo(-arginilglicil-\text{L-}\alpha-aspartil-d-fenilalanil-N-metil-L-valil)

*inhibidor de la angiogenesa*

C_{27}H_{40}N_{8}O_{7}  
188968-51-6

| Arg — Gly — Asp — D-Phe — MeVal |

**cipemastatum**

cipemastat

(\alpha R,\beta R)-\beta -(cyclopentylmethyl)-\gamma -oxo-\alpha -[(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)methyl]-1-piperidinebutyrohydroxamic acid

*matrix metalloproteinase inhibitor, antirheumatic*

cipémastat

(2R,3R)-3-(cyclopentylméthyl)-N-hydroxy-4-oxo-4-(pipérinid-1-yl)-2-[(3,4,4-triméthyl-2,5-dioxoimidazolidin-1-yl)méthyl]butanamide

*inhibiteur de la métalloprotéinase de la matrice, antirhumatismal*

cipemastat

ácido (\alpha R,\beta R)-\beta -(ciclopentilmetil)-\gamma -oxo-\alpha -[(3,4,4-trimetil-2,5-dioxo-1-imidazolidinil)métil]-1-piperidinabutirohidroxâmico

*inhibidor de la metaloproteinasa de matriz, antirreumático*
clamikalant
clamikalant
1-[5-[2-(5-chloro-o-anisamido)ethyl]-2-methoxyphenyl]sulfonyl]-3-methyl-2-thiourea
potassium channel blocker

clamikalant
antagoniste des canaux potassiques

clamikalant
1-[5-[2-(5-cloro-o-anisamido)etil]-2-metoxifenil]sulfonil]-3-metil-2-tiourea
antagonista del potasio

esketaminum
esketamine
(S)-2-(o-chlorophenyl)-2-(methylamino)cyclohexanone
anaesthetic

eskétamine
(2S)-2-(2-chlorophényl)-2-(méthylamino)cyclohexanone
anesthésique

esketamina
(S)-2-(a-clorofenil)-2-(metilamino)ciclohexanona
anestésico

etanerceptum

etanercept
1-235-tumor necrosis factor receptor (human) fusion protein with 236-467-immunoglobulin G1 (human γ1-chain Fc fragment), dimer immunomodulator

etanercept
1-235-récepteur du facteur de nécrose tumorale (humain)-236-467-immunoglobuline G1 (chaîne γ1 du fragment Fc humain), dimère immunomodulateur

etanercept
dímero de la proteína de fusión del 1-235 receptor del factor de necrosis tumoral (humano) con la 236-467-immunoglobulina G1 (cadena γ1 del fragmento Fc humano) immunomodulador

C_{2224}H_{3472}N_{618}O_{701}S_{36} (monomer) 185243-69-0

LPAQVAFTPY APEPGSTCRL REYYDQTAQM CCKCSGPGQH
AKVFCGTKTD TVCSDCEDST YTQLWNWVPE CLSCGSRCSS
DQVETQACTR EQNRICTCRP GWYCALSKQE GCRCLAPLRK
CRPGFGVARP GTETSDVVCX PCAPGQFSNT TSSTDICRPH
QICNVVAIPG NASMDAVCTS TSPTRSMAPG AVHLQPVPST
RSQHTQPTPE PSTAPSTFL LPMGPSPPAE GSTGDEPKSC
DKHTCPPCP APELLGGPSV FLFPKPDKT LMISRPEVT
CVVVDVSHED PENVWNYVD GVEVHNAKTK PEEQYNSTY
RVVSVLTVLH QDWLNGKEYK CKVSNKALPA PIEKTSKAK
GQPREPVQVY LPPLREEMTK NQVSLTCLVK GFYPSIAVE
WESNGQPPEN YKTTPVQLDS DGSFFLYSKL TVDKSRWQQG

NVFSCSVMHE ALHNHYTQKS LSLSPGK

exatecanum

exatecan
(1S,9S)-1-amino-9-ethyl-5-fluoro-1,2,3,9,12,15-hexahydro-9-hydroxy-4-methyl-10H,13H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinoline-10,13-dione antineoplastic

exatécan

exatecán
falnidamolum

falnidamol
8-(3-chloro-4-fluoroanilino)-2-[(1-methyl-4-piperidyl)amino]pyrimido-[5,4-d]pyrimidine
antineoplastic

falnidamol
$N^8$-(3-chloro-4-fluorophenyl)-$N^2$-(1-methylpiperidin-4-yl)pyrimido-[5,4-d]pyrimidine-2,8-diamine
antineoplasique

falnidamol
8-(3-chloro-4-fluoroanilino)-2-[(1-metil-4-piperidil)amino]pirimido-[5,4-d]pirimidina
antineoplásico

finrozolum

finrozole
$\text{p-}[3-(p$-fluorofenil)$-2$-hidroxi$-1$-$(1H,1,2,4$-triazol$-1$-yl)propil$]benzonitrilo$
antineoplastic, aromatase inhibitor

finrozole
$\text{4-}[3-(4$-fluorophenil)$-2$-hidroxi$-1$-$(1H,1,2,4$-triazol$-1$-yl)propil$]benzonitrile$
antineoplasique, inhibiteur de l’aromatase

finrozol
$\text{p-}[3-(p$-fluorofenil)$-2$-hidroxi$-1$-$(1H,1,2,4$-triazol$-1$-il)propil$]benzonitrilo$
antineoplásico, inhibidor de la aromatasa

C$_{18}$H$_{19}$ClFN$_7$ 196612-93-8
foslfructosum
fosfructose 1,6-bis(dihydrogen phosphate)  
cardioprotectant
foslfructose 1,6-bis(dihydrogenophosphate) de D-araibo-2-hexulofuranose  
cardioprotecteur
fosfructosa 1,6-bis(dihidrógenofosfato) de D-fructosa  
cardioprotector
C₆H₁₄O₁₂P₂  488-69-7

and epimer at C*  
et l'épimère en C*  
y el epímero en el C*

frakfamidum
frakefamide L-tyrosyl-D-alanyl-(4-fluoro-L-phenylalanyl)-L-phenylalaninamide  
analgésic
frakfamida L-tirosil-D-alanil-(4-fluoro-L-fenilalil)-L-fenilalaninamida  
analgésico
C₃₀H₃₄FN₅O₅  188196-22-7

ganstigminum
ganstigmine (4aS,9aS)-2,3,4,4a,9,9a-hexahydro-2,4a,9-trimethyl-1,2-oxazino[6,5-b]indol-6-yl-o-ethylcarbanilate  
cholinesterase inhibitor
ganstigmine (2-éthylphényl)carbamate de (4aS,9aS)-2,4a,9-triméthyl-2,3,4,4a,9,9a-hexahydro-1,2-oxazino[6,5-b]indol-6-ylo  
inhibiteur de cholinestérase
ganstigmina o-etilcarbanilato de (4aS,9aS)-2,3,4,4a,9,9a-hexahidro-2,4a,9-trimetil-1,2-oxazino[6,5-b]indol-6-ilo  
inhibidor de la colinesterasa
gemifloxacinum

Gemifloxacin

(±)-7-[3-(aminomethyl)-4-oxo-1-pyrrolidinyl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid, 74−(Z)-(O-methyloxime)

Antibacterial

gémifloxacine

Acide 7-[3[RS,4Z]-3-[aminométhyl]-4-(méthoxyimino)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphtyridine-3-carboxylique

Antibactérien

gemifloxacino

74−(Z)-(O-metiloxima) del ácido (±)-7-[3-(aminometil)-4-oxo-1-pirrolidinil]-1-ciclopropil-6-fluoro-1,4-dihidro-4-oxo-1,8-naftiridina-3-carboxílico

Antibacteriano

C18H20FN5O4

204519-64-2

ibritumomab tiuxetanum

Ibritumomab tiuxetan

Immunoglobulin G1, anti-(human CD20 (antigen)) (mouse monoclonal IDEC-Y2B8 γ1-chain), disulfide with mouse monoclonal IDEC-Y2B8 κ-chain, dimer, N-[2-[bis(carboxymethyl)amino]-3-(4-isothiocyanatophenyl)propyl]-N-[2-[bis(carboxymethyl)amino]propyl]glycine conjugate

Immunomodulator

Ibritumomab tiuxétan

Produit de la réaction entre l’immunoglobuline G1, anti-(antigène CD20 humain) (chaîne γ1 de l’anticorps monoclonal de souris IDEC-Y2B8), dimère du disulfure avec la chaîne κ de l’anticorps monoclonal de souris IDEC-Y2B8 et la N-[2-[bis(carboxyméthyl)amino]-3-(4-isothiocyanatophényl)propyl]-N-[2-[bis(carboxyméthyl)amino]propyl]glycine

Immunomodulateur

Ibritumomab tiuxetán


Inmunomodulador
idremcinalum

8,9-didehydro-N-demethyl-9-deoxy-6-deoxy-6,9-epoxy-N-isopropylerythromycin
motilin agonist

idremcinal

(2R,3R,4S,5R,8R,9S,10S,11R,12R)-5-éthyl-3,4-dihydroxy-2,4,8,10,12,14-hexaméthyl-9-[(3-C-méthyl-3-O-méthyl-2,6-didésoxy-\(\alpha\)-ribo-hexopyranosyl)oxy]-11-[(3-[méthyl(1-méthyléthyl)amino]-3,4,6-tridésoxy-\(\beta\)-xylo-hexopyranosyl]oxy]-6,15-dioxabicyclo[10.2.1]pentadec-1(14)-én-7-one
agoniste de la motilin

idremcinal

8,9-dideshidro-N-desmetil-9-desoxo-6-desoxi-6,9-epoxi-N-isopropileritromicina
agonista de la motilina

C\(_{39}\)H\(_{69}\)NO\(_{12}\) 110480-13-2

ilodecakinum

interleukin 10 (human clone pH15C)
immunosuppressant

ilodécakine

interleukine 10 (clone humain pH15C)
immunosupresseur

ilodecakina

interleuquina 10 (clon humano pH15C)
imunosupresor
izonsteridum
izonsteride
(4aR,10bR)-8-[(4-ethyl-2-benzothiazolyl)thio]-1,4,4a,5,6,10b-hexahydro-4,10b-dimethylbenzo[f]quinolin-3(2H)-one
antineoplastic

izonstéride
(4aR,10bR)-8-[(4-éthylbenzothiazol-2-yl)sulfanyl]-4,10b-diméthyl-1,4,4a,5,6,10b-hexahydrobenzo[f]quinoléin-3(2H)-one
antinéoplasique

izonsterida
(4aR,10bR)-8-[(4-etil-2-benzotiazolil)tio]-1,4,4a,5,6,10b-hexahidro-4,10b-dimetilbenzo[f]quinolin-3(2H)-ona
antineoplásico

C_{24}H_{26}N_{2}OS_{2} 176975-26-1

lsasoxifenum
lsasoxifene
(-)-cis-5,6,7,8-tetrahydro-6-phenyl-5-[p-{2-[1-pyrrolidinyl]ethoxy}phenyl]-2-naphthol
partial estrogen agonist/antagonist

lsasoxifène
(-)-(5RS,6SR)-6-phényle-5-[4-[(1R)-pyrrolidin-1-yl]ethoxy]phényl]-5,6,7,8-tétrahydranaphtalén-2-ol
agoniste/antagoniste partiel des œstrogènes

lsasoxifeno
(-)-cis-5,6,7,8-tetrahidro-6-fenil-5-[p-{2-(1-pirrolidinil)etoxi]fenil}-2-naftol
agonista/antagonista partial de estrógenos
C_{28}H_{31}NO_{2} 180916-16-9

or enantiomer
ou énantiomère
o enantiómero
licaterminum

licatermin

$N$-methionylneurotrophic factor (human glial-derived), dimer transforming growth factor

licateme

$N$-méthionylfacteur neurotrope (humain, dérivé de la glia), dimère facteur de croissance transformant

licatema

dímero del factor $N$-metionilneurotrófico (humano derivado de la glia) factor de crecimiento transformador

$C_{1290}H_{2110}N_{420}O_{394}S_{18}$ 188630-14-0

licarbazepinum

licarbazepine

10,11-dihydro-10-hydroxy-5$H$-dibenz[b,f]azepine-5-carboxamide anticonvulsant

licarbazépine

$(10RS)$-10-hydroxy-10,11-dihydro-5$H$-dibenz[b,f]azépine-5-carboxamide anticonvulsivant

licarbazepina

10,11-dihidro-10-hidroxi-5$H$-dibenz[b,f]azepina-5-carboxamida anticonvulsivo

$C_{15}H_{14}N_{2}O_{2}$ 29331-92-8

mepolizumabum

mepolizumab

immunoglobulin G1, anti-(human interleukin 5) (human-mouse monoclonal SB-240563 $\gamma$1-chain), disulfide with human-mouse monoclonal SB-240563 $\kappa$-chain, dimer immunomodulator

mépolizumab

immunoglobuline G1, anti-(interleukine 5 humaine) (chaîne $\gamma$1 de l’anticorps monoclonal de souris SB-240563 humanisé), dimère du disulfure avec la chaîne $\kappa$ de l’anticorps monoclonal de souris SB-240563 humanisé immunomodulateur

mepolizumab

inmunoglobulina G1, anti-(interleukina 5 humana) (cadena $\gamma$1 del anticuerpo monoclonal de ratón SB-240563 humanizado), dímero del disulfuro con la cadena $\kappa$ del anticuerpo monoclonal de ratón SB-240563 humanizado inmunomodulador

196078-29-2
### olanexidinum

**olanexidine**
1-(3,4-dichlorobenzyl)-5-octylbiguanide  
*antimicrobial*

**olanexidine**
1-(3,4-dichlorobenzyl)-5-octylbiguanide  
*antimicrobien*

**olanexidina**
1-(3,4-diclorobencil)-5-octilbiguanida  
*antimicrobiano*

\[ \text{C}_{17} \text{H}_{27} \text{Cl}_{2} \text{N}_{5} \]
146510-36-3

![Molecular Structure of Olanexidine](image)

### pibrozelesinum

**pibrozelesin**
methyl (S)-8-(bromomethyl)-3,6,7,8-tetrahydro-4-hydroxy-2-methyl-6-\{5,6,7-trimethoxyindol-2-yl\}carbonyl\[1,2-b:4,3-b'\]dipyrrrole-1-carboxylate, 4-methyl-1-piperazinecarboxylate (ester)  
*antineoplastic*

**pibrozélésine**
(8S)-8-(bromométhyl)-2-méthyl-4-\{[(4-méthylpipérazin-1-yl)carbonyloxy]-6-\{5,6,7-triméthoxy-1\text{H}-indol-2-yl\}carbonyl\}-3,6,7,8-tétrahydrobenzo= [1,2-b:4,3-b']dipyrrrole-1-carboxylate de méthyle  
*antinéoplasique*

**pibrozelesina**
(8S)-(bromometil)-3,6,7,8-tetrahidro-2-metil-4-\{[(4-metil-1-piperaziniil)= carboniloxy]-6-\{5,6,7-trimetoxy-1\text{H}-indol-2-il\}carbonilo\}benzo= [1,2-b:4,3-b']dipirrol-1-carboxilato de metilo  
*antineoplásico*

\[ \text{C}_{32} \text{H}_{36} \text{BrN}_{5} \text{O}_{6} \]
154889-68-6

![Molecular Structure of Pibrozelesin](image)
**pimecrolimusum**

**pimecrolimus**

(3S,4R,5S,8R,9E,12S,14S,15R,16S,18R,19R,26aS)-3-[(E)-2-[(1R,3R,4S)-4-chloro-3-methoxy(cyclohexyl)-1-methylvinyl]-8-ethyl-
5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-hexadecahydro-
5,19-dihydroxy-14,16-dimethoxy-4,10,12,18-tetramethyl-15,19-epoxy-
3H-pyrido[2,1-c][1,4]oxazacyclotricosine-1,7,20,21(4H,23H)-tetrone

**immunosuppressant**

**pimecrolimus**

12-[(E)-2-[(1R,3R,4S)-4-chloro-3-methoxy(cyclohexyl)-1-methyléthényl]-
17-éthyl-1,14-dihydroxy-23,25-diméthoxy-13,19,21,27-tétraméthyl-
11,28-dioxo-4-azatricyclo[22.3.1.04,9]octacos-18-ène-2,3,10,16-tétrone

**immunosuppresseur**

**pimecrolimus**

(3S,4R,5S,8R,9E,12S,14S,15R,16S,18R,19R,26aS)-3-[(E)-2-[(1R,3R,4S)-
4-cloro-3-metoxiciclohexil]-1-metilvinil]-8-etil-
5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-hexadecahidro-
5,19-dihiidroxi-14,16-dimetoxi-4,10,12,18-tetrametil-15,19-epixo-
3H-pirido[2,1-c][1,4]oxazaciclotricosina-1,7,20,21(4H,23H)-tetrona

**inmunosupresor**

C_{43}H_{68}ClNO_{11}  137071-32-0

**prazarelixum**

**prazarelix**

\[N\text{-}acetyl-3-(2-naphthyl)-d\text{-}alanyl\text{-}p\text{-}chloro-d\text{-}phenylalaninyl\text{-}3\text{-}(3\text{-}pyridyl)
d\text{-}alanyl\text{-}L\text{-}seryl\text{-}p\text{-}[5\text{-}amino\text{-}s\text{-}triazol\text{-}3\text{-}yl]amino\text{-}d\text{-}phenylalaninyl\text{-}p\text{-}[5\text{-}amino\text{-}s\text{-}triazol\text{-}3\text{-}yl]amino\text{-}d\text{-}alaninamide\]

**gonadotropin-releasing hormone antagonist**

**prazarélix**

\([N\text{-}acétyl-3-(naftalén-2-yl)-d\text{-}alaninyl\text{-}(4\text{-}cloro-d\text{-}phénylalaninyl\text{-}[3\text{-}(pyridin-3-yl)-d\text{-}alaninyl\text{-}L\text{-}séryl\text{-}[4\text{-}[5\text{-}amino\text{-}1H\text{-}1,2,4\text{-}triazol\text{-}3\text{-}yl]amino\text{-}d\text{-}phenylalaninyl\text{-}[4\text{-}[5\text{-}amino\text{-}1H\text{-}1,2,4\text{-}triazol\text{-}3\text{-}yl]amino\text{-}d\text{-}phénylalanynyl\text{-}L\text{-}leucyl\text{-}[N\text{\textsuperscript{6}}\text{-}(1\text{-}méthyléthyl)-L\text{-}lysyl]-L\text{-}prolyl-d\text{-}alaninamide\]

**agoniste de l’hormone de libération de la gonadotropine**

**prazarelix**

\(N\text{-}acetil-3-(2-naftil)-d\text{-}alaninyl\text{-}p\text{-}cloro-d\text{-}fenilalaninyl\text{-}3\text{-}(3\text{-}piridil)-d\text{-}alaninyl\text{-}L\text{-}seryl\text{-}p\text{-}[5\text{-}amino\text{-}s\text{-}triazol\text{-}3\text{-}yl]amino\text{-}d\text{-}fenilalaninyl\text{-}L\text{-}leucil\text{-}[N\text{\textsuperscript{6}}\text{-}isopropil\text{-}L\text{-}lisil\text{-}L\text{-}proli\text{-}d\text{-}alaninamida\]

**antagonista de la hormona de liberación de la gonadotropina**
**ranpirnasum**

**ranpirnase**

ribozyme (Rana pipiens) 
*antineoplastics*

**ranpirnase**

ribozyme (Rana pipiens) 
*antineoplastique*

**ranpirnasa**

ribozyme (Rana pipiens) 
*antineoplastic*

C₈₂H₁₀₂ClN₂₃O₁₂ 134457-28-6

![Chemical structure of ranpirnasum](image)

**rasburicasum**

**rasburicase**

urate oxidase (tetramer of the N-acetylpolypeptide of 301 amino acids) 
*enzyme*

**rasburicase**

urate oxidase (tétramère du N-acétylpolypeptide de 301 amino-acides) 
*enzyme*

**rasburicasa**

urate oxidasa (tétramero del N-acetilpolipeptido de 301 amino-ácidos) 
*enzima*

C₁₅₂₃H₂₃₈₃N₄₁₇O₄₆₂S₇ (monomer)

![Chemical structure of rasburicasum](image)
rovelizumab

rovelizumab

rovelizumab

rovelizumab

sarakalimum

sarakalimum

sarakalimum

197099-66-4

C_{20}H_{19}F_{3}N_{2}O_{4} 148430-28-8
**selamectinum**

**selamectin**


**sélamectine**


**selamectina**


C_{43}H_{63}NO_{11} 165108-07-6

**sibrotuzumabum**

**sibrotuzumab**

immunoglobulin G1, anti-(human FAP (fibroblast activation protein)) (human-mouse monoclonal BIBH1 \(\gamma_1\)-chain), disulfide with human-mouse monoclonal BIBH1 \(\kappa\)-chain, dimer

**immunomodulator**

**sibrotuzumab**

immunoglobuline G1, anti-(FAP (protéine activant le fibroblaste) humaine) (chaîne \(\gamma_1\) de l’anticorps monoclonal de souris BIBH1, humanisé), dimère du disulfure avec la chaîne \(\kappa\) de l’anticorps monoclonal de souris BIBH1, humanisé

**immunomodulateur**

**sibrotuzumab**

inmunoglobulina G1, anti-(FAP humano (proteína de activación de los fibroblastos)) (cadena \(\gamma_1\) del anticuerpo monoclonal de ratón BIBH1), dímero del disulfuro con la cadena \(\kappa\) del anticuerpo monoclonal de ratón BIBH1

**inmunomodulador**
siramesinum
siramesine
1'-[4-[1-((p-fluorophenyl)indol-3-yl)]butyl]spiro[phthalan-1,4'-piperidine]
anxiolytic, σ-ligand

siramesina
siramésine
1'-[4-[1-((4-fluorophényle)-1H-indol-3-yl)]butyl]spiro[isobenzofurane-1(3H), 4' piperidine]
anxiolytique, ligand σ

siramesina
siramesina
1'-[4-[1-((p-fluorofenil)indol-3-il)]butil]espiro[ftalan-1,4'-piperidina]
ansiolítico, ligando σ

C_{30}H_{31}FN_{2}O_{14} 147817-50-3

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talnetantum
talnetant
N-[(S)-α-ethylbenzyl]-3-hydroxy-2-phenylcinchinonamid
neurokinin NK-3 receptor antagonist

talnétant
3-hydroxy-2-phényl-N-[(1S)-1-phénylpropyl]quinoléine-4-carboxamide
antagoniste du récepteur de la neurokinine NK-3

talnetant
N-[(S)-α-etilbencil]-3-hidroxi-2-fenilcinconinamida
antagonista del receptor de la neurokinina NK-3

C_{25}H_{22}N_{2}O_{2} 174636-32-9

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tesmilifenum	
tesmilifene
2-[(α-phenyl-p-tolyl)oxy]triethylamine
anistrogen

tesmílíene
2-(4-benzyolphénoxy)-N,N-diéthyléthanamine
antioestrogène

tesmilifeno
2-[(α-fenil-p-tolil)oxi]trietilamina
antiestrógeno
tezosentanum
tezosentan

$N-[6-(2\text{-hydroxyethoxy})-5-(\text{o-methoxyphenoxy})-2-[2-(1\text{-H-tetrazol-5-yl})-4\text{-pyridyl}]-4\text{-pyrimidinyl}]-5\text{-isopropyl}-2\text{-pyridinesulfonamide}$

*endothelin receptor antagonist*

tézosentan
tézosentan

$N-[6-(2\text{-hydroxyéthoxy})-5-(2\text{-méthoxyphénoxy})-2-[2-(1\text{-H-tétrazol-5-yl})\text{pyridin}4\text{-yl}]-4\text{-yl}]-5-(1\text{-méthyléthyl})\text{pyridine-2-sulfonamide}$

*antagoniste du récepteur de l’endothélane*

tezosentano
tezosentano

$N-[6-(2\text{-hidroxietoxi})-5-(\text{o-metoxifenoxi})-2-[2-(1\text{-H-tetrazol-5-il})-4\text{-piridil}]-4\text{-pirimidinil}]-5\text{-isopropil}-2\text{-piridinasulfonamida}$

*antagonista del receptor de la endotelina*

\[\text{C}_{27}\text{H}_{27}\text{N}_{9}\text{O}_{6}\text{S}\]

180384-57-0

tocladesinum
tocladesine

8-chloroadenosine 3',5'-cyclic phosphate

*immunomodulator*

tocoladésine

3',5'-hydrogénophosphate cyclique de 8-chloradénosine

*immunomodulateur*

tocladesina

3',5'-hidrógenofosfato cíclico de 8-cloroadenosina

*immunomodulador*

\[\text{C}_{10}\text{H}_{11}\text{ClN}_{5}\text{O}_{6}\text{P}\]

41941-56-4
troxacitabinum

troxacitabine  
(-)-1-[(2S,4S)-2-(hydroxymethyl)-1,3-dioxolan-4-yl]cytosine  
antineoplastic

troxacitabine  
(-)-4-amino-1-[(2S,4S)-2-(hydroxyméthyl)-1,3-dioxolan-4-yl]pyrimidin-2(1H)-one  
antinéoplastique

troxacitabina  
(-)-1-[(2S,4S)-2-(hidroximetil)-1,3-dioxolan-4-il]citosina  
antineoplásico

C₈H₁₁N₃O₄  145918-75-8
AMENDMENTS TO PREVIOUS LISTS
MODIFICATIONS APPORTÉES AUX LISTES ANTÉRIEURES
MODIFICACIONES A LAS LISTAS ANTERIORES

Proposed International Nonproprietary Names (Prop. INN): List 59

p. 5  dexmedetomidinum  replace the chemical name and the graphic formula by the following:
        (±)-(S)-4-[1-(2,3-dimethylphenyl)ethyl]-1H-imidazole

Dénominations communes internationales proposées (DCI Prop.): Liste 59

p. 5  dexamétdétomidine  remplacer le nom chimique et la formule développée par:
        (±)-(S)-4-[1-(2,3-diméthylphényl)éthyl]-1H-imidazole

Denominaciones Comunes Internacionales Propuestas (DCI Prop.): Lista 59

p. 5  dexametnomidina  sustitúyanse el nombre químico y la fórmula desarrollada por:
        (±)-(S)-4-[1-(2,3-dimetilfenil)etil]-1H-imidazol
Proposed International Nonproprietary Names (Prop. INN): List 73
Dénominations communes internationales proposées (DCI Prop.): Liste 73
Denominaciones Comunes Internacionales Propuestas (DCI Prop.): Lista 73

(WHO Drug Information, Vol. 9, No. 2, 1995)

p. 14  odulimomab

replace the description by the following:
immunoglobulin G1, anti-(human CD11 (antigen) α-chain) (mouse monoclonal 25.3 γ1-chain), disulfide with mouse monoclonal 25.3 light chain, dimer

remplacer la description par la suivante:
immunoglobuline G1, anti-(chaîne α de l’antigène CD11 humain) (chaîne γ1 de l’anticorps monoclonal de souris 25.3), dimère du disulfure avec la chaîne légère de l’anticorps monoclonal de souris 25.3

sustitúyase la descripción por la siguiente:
inmunoglobulina G1, anti-(cadena α del antígeno CD11 humano) (cadena γ1 del anticuerpo monoclonal de ratón 25.3), dímero del disulfuro con la cadena ligera del anticuerpo monoclonal de ratón 25.3

Proposed International Nonproprietary Names (Prop. INN): List 75
Dénominations communes internationales proposées (DCI Prop.): Liste 75
Denominaciones Comunes Internacionales Propuestas (DCI Prop.): Lista 75


p. 93  bectumomab

replace the description by the following:
immunoglobulin G2a, anti-(human CD22 (antigen)) Fab’ fragment (mouse monoclonal IMMU-LL23 γ2a-chain), disulfide with mouse monoclonal IMMU-LL2 light chain

remplacer la description par la suivante:
immunoglobuline G2a, anti-(antigène CD22 humain) fragment Fab’ (chaîne γ2a de l’anticorps monoclonal de souris IMMU-LL2), disulfure avec la chaîne légère de l’anticorps monoclonal de souris IMMU-LL2

sustitúyase la descripción por la siguiente:
inmunoglobulina G2a, anti-(antígeno CD22 humano) fragmento Fab’ (cadena γ2a del anticuerpo monoclonal de ratón IMMU-LL2), disulfuro con la cadena ligera del anticuerpo monoclonal de ratón IMMU-LL2
sulesomab

replace the description by the following:
immunoglobulin G1, anti-(human NCA-90 granulocyte cell antigen) Fab' fragment (mouse monoclonal IMMU-MN3 γ1-chain), disulfide with mouse monoclonal IMMU-MN3 light chain

sulésomab

remplacer la description par la suivante:
immunoglobuline G1, anti-(antigène cellulaire NCA-90 de granulocyte humain) fragment Fab' (chaîne γ1 de l’anticorps monoclonal de souris IMMU-MN3), disulfure avec la chaîne légère de l’anticorps monoclonal de souris IMMU-MN3

sulesomab

sustitúyase la descripción por la siguiente:
inmunoglobulina G1, anti-(antígeno NCA-90 de células 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

technetium (99mTc) pintumomabum

replace the description by the following:
immunoglobulin G1, anti-(human adenocarcinoma antigen) (mouse monoclonal 170 γ1-chain), disulfide with mouse monoclonal 170 κ-chain, dimer, technetium [99mTc] salt

technétium (99mTc) pintumomab

remplacer la description par la suivante:
sel de [99mTc]technétium de l’immunoglobuline G1, anti-(antigène associé aux adénocarcinomes humains) (chaîne γ1 de l’anticorps monoclonal de souris 170), dimère du disulfure avec la chaîne κ de l’anticorps monoclonal de souris 170

tecnecio (99mTc) pintumomab

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

basiliximab

replace the description by the following:
immunoglobulin G1, anti-(human interleukin 2 receptor) (human-mouse monoclonal CHI621 γ1-chain), disulfide with human-mouse monoclonal CHI621 light chain, dimer
<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>basiliximab</td>
<td><em>remplacer la description par la suivante:</em> immunoglobuline G1, anti-(récepteur de l'interleukine 2 humain) (chaîne γ1 de l'anticorps monoclonal chimérique homme-souris CHI621), dimère du disulfure avec la chaîne légère de l'anticorps monoclonal chimérique homme-souris CHI621</td>
</tr>
<tr>
<td>basiliximab</td>
<td><em>sustitúyase la descripción por la siguiente:</em> inmunoglobulina G1, anti-(receptor de interleukina 2 humano) (cadena γ1 del anticuerpo monoclonal hombre-ratón CHI621), dímero del disulfuro con la cadena ligera del anticuerpo monoclonal quimérico hombre-ratón CHI621</td>
</tr>
<tr>
<td>faralimomab</td>
<td><em>replace the description by the following:</em> immunoglobulin G1, anti-(human interferon type I receptor) (mouse monoclonal 64G12 γ1-chain), disulfide with mouse monoclonal 64G12 light chain, dimer</td>
</tr>
<tr>
<td>faralimomab</td>
<td><em>remplacer la description par la suivante:</em> immunoglobuline G1, anti-(récepteur humain des interférons de type I) (chaîne γ1 de l'anticorps monoclonal de souris 64G12), dimère du disulfure avec la chaîne légère de l’anticorps monoclonal de souris 64G12</td>
</tr>
<tr>
<td>faralimomab</td>
<td><em>sustitúyase la descripción por la siguiente:</em> inmunoglobulina G1, anti-(receptor humano de los interferones del tipo I) (cadena γ1 del anticuerpo monoclonal de ratón 64G12), dímero del disulfuro con la cadena ligera del anticuerpo monoclonal de ratón 64G12</td>
</tr>
<tr>
<td>keliximab</td>
<td><em>replace the description by the following:</em> immunoglobulin G1, anti-(human CD4 (antigen)) (human-macaca monoclonal CE9.1 γ1-chain), disulfide with human-macaca monoclonal CE9.1 λ-chain, dimer</td>
</tr>
<tr>
<td>keliximab</td>
<td><em>remplacer la description par la suivante:</em> immunoglobuline G1, anti-(antigène CD4 humain) (chaîne γ1 de l’anticorps monoclonal chimérique homme-macaque CE9.1), dimère du disulfure avec la chaîne λ de l’anticorps monoclonal chimérique homme-macaque CE9.1</td>
</tr>
<tr>
<td>keliximab</td>
<td><em>sustitúyase la descripción por la siguiente:</em> inmunoglobulina G1, anti-(antígeno CD4 humano) (cadena γ1 del anticuerpo monoclonal hombre-macaco CE9.1), dímero del disulfuro con la cadena λ del anticuerpo monoclonal quimérico hombre-macaco CE9.1</td>
</tr>
</tbody>
</table>
p. 209 **lintuzumabum**

*lintuzumab*

replace the description by the following:
immunoglobulin G1, anti-(human CD33 (antigen)) (human-mouse monoclonal HuM195 γ1-chain), disulfide with human-mouse monoclonal HuM195 κ-chain, dimer

p. 212 **nerelimomabum**

*nerelimomab*

replace the description by the following:
immunoglobulin G1, anti-(human tumor necrosis factor α) (mouse monoclonal BAYX1351 γ1-chain), disulfide with mouse monoclonal BAYX1351 light chain, dimer

p. 217 **technetium (99mTc) nofetumomabum**

*merpentanum*

*technetium (99mTc) nofetumomab*

replace the description by the following:
immunoglobulin G2b, anti-(human tumor) Fab fragment (mouse monoclonal NR-LU-10 γ2b-chain), disulfide with mouse monoclonal NR-LU-10 κ-chain, oxo[[N,N'-[1-(3-oxopropyl)-1,2-ethanediyl]bis[2-mercaptoacetamidato]]=(4-)-N,N',S,S']technetate(1-)[99mTc] conjugate

remplacer la description par la suivante:
immunoglobuline G1, anti-(antigène CD33 humain) (chaîne γ1 de l’anticorps monoclonal de souris HuM195, humanisé), dimère du disulfure avec la chaîne κ de l’anticorps monoclonal de souris HuM195, humanisé

sustituyase la descripción por la siguiente:
immunoglobulina G1, anti-(antigeno CD33 humano) (cadena γ1 del anticuerpo monoclonal hombre-ratón HuM195), dímero del disulfuro con la cadena κ del anticuerpo monoclonal hombre-ratón HuM195

remplacer la description par la suivante:
immunoglobuline G1, anti-(facteur de nécrose tumorale α humain) (chaîne γ1 de l’anticorps monoclonal de souris BAYX1351), dimère du disulfure avec la chaîne légère de l’anticorps monoclonal de souris BAYX1351

sustitúyase el nombre químico por:
immunoglobulina G1, anti-(factor de necrosis tumoral α humano) (cadena γ1 del anticuerpo monoclonal de ratón BAYX1351), dímero del disulfuro con la cadena ligera del anticuerpo monoclonal de ratón BAYX1351

remplacer la description par la suivante:
immunoglobuline G1, anti-(tumeur humaine) fragment Fab (chaîne γ2b de l’anticorps monoclonal de souris NR-LU-10), disulfure avec la chaîne κ de l’anticorps monoclonal de souris NR-LU-10, conjuguée avec l’oxo=[[N,N'-[1-(3-oxopropyl)éthylène]bis[2-sulfanylacétamidato]]=(4-)-N,N',S,S'][99mTc]technétate(1-)}
técneio (99mTc) nofetumomb
merpentán

sustitúyase el nombre químico por:
imunoglobulina G2b, anti- (tumor humano) fragmento Fab (cadena γ2b del anticuerpo monoclonal de ratón NR-LU-10), disulfuro con la cadena κ del anticuerpo monoclonal de ratón NR-LU-10, conjugado con el oxo[[N,N’-[1-(3-oxopropil)etano-1,2-diil]bis[2-sulfanilacetamidato]]= (4-)N,N’,S,S’[99mTc]tecnetato(1-)

Proposed International Nonproprietary Names (Prop. INN): List 77
Dénominations communes internationales proposées (DCI Prop.): Liste 77
Denominaciones Comunes Internacionales Propuestas (DCI Prop.): Lista 77

(WHO Drug Information, Vol. 11, No. 2, 1997)

p. 88 cedelizumabum

replace the description by the following:
imunoglobulina G4, anti- (antígeno CD4 humano) (cadena γ4 del anticuerpo monoclonal humanizado de ratón OKTcdr4a), dímero del disulfuro con la cadena ligera del anticuerpo monoclonal humanizado de ratón OKTcdr4a

p. 106 igovomabum

replace the description by the following:
imunoglobulina G1, anti- [(antígeno hidrato de carbono) CA 125 humano] (fragmento F(αβ)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)
Proposed International Nonproprietary Names (Prop. INN): List 80
Dénominations communes internationales proposées (DCI Prop.): Liste 80
Denominaciones Comunes Internacionales Propuestas (DCI Prop.): Lista 80
(WHO Drug Information, Vol. 12, No. 4, 1998)

p. 283 vilazodonum
vilazodone
vilazodone
vilazodona
replace the molecular formula by the following:
remplacer la formule brute par:
sustituyase la fórmula molecular por:
\[ C_{26}H_{27}N_5O_2 \]
p. 287 satumomab

*replace the description by the following:*
immunoglobulin G1, anti-(human tumor-associated glycoprotein 72) (mouse monoclonal B72.3 γ1-chain), disulfide with mouse monoclonal B72.3 light chain, dimer

satumomab

*remplacer la description par la suivante:*
immunoglobuline G1, anti-(glycoprotéine 72 humaine associée aux tumeurs) (chaîne γ1 de l'anticorps monoclonal de souris B72.3), dimère du disulfure avec la chaîne légère de l'anticorps monoclonal de souris B72.3

satumomab

*sustitúyase la descripción por la siguiente:*
inmunoglobulina G1, anti-(glicoproteína 72 humana asociada a los tumores) (cadena γ1 del anticuerpo monoclonal de ratón B72.3), dímero del disulfuro con la cadena ligera del anticuerpo monoclonal de ratón B72.3
Annex 1

PROCEDURE FOR THE SELECTION OF RECOMMENDED INTERNATIONAL NONPROPRIETARY NAMES FOR PHARMACEUTICAL SUBSTANCES*

The following procedure shall be followed by the World Health Organization in the selection of recommended international nonproprietary names for pharmaceutical substances, in accordance with the World Health Assembly resolution WHA3.11:

1. Proposals for recommended international nonproprietary names shall be submitted to the World Health Organization on the form provided therefor.

2. Such proposals shall be submitted by the Director-General of the World Health Organization to the members of the Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations designated for this purpose, for consideration in accordance with the “General principles for guidance in devising International Nonproprietary Names”, appended to this procedure. The name used by the person discovering or first developing and marketing a pharmaceutical substance shall be accepted, unless there are compelling reasons to the contrary.

3. Subsequent to the examination provided for in article 2, the Director-General of the World Health Organization shall give notice that a proposed international nonproprietary name is being considered.

   A. Such notice shall be given by publication in the Chronicle of the World Health Organization and by letter to Member States and to national pharmacopoeia commissions or other bodies designated by Member States.

      (i) Notice may also be sent to specific persons known to be concerned with a name under consideration.

   B. Such notice shall:

      (i) set forth the name under consideration;

      (ii) identify the person who submitted a proposal for naming the substance, if so requested by such person;

      (iii) identify the substance for which a name is being considered;

      (iv) set forth the time within which comments and objections will be received and the person and place to whom they should be directed;

      (v) state the authority under which the World Health Organization is acting and refer to these rules of procedure.

   C. In forwarding the notice, the Director-General of the World Health Organization shall request that Member States take such steps as are necessary to prevent the acquisition of proprietary rights in the proposed name during the period it is under consideration by the World Health Organization.

4. Comments on the proposed name may be forwarded by any person to the World Health Organization within four months of the date of publication, under article 3, of the name in the Chronicle of the World Health Organization.

5. A formal objection to a proposed name may be filed by any interested person within four months of the date of publication, under article 3, of the name in the Chronicle of the World Health Organization.

   A. Such objection shall:

      (i) identify the person objecting;

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† The title of this publication was changed to WHO Chronicle in January 1959. From 1987 onwards lists of INNs are published in WHO Drug Information.
(ii) state his interest in the name;
(iii) set forth the reasons for his objection to the name proposed.

6. Where there is a formal objection under article 5, the World Health Organization may either reconsider the proposed name or use its good offices to attempt to obtain withdrawal of the objection. Without prejudice to the consideration by the World Health Organization of a substitute name or names, a name shall not be selected by the World Health Organization as a recommended international nonproprietary name while there exists a formal objection thereto filed under article 5 which has not been withdrawn.

7. Where no objection has been filed under article 5, or all objections previously filed have been withdrawn, the Director-General of the World Health Organization shall give notice in accordance with subsection A of article 3 that the name has been selected by the World Health Organization as a recommended international nonproprietary name.

8. In forwarding a recommended international nonproprietary name to Member States under article 7, the Director-General of the World Health Organization shall:

A. request that it be recognized as the nonproprietary name for the substance; and

B. request that Member States take such steps as are necessary to prevent the acquisition of proprietary rights in the name, including prohibiting registration of the name as a trade-mark or trade-name.

Annex 2

GENERAL PRINCIPLES FOR GUIDANCE IN DEVISING INTERNATIONAL NONPROPRIETARY NAMES FOR PHARMACEUTICAL SUBSTANCES*

1. International Nonproprietary Names (INN) should be distinctive in sound and spelling. They should not be inconveniently long and should not be liable to confusion with names in common use.

2. The INN for a substance belonging to a group of pharmacologically related substances should, where appropriate, show this relationship. Names that are likely to convey to a patient an anatomical, physiological, pathological or therapeutic suggestion should be avoided.

These primary principles are to be implemented by using the following secondary principles:

3. In devising the INN of the first substance in a new pharmacological group, consideration should be given to the possibility of devising suitable INN for related substances, belonging to the new group.

4. In devising INN for acids, one-word names are preferred; their salts should be named without modifying the acid name, e.g. “oxacillin” and “oxacillin sodium”, “ibufenac” and “ibufenac sodium”.

5. INN for substances which are used as salts should in general apply to the active base or the active acid. Names for different salts or esters of the same active substance should differ only in respect of the name of the inactive acid or the inactive base.

For quaternary ammonium substances, the cation and anion should be named appropriately as separate components of a quaternary substance and not in the amine-salt style.

6. The use of an isolated letter or number should be avoided; hyphenated construction is also undesirable.

* In its twentieth report (WHO Technical Report Series, No. 581, 1975), the WHO Expert Committee on Nonproprietary Names for Pharmaceutical Substances reviewed the general principles for devising, and the procedures for selecting, international nonproprietary names (INN) in the light of developments in pharmaceutical compounds in recent years. The most significant change has been the extension to the naming of synthetic chemical substances of the practice previously used for substances originating in or derived from natural products. This practice involves employing a characteristic “stem” indicative of a common property of the members of a group. The reasons for, and the implications of, the change are fully discussed.
7. To facilitate the translation and pronunciation of INN, “f” should be used instead of “ph”, “t” instead of “th”, “e” instead of “ae” or “oe”, and “i” instead of “y”; the use of the letters “h” and “k” should be avoided.

8. Provided that the names suggested are in accordance with these principles, names proposed by the person discovering or first developing and marketing a pharmaceutical preparation, or names already officially in use in any country, should receive preferential consideration.

9. Group relationship in INN (see Guiding Principle 2) should if possible be shown by using a common stem. The following list contains examples of stems for groups of substances, particularly for new groups. There are many other stems in active use. Where a stem is shown without any hyphens it may be used anywhere in the name.

<table>
<thead>
<tr>
<th>Latin</th>
<th>English</th>
</tr>
</thead>
<tbody>
<tr>
<td>-acum</td>
<td>-ac</td>
</tr>
<tr>
<td>-actidum</td>
<td>-actide</td>
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<tr>
<td>-adolum</td>
<td>-adol</td>
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<tr>
<td>-adol-</td>
<td>-adol-</td>
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<tr>
<td>-astum</td>
<td>-ast</td>
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<tr>
<td>-astinum</td>
<td>-astine</td>
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<tr>
<td>-azepamum</td>
<td>-azepam</td>
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<tr>
<td>-bactamum</td>
<td>-bactam</td>
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<tr>
<td>bol</td>
<td>bol</td>
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<td>-buzonum</td>
<td>-buzone</td>
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<td>-cain-</td>
<td>-cain-</td>
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<td>-cainum</td>
<td>-caine</td>
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<td>-conazole</td>
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<td>cort</td>
<td>cort</td>
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<td>-dipinum</td>
<td>-dipine</td>
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<td>-fibratum</td>
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<td>-nidazole</td>
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<td>-oxacinum</td>
<td>-oxacin</td>
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<td>-pridum</td>
<td>-pride</td>
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<tr>
<td>-pril(at)um</td>
<td>-pril(at)</td>
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<tr>
<td>-profenum</td>
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<td>prost</td>
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<td>vin-</td>
<td>vin-</td>
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<td>-vin-</td>
<td>-vin-</td>
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</table>

1 A more extensive listing of stems is contained in the working document WHO/EDM/QSM 99.6 which is regularly updated and can be requested from the INN Programme, WHO, Geneva.
Annexe 1

PROCEDURE A SUIVRE EN VUE DU CHOIX DE
DENOMINATIONS COMMUNES INTERNATIONALES
RECOMMANDÉES POUR LES SUBSTANCES PHARMACEUTIQUES* 

L’Organisation mondiale de la Santé observe la procédure exposée ci-dessous pour l’attribution de dénominations communes internationales recommandées pour les substances pharmaceutiques, conformément à la résolution WHA3.11 de l’Assemblée mondiale de la Santé:

1. Les propositions de dénominations communes internationales recommandées sont soumises à l’Organisation mondiale de la Santé sur la formule prévue à cet effet.

2. Ces propositions sont soumises par le Directeur général de l’Organisation mondiale de la Santé aux experts désignés à cette fin parmi les personnalités inscrites au Tableau d’experts de la Pharmacopée internationale et des Préparations pharmaceutiques; elles sont examinées par les experts conformément aux “Directives générales pour la formation des dénominations communes internationales”, reproduites ci-après. La dénomination acceptée est la dénomination employée par la personne qui découvre ou qui, la première, fabrique et lance sur le marché une substance pharmaceutique, à moins que des raisons majeures n’obligent à s’écarter de cette règle.

3. Après l’examen prévu à l’article 2, le Directeur général de l’Organisation mondiale de la Santé notifie qu’un projet de dénomination commune internationale est à l’étude.

   A. Cette notification est faite par une insertion dans la Chronique de l’Organisation mondiale de la Santé et par l’envoi d’une lettre aux États Membres et aux commissions nationales de pharmacopée ou autres organismes désignés par les États Membres.

      (i) Notification peut également être faite à toute personne portant à la dénomination mise à l’étude un intérêt notoire.

   B. Cette notification contient les indications suivantes:

      (i) dénomination mise à l’étude;

      (ii) nom de l’auteur de la proposition tendant à attribuer une dénomination à la substance, si cette personne le demande;

      (iii) définition de la substance dont la dénomination est mise à l’étude;

      (iv) délai pendant lequel seront reçues les observations et les objections à l’égard de cette dénomination; nom et adresse de la personne habilitée à recevoir ces observations et objections;

      (v) mention des pouvoirs en vertu desquels agit l’Organisation mondiale de la Santé et référence au présent règlement.

   C. En envoyant cette notification, le Directeur général de l’Organisation mondiale de la Santé demande aux États Membres de prendre les mesures nécessaires pour prévenir l’acquisition de droits de propriété sur la dénomination proposée pendant la période au cours de laquelle cette dénomination est mise à l’étude par l’Organisation mondiale de la Santé.

4. Des observations sur la dénomination proposée peuvent être adressées à l’Organisation mondiale de la Santé par toute personne, dans les quatre mois qui suivent la date de publication de la dénomination dans la Chronique de l’Organisation mondiale de la Santé (voir l’article 3).


1 Depuis janvier 1959, cette publication porte le titre de Chronique OMS. À partir de 1987, les listes des DCIs sont publiées dans les Informations pharmaceutiques OMS.
5. Toute personne intéressée peut formuler une objection formelle contre la dénomination proposée dans les quatre mois qui suivent la date de publication de la dénomination dans la *Chronique de l’Organisation mondiale de la Santé* (voir l’article 3).

   A. Cette objection doit s’accompagner des indications suivantes:

   i) nom de l’auteur de l’objection;

   ii) intérêt qu’il porte à la dénomination en cause;

   iii) raisons motivant l’objection contre la dénomination proposée.

6. Lorsqu’une objection formelle est formulée en vertu de l’article 5, l’Organisation mondiale de la Santé peut soit soumettre la dénomination proposée à un nouvel examen, soit intervenir pour tenter d’obtenir le retrait de l’objection. Sans préjudice de l’examen par elle d’une ou de plusieurs appellations de remplacement, l’Organisation mondiale de la Santé n’adopte pas d’appellation comme dénomination commune internationale recommandée tant qu’une objection formelle présentée conformément à l’article 5 n’est pas levée.

7. Lorsqu’il n’est formulé aucune objection en vertu de l’article 5 ou que toutes les objections présentées ont été levées, le Directeur général de l’Organisation mondiale de la Santé fait une notification conformément aux dispositions de la sous-section A de l’article 3, en indiquant que la dénomination a été choisie par l’Organisation mondiale de la Santé en tant que dénomination commune internationale recommandée.

8. En communiquant aux Etats Membres, conformément à l’article 7, une dénomination commune internationale recommandée, le Directeur général de l’Organisation mondiale de la Santé:

   A. demande que cette dénomination soit reconnue comme dénomination commune de la substance considérée, et

   B. demande aux Etats Membres de prendre les mesures nécessaires pour prévenir l’acquisition de droits de propriété sur cette dénomination, notamment en interdisant le dépôt de cette dénomination comme marque ou appellation commerciale.

Annexe 2

**DIRECTIVES GÉNÉRALES POUR LA FORMATION DE DÉNOMINATIONS COMMUNES INTERNATIONALES APPLICABLES AUX SUBSTANCES PHARMACEUTIQUES**

1. Les dénominations communes internationales (DCI) devront se distinguer les unes des autres par leur consonance et leur orthographe. Elles ne devront pas être d’une longueur excessive, ni prêter à confusion avec des appellations déjà couramment employées.

2. La DCI de chaque substance devra, si possible, indiquer sa parenté pharmacologique. Les dénominations susceptibles d’évoquer pour les malades des considérations anatomiques, physiologiques, pathologiques ou thérapeutiques devront être évitées dans la mesure du possible.

   *Outre ces deux principes fondamentaux, on respectera les principes secondaires suivants:*

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*Dans son vingtième rapport (Série de Rapports techniques de l’OMS, No. 581, 1975), le Comité OMS d’experts des Dénominations communes pour les Substances pharmaceutiques a examiné les directives générales pour la formation des dénominations communes internationales et la procédure à suivre en vue de leur choix, compte tenu de l’évolution du secteur pharmaceutique au cours des dernières années. La modification la plus importante a été l’extension aux substances de synthèse de la pratique normalement suivie pour désigner les substances tirées ou dérivées de produits naturels. Cette pratique consiste à employer des syllabes communes ou groupes de syllabes communes (segments clés) qui sont caractéristiques et indiquent une propriété commune aux membres du groupe des substances pour lequel ces segments clés ont été retenus. Les raisons et les conséquences de cette modification ont fait l’objet de discussions approfondies.*
3. Lorsqu’on formera la DCI de la première substance d’un nouveau groupe pharmacologique, on tiendra compte de la possibilité de former ultérieurement d’autres DCI appropriées pour les substances apparentées du même groupe.

4. Pour former des DCI des acides, on utilisera de préférence un seul mot. Leurs sels devront être désignés par un terme qui ne modifie pas le nom de l’acide d’origine: par exemple “oxacilline” et “oxacilline sodique”, “ibufénac” et “ibufénac sodique”.

5. Les DCI pour les substances utilisées sous forme de sels devront en général s’appliquer à la base active (ou à l’acide actif). Les dénominations pour différents sels ou esters d’une même substance active ne différeront que par le nom de l’acide inactif (ou de la base inactive).

En ce qui concerne les substances à base d’ammonium quaternaire, la dénomination s’appliquera de façon appropriée au cation et à l’anion en tant qu’éléments distincts d’une substance quaternaire. On évitera de choisir une désignation évoquant un sel aminé.

6. On évitera d’ajouter une lettre ou un chiffre isolé; en outre, on renoncera de préférence au trait d’union.

7. Pour simplifier la traduction et la prononciation des DCI, la lettre “t” sera utilisée à la place de “ph”, “t” à la place de “th”, “e” à la place de “ae” ou “oe” et “i” à la place de “y”; l’usage des lettres “h” et “k” sera aussi évité.

8. On retiendra de préférence, pour autant qu’elles respectent les principes énoncés ici, les dénominations proposées par les personnes qui ont découvert ou qui, les premières, ont fabriqué et lancé sur le marché les préparations pharmaceutiques considérées, ou les dénominations déjà officiellement adoptées par un pays.

9. La parenté entre substances d’un même groupe (voir Directive générale 2) sera si possible indiquée dans les DCI par l’emploi de segments clés communs. La liste ci-après contient des exemples de segments clés pour des groupes de substances, surtout pour des groupes récents. Il y a beaucoup d’autres segments clés en utilisation active.\(^1\) Les segments clés indiqués sans trait d’union pourront être insérés n’importe où dans une dénomination.

<table>
<thead>
<tr>
<th>Latin</th>
<th>Français</th>
</tr>
</thead>
<tbody>
<tr>
<td>-acum</td>
<td>substances anti-inflammatoires du groupe de l’ibufénac</td>
</tr>
<tr>
<td>-actidum</td>
<td>polypeptides synthétiques agissant comme la corticotropine</td>
</tr>
<tr>
<td>-adolum</td>
<td>analgésiques</td>
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<tr>
<td>-adol-</td>
<td></td>
</tr>
<tr>
<td>-astum</td>
<td>antiasthmaticues, antiallergiques n’agissant pas principalement en tant qu’antihistaminiques</td>
</tr>
<tr>
<td>-azturnum</td>
<td>substances du groupe du diazépam</td>
</tr>
<tr>
<td>-bactamum</td>
<td>inhibiteurs de β-lactamases</td>
</tr>
<tr>
<td>bol</td>
<td>stéroïdes anabolisants</td>
</tr>
<tr>
<td>-buzonum</td>
<td>analogésiques anti-inflammatoires du groupe de la phénylbutazone</td>
</tr>
<tr>
<td>-caïn-</td>
<td>substances antifibrillantes à action anesthésique locale</td>
</tr>
<tr>
<td>-caïnum</td>
<td>anesthésiques locaux</td>
</tr>
<tr>
<td>-cif-</td>
<td>antibiotiques, dérivés de l’acide céphalosporanique</td>
</tr>
<tr>
<td>-cilinum</td>
<td>antibiotiques, dérivés de l’acide 6-aminopénicillanique</td>
</tr>
<tr>
<td>-conazolum</td>
<td>agents antifongiques systémiques du groupe du miconazole</td>
</tr>
<tr>
<td>cort</td>
<td>corticostéroïdes, autres que les dérivés de la prednisolone</td>
</tr>
<tr>
<td>-dipinum</td>
<td>inhibiteurs du calcium du groupe de la nifédipine</td>
</tr>
<tr>
<td>-fibratum</td>
<td>substances du groupe du clofibrate</td>
</tr>
<tr>
<td>gest</td>
<td>stéroïdes progestogènes</td>
</tr>
<tr>
<td>-glu-</td>
<td>sulfamides hypoglycémiants</td>
</tr>
<tr>
<td>io-</td>
<td>produits de contraste iodés</td>
</tr>
<tr>
<td>-ium</td>
<td>ammoniums quaternaires</td>
</tr>
<tr>
<td>-metacinum</td>
<td>substances anti-inflammatoires du groupe de l’indométacine</td>
</tr>
</tbody>
</table>

\(^1\) Une liste plus complète de segments clés est contenue dans le document de travail WHO/EDM/QSM 99.6 qui est régulièrement mis à jour et qui peut être demandé auprès du Programme des DCI, OMS, Genève.
WHO Drug Information, Vol. 13, No. 2, 1999

Procedimiento de selección de denominaciones comunes internacionales recomendadas para las sustancias farmacéuticas

La Organización Mundial de la Salud seguirá el procedimiento que se expone a continuación para la selección de denominaciones comunes internacionales recomendadas para las sustancias farmacéuticas, de conformidad con lo dispuesto en la resolución WHA3.11 de la Asamblea Mundial de la Salud:

1. Las propuestas de denominaciones comunes internacionales recomendadas se presentarán a la Organización Mundial de la Salud en los formularios que se proporcionen a estos efectos.

2. Estas propuestas serán sometidas por el Director General de la Organización Mundial de la Salud a los Miembros del Cuadro de Expertos de la Farmacopea Internacional y las Preparaciones Farmacéuticas encargados de su estudio, para que las examinen de conformidad con los “Principios Generales de Orientación para formar Denominaciones Comunes Internacionales para Sustancias Farmacéuticas”, anexos a este Procedimiento. A menos que haya poderosas razones en contra, la denominación aceptada será la empleada por la persona que haya descubierto, fabricado o puesto a la venta por primera vez una sustancia farmacéutica.

3. Una vez terminado el estudio a que se refiere el artículo 2, el Director General de la Organización Mundial de la Salud notificará que está en estudio un proyecto de denominación internacional.

A. Esta notificación se hará mediante una publicación en la Crónica de la Organización Mundial de la Salud y el envío de una carta a los Estados Miembros y a las comisiones nacionales de las farmacopeas u otros organismos designados por los Estados Miembros.

(i) La notificación puede enviarse también a las personas que tengan un interés especial en una denominación objeto de estudio.

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Anexo 1

**PROCEDIMIENTO DE SELECCION DE DENOMINACIONES COMUNES INTERNACIONALES RECOMENDADAS PARA LAS SUSTANCIAS FARMACEUTICAS**

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>-mycinum</td>
<td>mycine</td>
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<tr>
<td>-nidazolum</td>
<td>nidazole</td>
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<td>ololum</td>
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<td>-oxacinum</td>
<td>oxacine</td>
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<td>-pridum</td>
<td>prid</td>
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<td>-pril(at)um</td>
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<td>réline</td>
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<td>-terolum</td>
<td>térol</td>
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<td>-tidinum</td>
<td>tidine</td>
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<td>-trematum</td>
<td>tremate</td>
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<td>vérine</td>
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<td>vin-</td>
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B. En estas notificaciones se incluyen los siguientes datos:

(i) denominación sometida a estudio;

(ii) nombre de la persona que ha presentado la propuesta de denominación de la sustancia si lo pide esta persona;

(iii) definición de la sustancia cuya denominación está en estudio;

(iv) plazo fijado para recibir observaciones y objeciones, así como nombre y dirección de la persona a quien deban dirigirse, y

(v) mención de los poderes conferidos para el caso a la Organización Mundial de la Salud y referencia al presente procedimiento.

C. Al enviar esta notificación, el Director General de la Organización Mundial de la Salud solicitará de los Estados Miembros la adopción de todas las medidas necesarias para impedir la adquisición de derechos de propiedad sobre la denominación propuesta, durante el periodo en que la Organización Mundial de la Salud tenga en estudio esta denominación.

4. Toda persona puede formular a la Organización Mundial de la Salud observaciones sobre la denominación propuesta, dentro de los cuatro meses siguientes a su publicación en la Crónica de la Organización Mundial de la Salud, conforme a lo dispuesto en el artículo 3.

5. Toda persona interesada puede presentar una objeción formal contra la denominación propuesta, dentro de los cuatro meses siguientes a su publicación en la Crónica de la Organización Mundial de la Salud, conforme a lo dispuesto en el artículo 3.

A. Esta objeción deberá acompañarse de los siguientes datos:

i) nombre de la persona que formula la objeción;

ii) causas que motivan su interés por la denominación, y

iii) causas que motivan su objeción a la denominación propuesta.

6. Cuando se haya presentado una objeción formal en la forma prevista en el artículo 5, la Organización Mundial de la Salud puede someter a nuevo estudio la denominación propuesta, o bien utilizar sus buenos oficios para lograr que se retire la objeción. Sin perjuicio de que la Organización Mundial de la Salud estudie una o varias denominaciones en sustitución de la primitiva, ninguna denominación podrá ser seleccionada por la Organización Mundial de la Salud como denominación común internacional recomendada en tanto que exista una objeción formal, presentada como previene el artículo 5, que no haya sido retirada.

7. Cuando no se haya formulado ninguna objeción en la forma prevista en el artículo 5, o cuando todas las objeciones presentadas hayan sido retiradas, el Director de la Organización Mundial de la Salud notificará, conforme a lo dispuesto en el párrafo A del artículo 3, que la denominación ha sido seleccionada por la Organización Mundial de la Salud como denominación común internacional recomendada.

8. Al comunicar a los Estados Miembros una denominación común internacional conforme a lo previsto en el artículo 7, el Director General de la Organización Mundial de la Salud:

A. solicitará que esta denominación sea reconocida como denominación común para la sustancia de que se trate, y

B. solicitará de los Estados Miembros la adopción de todas las medidas necesarias para impedir la adquisición de derechos de propiedad sobre la denominación, incluso la prohibición de registrarla como marca de fábrica o como nombre comercial.
PRINCIPIOS GENERALES DE ORIENTACION PARA FORMAR DENOMINACIONES COMUNES INTERNACIONALES PARA SUSTANCIAS FARMACEUTICAS*

1. Las Denominaciones Comunes Internacionales (DCI) deberán diferenciarse tanto fonéticamente como ortográficamente. No deberán ser incómodamente largas, ni dar lugar a confusión con denominaciones de uso común.

2. La DCI de una sustancia que pertenezca a un grupo de sustancias farmacológicamente emparentadas deberá mostrar apropiadamente este parentesco. Deberán evitarse los nombres que puedan inducir fácilmente en el paciente sugestiones anatómicas, fisiológicas, patológicas o terapéuticas.

Estos principios primarios deberán ser tenidos en cuenta al aplicar los siguientes principios secundarios:

3. Al idear la DCI de la primera sustancia de un nuevo grupo farmacológico, deberá tenerse en cuenta la posibilidad de formar DCI convenientes para las sustancias emparentadas que vengan a incrementar el nuevo grupo.

4. Al idear DCI para ácidos, se preferirán las de una sola palabra; sus sales deberán denominarse sin modificar el nombre de ácido; p. ej., “oxacilina” y “oxacilina sódica”, “ibufenaco” e “ibufenaco sódico”.

5. Las DCI para las sustancias que se usan en forma de sal, deberán en general aplicarse a la base activa o, respectivamente, al ácido activo. Las denominaciones para diferentes sales o ésteres de la misma sustancia activa solamente deberán diferir en el nombre de ácido o de la base inactivos.

En los compuestos de amonio cuaternario, el catión y el anión deberán denominarse adecuadamente por separado, como componentes independientes de una sustancia cuaternaria y no como sales de una amina.

6. Deberá evitarse el empleo de una letra o un número aislados; también es indeseable el empleo de guiones.

7. Para facilitar la traducción y la pronunciación se emplearán de preferencia las letras “f” en lugar de “ph”, “t” en lugar de “th”, “e” en lugar de “ae” u “oe” e “i” en lugar de “y”; se deberá evitar el empleo de las letras “h” y “k”.

8. Siempre que las denominaciones que se sugieran estén de acuerdo con estos principios, recibirán una consideración preferente las denominaciones propuestas por la persona que haya descubierto la sustancia, o la que primeramente fabrique o ponga a la venta la sustancia farmacéutica, así como las denominaciones oficialmente adoptadas en cualquier país.

9. En las DCI, la relación de grupo o parentesco (véanse los Principios Generales de Orientación, apartado 2) se indicará en lo posible utilizando una partícula común. En la lista siguiente se dan algunos ejemplos de estas partículas en relación con diversos grupos de sustancias, en particular los de nuevo cuño. Hay otras muchas partículas comunes en uso.1 Cuando la partícula no lleva ningún guión, cabe utilizarla en cualquier parte de la denominación.

* En su 20° informe (OMS, Serie de Informes Técnicos, No. 581, 1975) el Comité de Expertos de la OMS en Denominaciones Comunes para Sustancias Farmacéuticas examina los principios generales de orientación para formar denominaciones comunes internacionales (DCI) y el procedimiento de selección de las mismas, teniendo en cuenta las novedades registradas en los últimos años en materia de preparaciones farmacéuticas. Entre las modificaciones, la más importante ha sido la extensión a las sustancias químicas sintéticas de la práctica reservada anteriormente para sustancias originarias o derivadas de productos naturales. Esta práctica consiste en emplear una partícula característica que indique una propiedad común a los miembros de un determinado grupo de sustancias. En el informe se examinan a fondo las razones de esta modificación y sus consecuencias.

1 El documento de trabajo WHO/EDM/QSM 99.6, que se pone al día regularmente, contiene una lista más extensa de partículas comunes. Las personas que deseen recibirlo deberán solicitar su envío al Programa DCI, OMS, Ginebra (Suiza).
<table>
<thead>
<tr>
<th>Latin</th>
<th>Español</th>
</tr>
</thead>
<tbody>
<tr>
<td>-acum</td>
<td>-aco antiinflamatorios del grupo del ibufenaco</td>
</tr>
<tr>
<td>-actidum</td>
<td>-actida polipéptidos sintéticos de acción semejante a la corticotropina</td>
</tr>
<tr>
<td>-adol-</td>
<td>-adol analgésicos</td>
</tr>
<tr>
<td>-astum</td>
<td>-ast antiasmáticos y antialérgicos que no actúan principalmente como antihistamínicos</td>
</tr>
<tr>
<td>-astinum</td>
<td>-astina antihistamínicos</td>
</tr>
<tr>
<td>-azepum</td>
<td>-azepam sustancias del grupo del diazepam</td>
</tr>
<tr>
<td>-bactam</td>
<td>-bactam inhibidores de β-lactamasas</td>
</tr>
<tr>
<td>bol</td>
<td>bol esteroides anabólicos</td>
</tr>
<tr>
<td>-buzonum</td>
<td>-buzona analgésicos antiinflamatorios del grupo de la fenilbutazona</td>
</tr>
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<td>-cain-</td>
<td>-cain- antifibrilantes con actividad anestésica local</td>
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<td>-cainum</td>
<td>-caina anestésicos locales</td>
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<td>cef- antibióticos derivados del ácido cefalosporánico</td>
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<td>-cilinum</td>
<td>-cilina antibióticos derivados del ácido 6-aminopenicilínico</td>
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<td>-conazolum</td>
<td>-conazol antifúngicos sistémicos del grupo del miconazol</td>
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<td>cort</td>
<td>cort corticosteroides, excepto los del grupo de la prednisolona</td>
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<td>-dipinum</td>
<td>-dipino antagonistas del calcio del grupo del nifedipino</td>
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<td>-fibratum</td>
<td>-fibrato sustancias del grupo del clofibrato</td>
</tr>
<tr>
<td>gest</td>
<td>gest esteroides progestágenos</td>
</tr>
<tr>
<td>gli-</td>
<td>gli- sulfonamidas hipoglucemiantes</td>
</tr>
<tr>
<td>io-</td>
<td>io- medios de contraste que contienen yodo</td>
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<tr>
<td>-ium</td>
<td>-io compuestos de amonio cuaternario</td>
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<td>-metacina antiinflamatorios del grupo de la indometacina</td>
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<td>-micina antibióticos, producidos por cepas de <em>Streptomyces</em></td>
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<td>-pril(at) inhibidores de la enzima transformadora de la angiotensina</td>
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<td>-profenum</td>
<td>-profeno antiinflamatorios del grupo del ibuprofeno</td>
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<td>-relina péptidos estimulantes de la liberación de hormonas hipofisarias</td>
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<td>-terol broncodilatadores derivados de la fenetilamina</td>
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<td>-tadinum</td>
<td>-tadina antagonistas del receptor H₂ de la histamina</td>
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