WHO Drug Information

*WHO Drug Information* provides an overview of topics relating to drug development and regulation that are of current relevance and importance, and will include the lists of proposed and recommended International Nonproprietary Names for Pharmaceutical Substances (INN). Its contents reflect, but do not present, WHO policies and activities and they embrace socio-economic as well as technical matters.

The objective is to bring issues that are of primary concern to drug regulators and pharmaceutical manufacturers to the attention of a wide audience of health professionals and policy-makers concerned with the rational use of drugs. In effect, the journal seeks to relate regulatory activity to therapeutic practice. It also aims to provide an open forum for debate. Invited contributions will portray a variety of viewpoints on matters of general policy with the aim of stimulating discussion not only in these columns but wherever relevant decisions on this subject have to be taken.

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General Policy Topics

Trademarks versus generic names for pharmaceuticals

A conflict that requires resolution

Generic Names

Generic, nonproprietary or common names are selected by national or international nomenclature committees to designate pharmacologically active drug substances. As a matter of definition, they cannot be owned by a private party. They are a form of public property which anyone is free to use.

The international nonproprietary names (INNs) designated and recommended by WHO offer a means of identifying each drug substance by a unique, globally applicable and accepted generic name (1). This is of critical importance in facilitating and rationalizing communication in medical science as well as in the labelling and advertising of medicinal products. Since 1953 some 5,500 INNs have been selected. These are first published in the form of proposals to enable comments and objections to be made during a fixed consultative period. Proposed names become definitive only in the absence of valid objections.

Protection of Generic Names

The INN nomenclature is based on the use of common stems for substances that are chemically or pharmacologically related. Thus each name indicates the chemical or pharmacological genus to which the substance belongs. For example:

- ß-adrenoreceptor-blocking agents are identified by the suffix -olol (pindolol, propranolol, timolol, etc.)
- penicillins end with the suffix -cillin (ampicillin, cloxacillin, etc.)

A general requirement for both trademarks and INNs is that they should be distinctive in sound and spelling, succinct, and readily distinguishable from other names in common use. However, trademarks, unlike INNs, are not required to connote a particular class of products.

In order to avoid potential conflicts between names the Procedure for the Selection of INNs (2) includes provision for companies to object to proposed names that are either identical or similar to registered trademarks. INNs are less well protected in that, formally, trademarks can be refused only if they are identical to existing INNs. However, many companies as well as regulatory authorities now accept that a need exists for a broader protective mandate.
The potential for conflict

Protection of INNs could be better assured by including them in—or associating them with—trademark registries. Any proposed trademark would then invariably be checked for potential conflict not only with other trademarks but also with INNs.

Before the INN system was introduced in the early 1950's stems like -caine and -mycin were commonly incorporated into trademarks. However, perpetuation of this practice now seriously endangers the systematic selection of new INNs. Great advantage could accrue if manufacturers took the initiative to refrain from using INN stems in trademarks. This, and other relevant proposals are contained in a draft Code of Practice for Pharmaceutical Trademarks that has recently been drawn up by the British Pharmacopoeia Secretariat in collaboration with the United Kingdom Licensing Authority (3). This has now been circulated as a consultative document to the Association of the British Pharmaceutical Industry, the Pharmaceutical Society of Great Britain and other interested parties. The ensuing debate could well stimulate reappraisal of the issue in a broader international context.

New Trends

For many years drug products listed in official pharmacopoeias such as quinine tablets, theophylline tablets and epinephrine injections were described exclusively by their generic names. More recently, however, commercial manufacturers of generic drugs have sought to distinguish their own products from those of their competitors by the use of trademarks. In many instances these trademarks are clearly derived from INNs. This practice disputes the very principle that INNs are public property; it can frustrate the rational selection of further INNs for related substances and, should it continue, will ultimately compromise the safety of patients by promoting confusion in drug nomenclature and drug prescribing.

These concerns would be resolved immediately if, in competitively promoting products no longer protected by patents, generic manufacturers were to rely on the registered name of their company, rather than product trademarks to establish "brand image".

A label that identifies a product only by its INN and the name of the manufacturer provides an unambiguous message to the prescriber. Moreover, in clearly distinguishing between products of competing companies, it serves not only a commercial function but also, on occasion, a therapeutic purpose.

This arises because two apparently interchangeable products, both of which meet relevant pharmacopeial specifications, may differ in other characteristics such as stability and bioavailability. This can be particularly important in products administered for serious conditions and for prolonged periods. Some national regulatory authorities, including the Food and Drug Administration of the United States of America (4), now direct considerable effort to assuring the therapeutic equivalence—or interchangeability—of approved generic drug products. Unless such guarantees can be offered, consistency of response is better assured in conditions such as diabetes and epilepsy if unnecessary interchange of products from different sources is avoided. "Brand loyalty" can thus sometimes operate to the advantage of the consumer as well as of the manufacturer. However, its cultivation is not necessarily dependent upon the generation of a confusing proliferation of registered trademarks.

References

Points of View

New trends in drug evaluation in Italy

by Duilio Poggiolini, Director-General, Pharmaceutical Department, Ministry of Health, Rome, Italy

The directives of the European Communities (EEC) require that an application to market a pharmaceutical product should include reports by experts on the supporting pharmaceutical, pharmaco-toxicological and clinical evidence.

These reports are intended to provide a brief but comprehensive description both of the tests performed to establish the quality of the product and of the various investigations performed on animals and human subjects. The experts are also required to provide a critical commentary on the characteristics of the product and, in particular, to provide a clear understanding of the properties of the active substances, the proposed methods of quality control, the efficacy and safety of the product, and any advantages or shortcomings associated with its use.

The Notice to Applicants published by the EEC in 1986 (1) emphasizes that each request for a marketing authorization must include a justification for the use of the product, particularly in the case of fixed combinations and new pharmaceutical forms. In fact, the main purpose of the clinical documentation is to compare the therapeutic efficacy of the new product with that of existing alternative therapies. The expert thus has a responsibility to state in his report whether the product is likely to be more or less efficacious and/or to produce more or less adverse effects than other drugs within the same therapeutic category. If the new product appears to have no advantages over existing products—or to involve more risks—it is evident that its use may be difficult to justify.

The Italian Ministry of Health has recently modified its procedures for evaluating a new product in order to focus particular attention on any specific therapeutic advantages that it may offer and its suitability for the proposed indications. To this end each application for marketing a new product is now subjected to a preliminary review in order to determine whether it meets such requirements. In order to facilitate the task of the authorities in evaluating the dossier, and to enable applications to be processed more rapidly, it is most important that the protocols should conform, in format, with the relevant EEC guidelines.

To expedite this preliminary review, the applicant is required to correlate the chemical structure of each active substance with that of analogous substances in use and to provide details of its route of synthesis. Similarly, the pharmacological, toxicological and clinical data must be compared with data on existing products in the same category and any differences in the pharmaceutical, biological or therapeutic properties must be described. Any claimed therapeutic advantages of a new chemical entity or of a new dosage form must thus be supported by documented evidence.

The introduction of these requirements raises the long-standing problem of how the comparator "reference drugs" should be chosen. The rules of the European Communities first introduced the concept of comparative evaluation as long ago as 1975: directive 75/318 includes a provision to relate "the therapeutic effect of a new product with that of an established medicinal product of proven therapeutic value" in the course of clinical trials (2). Indeed, such comparisons are already contained in many experts’ reports.

It is important to stress that the new requirements do not mean that a “need clause” has been introduced in Italy. The concept of the “need clause” has been rejected by the Commission of the
European Communities (3). Italy has no intention either to introduce it or to demand evidence that new products constitute "true innovations".

It is accepted, however, that a critical evaluation of the data submitted to support the marketing application of a new product should securely establish its place in therapy, and that this should be clearly and objectively stated in the approved information sheet (data sheet or package insert). This requirement is essential both in order to provide clear information to potential users on the product's characteristics and to prevent unsupported or exaggerated promotional claims. It may also be expected to discourage applications to market products that lack any element of innovation.

References


Reports on Individual Drugs

Ivermectin in onchocerciasis

For many years diethylcarbamazine and suramin have been the only drugs that have offered any possibility of arresting the progress of onchocerciasis, or river blindness. However, their toxicity and the need for medical supervision of the required multidose regimens renders them unsuitable for mass chemotherapy (see p. 83).

Control of the blackfly has thus far provided the only means of reducing the prevalence of the disease in the areas of most intense transmission. The World Health Organization, through its Onchocerciasis Control Programme, has maintained an extensive spraying campaign within the countries of the Volta River Basin in West Africa since 1974. It is estimated that this has reduced the attack rate by some 80%. However, effective larviciding programmes are impractical in other habitats in which the disease is endemic. Even in the Volta Basin continual invasion by flies from outside the area and the emergence of insecticide-resistant strains have rendered it necessary to extend the treated areas and to introduce new insecticides (1).

It has thus long been recognized that the existing benefits can be maintained only if more effective drugs can be developed; and three research-based pharmaceutical companies which have responded to this challenge are currently assessing candidate compounds. One of these, ivermectin (Merck, Sharp & Dohme), has already been submitted to extensive clinical evaluation in West Africa within a developmental programme involving the collaboration of WHO and the competent governmental authorities. The results, which are particularly encouraging, raise expectation that a preparation will become available for more extensive use within the near future.

Ivermectin, which is derived from one of several macrocyclic lactones produced by an actinomycete Streptomyces avermitilis isolated from soil samples in Japan (2), acts by disrupting central neurosynaptic transmission mediated by gamma-aminobutyric acid (3-5). It is well tolerated in mammalian experimental animals, provided it is excluded from penetrating the central nervous system by an effective blood-brain barrier (6), but it is lethal in single low-dose exposure to a variety of nematode and arthropod parasites. However, it has not thus far shown useful activity against trematode or cestode worms.

Its potential in the treatment of human onchocerciasis was suggested by its potent microfilaricidal action in analogous diseases in horses and cattle (7-9). Several studies have since been undertaken to demonstrate the efficacy of the compound as a microfilaricidal agent in man (10-23). These include preliminary dose-ranging studies and subsequent double-blind trials in which ivermectin was compared with diethylcarbamazine and placebo. Collectively, they have involved the administration of ivermectin to more than 1200 adult patients with onchocerciasis of varying severity. The results have been impressively consistent. They demonstrate that ivermectin in a single oral dose of 150 µg/kg rapidly depresses the dermal microfilarial density to a very low level which is maintained for over 12 months and that this is accompanied by a slow clearing of microfilariae from the anterior chamber of the eye. Histological studies of adult female worms suggest that this effect results, at least in part, from impairment of the normal intraterine development of the microfilariae and inhibition of their release from the uterus (14, 15).

The therapeutic effect is thus more prolonged than that of diethylcarbamazine and, presumably because its microfilaricidal action is less abrupt, its use has thus far not been associated with severe systemic or ocular adverse reactions. Fever, pruritus, tenderness of lymph nodes and mild transient hypotension have been reported in some patients, but these have generally been described as mild, and have rarely required steroid therapy. The
totality of the evidence consequently indicates that a single annual oral dose of ivermectin of the order of 100 µg/kg will be well tolerated by adult patients and will inhibit the symptoms of the disease and preserve imperilled sight. There is even a possibility, in view of its effects on the reproductive apparatus of the female worm, that multiple dosing may result in a macrofilaricidal action. Hope also exists that as a result of sustained depression of the dermal microfilarial density, use of ivermectin on a community scale will reduce the local intensity of transmission of the disease (24, 25).

There is, however, a particular and inevitable need for caution in proposing a new drug for community use. Careful surveillance of many more treated patients will be required before unanticipated rare reactions can be excluded with adequate confidence, and plans for extensive post-marketing surveillance are already in hand. Moreover, ivermectin has been shown to be teratogenic on repeated daily administration to mice at a dose some fivefold higher than the proposed single therapeutic dose. It is also toxic to suckling neonatal rats, which unlike human neonates, do not possess a highly developed blood-brain barrier at birth. Even if the potential for such toxicity exists in human beings, the therapeutic dose is likely to be well below the threshold for its expression. None the less, ivermectin should not, in the current state of knowledge, be administered to pregnant or lactating women or to young children (26). This imposes an important constraint on the use of a drug intended for community treatment and it underscores the need for effective and prolonged post-marketing surveillance.

Despite this important reservation, ivermectin remains a compound of outstanding promise. It is encouraging that Merck, Sharp & Dohme is continuing to support investigation of its potential in other parasitic diseases. This has recently been rewarded by preliminary clinical findings that, in the same dosage, it exerts a potent, but less prolonged microfilaricidal effect in bancroftian filariasis (27), a disease that affects some 80 million people in tropical and subtropical regions (28).

References
General Information

Continuous cell lines (CCLs) in the production of biologicals

Continuous cell lines (CCLs) are populations of cells, in some cases derived from tumour tissue, which possess the capacity to divide indefinitely in culture. They have assumed a new significance with the recent application of recombinant DNA technology and hybridoma technology to the production of biological products since they provide the vehicles in which these substances are synthesized.

There has been speculation that the transfer of components of these abnormal cells may constitute a health hazard to the recipients of these products. A Study Group on Biologicals was thus convened in November 1986 to advise WHO on:

• the acceptability of developing generic biological products in new cell systems when the same product is already being manufactured by an approved technology, and

• the degree of risk associated with certain classes of potential contaminants in the product, including heterogeneous DNA, viruses, and transforming proteins.

The Group concluded that, in general, CCLs are acceptable as substrates for the production of biological products, but that differences in the nature of the derived products and the specifics of the manufacturing process must always be taken into account in assessing the safety and acceptability of each product.

It also recommended that WHO should establish a number of banks of CCL cell seeds to enable Member States and manufacturers to create derivative cell banks that are assured of being in conformity with WHO requirements.


Focus on interferons

United States of America — A recent issue of Developments in Oncology (1), which surveys the current international literature, reviews current understanding of the interferons.

Two papers are cited that show interferon alfa induces regression in AIDS-related Kaposi's sarcoma. The greatest effect was obtained with high doses (up to 50 million IU per m$^2$ daily). This effect is of interest primarily as an academic demonstration of antitumour activity rather than as a practical approach to the treatment of Kaposi's sarcoma. Patients with AIDS rarely succumb to tumour progression since opportunistic infection is much more life-threatening.

However, experience with interferon alfa in hairy cell leukaemia leaves no doubt that this action has impressive therapeutic potential. Response rates have averaged 90% in three large studies, and interferon alfa-2 has now been approved by the Food and Drug Administration for this single indication. The degree to which survival may be prolonged is not yet evident, but good control has been obtained in patients with progressive disease after splenectomy, the only palliative measure previously available.

The interferons no longer represent a mysterious black box labelled "biologic response modifiers". It is now clear that the interferons are, in fact, cytotoxic to tumour cells and, to a lesser extent, to normal haematopoietic tissues. It is also evident
that the flu-like symptoms associated with administra
tion of interferon are not due to impurities present in natural material of low specific activity. The same reactions occur when the highly puriﬁed recombinant preparations are administered to patients with respiratory virus infections. They can be minimized, though not eliminated, by dose reduction (2).

References
1. Developments in Oncology, Volume II, No. 2, Advanced Therapeutic Communications, Inc, Secaucus, NJ 07094, USA.

Community pharmaceutical services in Nigeria: towards self-reliance

Nigeria — A paper recently published in Pharmacy World outlines possible approaches to the development of community pharmaceutical services in developing countries and calls on the support of allied professional groups to enable the community pharmacist to attain self-sufficiency. The case is argued that, if national primary health schemes are to attain their objectives, community pharmacists must be trained and equipped to become a primary source of counselling and drug information for patients.

• Particular emphasis is accorded to the disparities created by the inequitable concentration of pharmacies within the large cities, and the need for pharmaceutical services to be provided in the rural and peri-urban areas in support of primary health care programmes.

• A plea is also made for upgrading the level of education of pharmacists; for ensuring that they have rapid access to needed current information; for limiting unfair competition from unqualiﬁed traders; and for assuring that pharmacies are reliably supplied with stocks of essential drugs.

• Community pharmacists themselves, it is suggested, could do something to improve the situation if they were to come together in large units for operative purposes.

• It is proposed that consideration be given to amending the Pharmacy Laws in order to reﬂect contemporary realities, to provide a basis for instituting some of these proposals, and to offer an opportunity for integrating into the infrastructure of primary health care those aspects of traditional medicine that can be demonstrated to be efficacious.


Drugs and alternative medicine

Alternative medicine was the topic of discussion at a symposium held during the 46th International Congress of the International Pharmaceutical Federation, which was convened in Helsinki in September 1986.

• The Prevalence of Alternative Medicine: Dr Nils Östby (Stockholm) said that some 22% of the Swedish population aged 16-74 years have been treated by alternative therapies and that 57% of the remainder are positively disposed to such methods of treatment.

• Homoeopathy: Dr J.-P. Rhein (Switzerland) deﬁned homoeopathic drugs as substances which, when administered to a healthy subject, induce speciﬁc symptoms and, when administered to a patient, heal the same symptoms. He emphasized that, although recent developments in chemistry and physics have allowed new hypotheses to be developed on the mechanisms of action of homoeopathic drugs, their exact role still needs veriﬁcation.

• Phytotherapy: Dr Desmond Corrigan (Ireland) emphasized that the use of mixtures of substances from more than one plant makes it difﬁcult to assess the safety, efﬁcacy and quality of these products for regulatory purposes. Although many phytopharmaceuticals have not yet been fully tested, scientiﬁc studies have shown others to be effective. Similarly, although toxicity studies have conﬁrmed that a number of plants are innocuous, it cannot be assumed, in the absence of adequate
Evidence, that all plant medicines are harmless. Assurance must be provided that inherently toxic substances and components that might interact adversely with orthodox medicines have been excluded. He concluded that, whereas proponents of phytotherapy can sometimes over-estimate the medicinal properties of plants, sceptics can readily under-estimate them.

- Traditional Chinese Medicine: Prof. Ding Guang-Sheng (Shanghai, China) described how a scientific approach to herbal pharmacology already has provided a wide variety of new therapeutic leads including:
  - artemisinin for the treatment of malaria,
  - indirubin for chronic granulocytic leukaemia,
  - biphenyl dimethyl dicarboxylate and for hepatitis,
  - gossypol as a male contraceptive agent,
  - trichosanthin and yuanhuacine as abortifacients,
  - changrolin as an anti-arrhythmic agent,
  - 10-hydroxycamptothecin as an antineoplastic agent, and
  - tetrandrine as a calcium channel blocking agent.


Herbal medicines: safe and effective?

United Kingdom — The Drug and Therapeutics Bulletin of the Consumers’ Association has published a commentary on the safety and efficacy of herbal medicines. It is estimated that in the United Kingdom about 1000 products derived from a total of some 550 herbs are currently marketed and therefore subject to review by the Committee on the Review of Medicines. Many other herbal remedies which are sold without claims of efficacy or therapeutic activity do not require product licences. It is stressed that naturally-occurring herbal substances cannot be assumed to be safe in the absence of the appropriate scientific evidence and a list of herbs with potentially toxic properties is presented.


Continuous subcutaneous insulin infusion

Australia — Mechanical insulin delivery systems are discussed in the editorial columns of a recent issue of the Australian Prescriber.

Insulin Pumps — Devices that measure and respond to minute-by-minute fluctuations of the blood glucose level have been developed for research purposes. A commercial version (the Biostator, Miles Laboratories, U.S.A.) is now available for hospitalized patients but, because it is complex to use, it has only limited application outside research units.

Systems for outpatient use — Continuous subcutaneous infusions can be delivered by miniaturized pumps connected by a catheter to a small needle inserted in the abdominal subcutaneous tissue. This system requires frequent self-monitoring of blood glucose. The pump is programmed to satisfy mean basal requirements (about 55% of the total daily supply) and boluses are given before meals. If the basal delivery rate is altered, a new plateau blood insulin level is attained in 7-8 hours. Newer devices are smaller (down to a cigarette packet size) but more expensive.

Patient selection — Continuous subcutaneous insulin infusion is only recommended for patients who:

- have unsatisfactory control despite multiple conventional injections;
- are reliable and motivated;
- undertake regular and frequent self blood glucose monitoring;
- have participated in a formal diabetes education programme;
- will have access to expert advice at all times.

While these delivery systems offer important benefits, they also have disadvantages:

- needle site infection may occur if the needle position is not changed daily;
- needles may be dislodged from the skin;
- batteries may run down;
- if the infusion is inadvertently interrupted for more than 2 hours, ketosis may develop rapidly;
• confused hypoglycaemic patients could make inappropriate adjustments to the rate of infusion.

If the use of insulin infusion devices is to become widespread, they will need to become smaller, more reliable and less expensive. The editorial emphasizes that while the quality, safety and efficacy of new drugs imported to Australia are subjected to review by the Commonwealth Department of Health, no similar review is currently conducted on devices.


A new focus on pharmaceuticals

United Kingdom — A report issued by the Pharmaceutical Economic Development Committee of the National Economic Development Office reviews the contribution of the pharmaceutical industry to the UK economy. An earlier report was published in 1972. Information and data are provided on the relationship between the industry and the State-supported health services, current concerns in research and development, and future perspectives.

A chapter on Medicines and the Third World reviews the size and the expected growth of the pharmaceutical market in developing countries as well as the potential contribution of new drugs in resolving health problems in these countries. In considering research relevant to Third World needs, the report emphasizes that many medicines needed for tropical diseases fall into the category of “orphan drugs” because the industry is not in a position to recoup research and development costs. The WHO Special Programme for Tropical Disease Research is identified as offering challenging opportunities for joint ventures and disappointment is expressed that the programme is not supported by governments to the extent it deserves.

In its conclusions, the report points out that Third World countries require not only access to low-cost essential drugs but also an infrastructure capable of ensuring that the drugs are reliably delivered and safely administered to the patient. Whereas the large majority of the drugs included in WHO’s model list are out of patent and supplies are thus frequently available from a number of competitive sources, it is recognized that several drugs of crucial importance in the treatment of infections and vector-borne diseases such as rifampicin and praziquantel remain prohibitively expensive for most Third World purchasers.

The report recognizes that opportunities and frustrations are inherent in collaborative ventures between developed and developing countries. Many of the difficulties are conceded to be beyond the control of the pharmaceutical industry, but the need for solutions is regarded as imperative. Maintenance of a constructive dialogue between industry and the national and international bodies directly concerned is proposed as the most effective way of defining and assessing the options.


New recommended schedule for active immunization of infants and children

United States of America — Until recently, the recommended schedule for active immunization of normal infants and children involved administration of combined measles-mumps-rubella (MMR) vaccine at 15 months and the subsequent administration of both the fourth dose of diphtheria, tetanus toxoid and pertussis vaccine (DTP) and the third dose of oral poliovirus vaccine (OPV) at 18 months.

A large, randomized, double-blind trial has recently been completed, and sufficient data are now available to establish the safety and efficacy of the simultaneous administration of MMR, DTP, and OPV to all children aged 15 months or older who are eligible to receive these vaccines. It is anticipated
that implementation of this new schedule will result in:

• a decrease in the number of visits required for immunization during the second year of life,
• an accompanying decrease in costs, and
• an increase in the percentage of children who will be fully or partially immunized by 24 months of age.

The complete recommended vaccination schedule for normal infants and children is now as follows:

<table>
<thead>
<tr>
<th>Age</th>
<th>Vaccines</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 months</td>
<td>first DTP and OPV</td>
</tr>
<tr>
<td>4 months</td>
<td>second DTP and OPV</td>
</tr>
<tr>
<td>6 months</td>
<td>third DTP</td>
</tr>
<tr>
<td>15 months</td>
<td>MMR, fourth DTP and third OPV</td>
</tr>
<tr>
<td>24 months</td>
<td>Polysaccharide vaccine for <em>Haemophilus influenzae</em> type b</td>
</tr>
<tr>
<td>4-6 years</td>
<td>fifth DTP and fourth OPV</td>
</tr>
</tbody>
</table>


### Transmission of hepatitis B with jet-gun injections

**United States of America** — In March 1985, during the course of routine investigation of reported cases of hepatitis B, an epidemiologist at Long Beach (California) Department of Public Health noted that 3 of the patients had received jet-gun injections at the same weight-reduction clinic shortly before the onset of disease; 31 additional cases were subsequently found among individuals attending the clinic who had received similar injections.


### Screening for non-A, non-B hepatitis

**United States of America** — The American Association of Blood Banks has announced that its member organizations will be screening all donated blood for evidence of non-A, non-B hepatitis, which is now considered to represent a more serious health hazard than previously thought. Two different blood tests will be used to obtain an indirect indication of the potential for a donor to transmit this disease. One measures the level of alanine amino-transferase (ALT), commonly used as an indicator of liver dysfunction. The other detects the presence of antibodies to hepatitis-B core antigen (anti-HBc). High levels of donor ALT and the presence of anti-HBc both correlate with subsequent development of non-A, non-B hepatitis. The American Red Cross is also implementing ALT testing at its blood banks.

A major concern for blood centres will be the loss of donors from false positives from the ALT and anti-HBc tests, and it is estimated that the tests will increase the cost of a unit of blood by US$ 3. This comes at a time when screening for antibodies to HIV has already had a marked negative impact on the blood supply.

The evaluation of the teratogenicity of chemical substances

The Netherlands — A committee of the Health Council has issued a comprehensive report on the teratogenic potential of substances present in foods, the environment, the workplace and in medicines.

It describes the established methods of investigating teratogenicity and discusses the relevance of data generated in animals for defining acceptable levels for human beings. The necessity for complementing these studies with subsequent epidemiological studies is emphasized.

Although relatively few substances have been unequivocally demonstrated to be teratogenic in man, the report concludes that the totality of evidence derived from animal experiments, clinical observations and epidemiological investigations places a much larger number of substances under suspicion. These include some medicines, and a variety of occupational and environmental chemicals.

The difficulty of establishing causal correlations is compounded because certain effects, including functional disturbances of the central nervous system, may only become apparent long after birth.

It is suggested that more consideration should be given to developing methods capable of detecting damage occurring during gametogenesis and the pre-implantation stages and of demonstrating impairment in functional behaviour.

A chapter dealing with the predictive value of experimental methods concludes that further fundamental research should be undertaken into the apparent differences between man and other species in their sensitivity to teratogenic substances.


Definition of a teratogen

In a signed editorial published in Teratology Robert L. Brent presents the case for claiming that teratogenesis, in contrast to carcinogenicity, is in most instances a threshold phenomenon. He points out that a "no effect" dose can be demonstrated even with thalidomide and that both the incidence and severity of malformations increase with the dose. Graduation of response is even more evident in the response to less-potent teratogens including vitamin D, aspirin, insulin, vitamin A and meclozine.

It is argued, therefore, that the classification of substances into definite, probable, questionable and unlikely teratogens must be made with reference to anticipated exposure. As long as this remains below a critical threshold level, the risk of teratogenesis is not increased. The relative safety of a particular drug or chemical thus depends on the magnitude of the difference between the teratogenic dose and the recommended therapeutic dose or permitted chemical exposure.

<table>
<thead>
<tr>
<th>Teratogenic changes</th>
<th>Carcinogenic and mutagenic changes</th>
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<tbody>
<tr>
<td>Threshold phenomena</td>
<td>Stochastic phenomena</td>
</tr>
<tr>
<td>Caused by multicellular injury</td>
<td>Caused by damage to one or more cells</td>
</tr>
<tr>
<td>Affect discrete cellular or organ specific processes</td>
<td>Affect cellular DNA</td>
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<tr>
<td>Result in malformations, growth retardation, death, chemical toxicity, etc.</td>
<td>Result in neoplasia Mutation</td>
</tr>
<tr>
<td>Risk disappears completely below the threshold dose</td>
<td>Risk exists at all exposures, although at low exposure, the excess risk is less than the spontaneous risk</td>
</tr>
<tr>
<td>Both the severity and incidence of disease increase with high exposure</td>
<td>Incidence of disease increases with exposure, but severity and nature of disease remain unchanged</td>
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Fetal abnormalities and use of drugs during pregnancy

United Kingdom — The extent to which drugs are responsible for fetal abnormalities remains uncertain, if only because some apparently unexplained anomalies may be the result of a forgotten exposure. A recent prospective study in the UK indicates that about 10% of pregnant women are exposed to one or more drugs during the first trimester. Similarly, a survey in the United States of America has shown that about 45% of women use at least one prescription drug during pregnancy, and many more use over-the-counter products.

Defects are recorded in about 2% to 5% of babies at birth. Of these about 25% are regarded as genetic in origin and 65% have no known cause. Only 2% to 3% are suspected of being associated with drug treatment. None the less, it is recommended that routine consideration be given to the following points in the management of pregnant women who have taken, or who are currently taking drugs:

• the precise time of exposure. The period of maximum teratogenic sensitivity, which occurs during the stage of embryonic development, extends from 18 to 55 days after conception. During the fetal phase, from 56 days to term, the effects of drugs are usually limited to defects of growth and functional impairment rather than gross structural abnormalities;

• the exact nature of the drug, in order that the teratogenic risk can be assessed;

• the possibility of establishing a prenatal diagnosis of a particular teratogenic event. The most effective method is high-resolution ultrasound scanning. In optimal conditions this provides good images of the fetal brain and spine, the heart, the arms, legs and hands, and the face.


Reporting congenital malformations

United States of America — Several improvements introduced in 1981 in the system of recording congenital malformations on the birth certificates of newborns used by the Utah Valley Regional Medical Centre have now been demonstrated to be effective. They include:

• transfer of responsibility for reporting congenital malformations from the mother's physician to the paediatrician;

• inclusion of a reporting sheet for congenital malformations in each infant's file;

• according responsibility for reviewing hospital medical records and for completing birth certificates to a specified person.

Both the rate and accuracy of reporting have improved since these measures were introduced and a scheme for classifying birth defects is now being developed that is expected further to increase the utility of the system.


Post-marketing surveillance and medical databases

United States of America — Post-marketing drug surveillance frequently requires collection of data on unusually large sample sizes. In an article in Trends in Pharmacological Sciences B. L. Strom of the University of Pennsylvania Medical School reviews the types of medical database now being established.

Traditionally, post-marketing surveillance has been performed by physicians voluntarily reporting cases of suspected adverse drug reactions either to their national regulatory bodies, to pharmaceu-
tical companies, or to medical journals. Although this approach has undoubted value for generating "signals" of possible adverse effects, it does not provide information on the size of the total population using the drug (the denominator). Furthermore, reporting can vary considerably, even of events associated with drugs of the same therapeutic class, sometimes as a function of how recently the drug was marketed or how assiduous the manufacturer has been in soliciting reports.

Large-scale "cohort" studies are conducted by some pharmaceutical companies. Typically, a company's sales force is asked to recruit 2,000 cooperative physicians, each of whom is then asked to report on the experience of five patients who have received the drug. This approach, despite its cost which may be well over a million dollars, is subject to bias both in the mechanism of recruitment and because it provides no control group for comparison.

In an attempt to address some of the deficiencies of existing systems in a cost-effective way, investigators have begun to use existing medical databases compiled for other purposes. Among these are a number of computerized collections of medical billing data used by private health care organizations. However, whereas these databases provide some relevant information on large numbers of subjects quickly and inexpensively they cannot be expected to provide all the data ideally required within the context of the planned study.


3rd International Conference on Pharmacoepidemiology

United States of America — An International Conference "Contributions of Pharmacoepidemiology to Public Health" will be held from 9 to 11 September 1987 in Minneapolis. The purpose of the conference is to provide a forum for an exchange of views between academic researchers, medical practitioners, health care administrators, the pharmaceutical industry and regulatory agencies on pharmacoepidemiological approaches to studying the efficacy and safety of pharmaceuticals.

Information on the conference is available from the Division of Epidemiology, School of Public Health, University of Minnesota, 611 Beacon St St. SE, Minneapolis, MN 55455, USA.

Drug abuse in the Americas and the Caribbean

Cocaine

Coca leaf chewing has traditionally been accepted in cultures of the Andean highlands of South America, very much like the use of alcohol or tobacco elsewhere. Recently, however, this traditional custom has given rise to serious cocaine abuse in urban settings elsewhere. The leaves of the coca bush (Erythroxylon coca), which is grown mainly in Peru and Bolivia, are processed to yield cocaine hydrochloride which is largely smuggled to North America and Europe.

A different variety of coca grown in Colombia is commonly prepared as a sulfate salt in the form of basuco. Its greater rate of absorption when sniffed (90-95%) makes this a more dangerous substance than the hydrochloride.

Several recent reports indicate that simply chewing the coca leaf can cause permanent functional brain damage resulting in a cognitive deficit. In Bolivia and Peru epidemiological research has distinguished between the direct toxic effects of coca paste and the secondary effects of malnutrition. A clear-cut anorectic effect produces an extreme degree of malnutrition in chronic users of cocaine sulfate which is often exacerbated by abuse of alcohol and other drugs.

It is frequently reported from South America that abuse of coca and its derivatives is increasing, but there are no general population surveys to confirm this impression.
Cannabis

The drug now most commonly abused in the Americas is cannabis which is usually smoked as marihuana. This practice was uncommon until the 1950s, but it reached epidemic proportions in the United States by the 1960s, when it was adopted as a symbol of rebellion against the establishment by the hippie counterculture. Rates of increase in Latin America and the Caribbean are not as high as those in Canada and the United States, but they are important enough to be of concern in almost all countries throughout the region.

It is now evident that chronic heavy use induces both psychological dependence and tolerance, but these disturbances rapidly regress when the drug is withdrawn. However, there have been reports of brain damage, and particularly of residual cognitive deficit. Cannabis can also trigger different kinds of psychiatric disorders. The totality of the evidence now available establishes marihuana as a dangerous substance. It is certainly not as innocuous as it was assumed in the heyday of its popularity.

Although Colombia still seems to be the main supplier in the region, Jamaica has also become an important production centre of high-potency cannabis which is illicitly cultivated on a commercial basis. There is no firm epidemiological evidence on the extent and trend of marihuana use in Latin America and the Caribbean. Nevertheless, many countries have launched primary prevention campaigns, some of which, as in Mexico and Venezuela, are nationally directed.

Tranquillisers

The nonmedical use of psychotropic substances is less widely publicized than that of illicit narcotics and other drugs, but this does not reduce its importance. Clinical experience and anecdotal data indicate that the patterns of abuse of tranquillisers and other psychotropic compounds differ from those of other drugs. They seem to be predominantly abused by adults rather than by young people, and by women rather than by men. In most Latin American countries benzodiazepines are among the leading compounds produced by pharmaceutical companies.

Solvent Inhalation

In the last decade, the sniffing of glue and other volatile solvents has increased throughout large cities, especially among younger children within the lower socioeconomic strata.

References

Draft guidelines for the investigation of bioavailability

The scientific principles underlying the study of bioavailability were first published by WHO in 1974 (1). More recently these principles have been reformulated by many national and international bodies including the Commission of the European Communities (2).

To complement this information, the WHO Regional Office for Europe is preparing guidelines for the investigation of bioavailability intended for clinical and pharmacological investigators carrying out biopharmaceutical studies (3). The draft will be submitted for consultation to experts, institutions and governments and the definitive text will be settled by a working group.

References
Research on healthy volunteers

United Kingdom — The Royal College of Physicians has published a report at the request of the Medicines Commission on the testing of new drugs in healthy volunteers. Early drug development studies on healthy volunteers have increased both in number and in scale over recent years. In part this seems to have arisen as a result of a belief that the Licensing Authority will look more favourably on applications for new drugs if studies are presented involving large numbers of healthy subjects, rather than small precisely focused and carefully designed studies intended to produce specific and essential information for regulatory purposes.

The College considers that the Licensing Authority should clearly state its policy regarding the role and the scope of such studies in drug development programmes.

The report provides a useful working definition of a healthy volunteer and it proposes guidelines that are addressed not only to investigators, sponsors, Research and Ethics Committees and institutions where such research is undertaken, but also to the volunteers themselves. Suggestions are also made regarding provision of compensation for injury.


Pharmacovigilance: a decentralized system

France — The system of drug monitoring in France is unique insofar as it brings health professionals and the public into close contact at regional level and that it directly involves representatives from the pharmaceutical industry. At the heart of the system are the regional centres which play a key role in integrating the system on the one hand with the health care services and on the other hand with the companies responsible for the development of new drugs. This point is made by J. Dangoumau in his introduction to a book that is the first to explain the structure and the objectives of the system in detail.


Pharmacopoeias, compendia and texts of GMPs

An updated catalogue of national and international Pharmacopoeias, Compendia and texts of Good Manufacturing Practices (GMPs) can be obtained from the World Health Organization.

References: Documents WHO/PHARM/86.39 and 86.53, World Health Organization, 1211 Geneva 27, Switzerland.

Chemical analysis unnecessary for most drugs

United Kingdom — The Department of Health and Social Services proposes to change the basic drug testing scheme for controlling dispensing practices by pharmacists which it recommends to family practitioner committees. Under the new proposals, unit dose medicines (tablets, capsules, ampoules, etc.), which can be identified with reasonable certainty by appearance, size and weight, will not normally be chemically analysed. Instead, a sample will be subjected only to visual examination unless there is reason to suspect it does not conform to the prescribed medicine.


Pharmacists’ role in infection control

United States of America — The American Society of Hospital Pharmacists has issued a statement enumerating the responsibilities of the pharmacist in the control of nosocomial infections.
They include:

- advising the hospital authorities on the selection and use of appropriate antiseptics, disinfectants and sterilants;
- collaborating in the establishment of policies determining the prophylactic use of antibiotics and imposing restrictions on the use of specific antibiotics;
- conducting in-service training programmes in aseptic technique, antimicrobial therapy, and sterilization methods;
- participating in public health education campaigns on the control and spread of infectious diseases.


Research on new drugs involving human subjects

France — The report of a Study Group on Medical Ethics which met in Paris in October 1985 has recently been published. It presents a detailed discussion of the legal and ethical responsibilities of the medical investigator, of the pharmaceutical company and of the competent national authority in the study of a new drug in man.


Bleeding and antibiotic treatment

Belgium — The May 1986 issue of *Folia Pharmacotherapeutica*, a publication sponsored by the Ministry of Public Health and Family Affairs, includes a note on the increasing frequency of reports of bleeding associated with the administration of certain antibiotics. A variety of mechanisms is involved:

- Chloramphenicol and trimethoprim inhibit the bone marrow and bleeding results from thrombocytopenia.

- Carboxypenicillins (carbenicillin, ticarcillin), the ureidopenicillins (piperacillin) and some cephalosporins (latamoxef, ceftriaxone) present a particular risk to patients with kidney damage when they are administered at full dosage. At high plasma concentrations platelet receptors are blocked by the drug or its metabolites. This results in platelet aggregation and prolonged bleeding time.

- Latamoxef can cause bleeding as a result of hypoprothrombinaemia. It is important to remember that the administration of this substance and some other oral antibiotics is particularly dangerous after abdominal surgery.

Bleeding may also result from interactions between certain antibiotics and oral anticoagulants.


Blood disorders associated with pirenzepine

Two cases of agranulocytosis and thrombopenia associated with the use of pirenzepine (Gastrozepin® Boots) have been reported. The temporal relationship between the intake of pirenzepine and the onset of the blood disorders in both patients suggests that a causal relationship exists.


Intravaginal dinoprostone for induction of labour at term

Ireland — Like other inducing agents, dinoprostone can induce uterine hypertonus which, on occasion, may force the fetal head against the bony margin of the unprepared cervical canal and vagina. An instance in which this led not only to fetal loss but also to death of the mother from...
intravascular coagulation and cerebral haemorrhage is reported. This is a rare occurrence, but it illustrates the need for monitoring uterine activity and fetal well-being until the time of delivery, once these products have been administered.


Tardive dyskinesia in antipsychotic therapy

Ireland — The National Drugs Advisory Board requires that the following warning be included in the prescribing information for antipsychotic drugs and major tranquillizers:

Tardive dyskinesia, a syndrome characterized by involuntary dyskinetic movements, may develop in patients on antipsychotic therapy and occasionally even in those who have discontinued such treatment. Those at particular risk include the elderly, females, and patients who have received high dosages or prolonged treatment. Fine vermicular movements of the tongue are an early sign and, provided treatment is promptly discontinued, the syndrome may not progress. In some cases, however, it is irreversible or slow to resolve.

There is no effective treatment for the syndrome, which may be masked by antipsychotic drugs or anticholinergic agents. The latter do not predispose to tardive dyskinesia but they should not be used routinely to reduce the parkinsonian effects of antipsychotic drugs because of the danger that they will also obscure the early signs of tardive dyskinesia.


Ibuprofen and aspirin safe in over-the-counter use

United States of America — The widespread use of nonsteroidal anti-inflammatory drugs (NSAIDs) has produced concern over their possible renal toxicity. The incidence of potentially serious drug-related elevations of BUN and serum creatinine was studied within a group of 1468 patients with rheumatoid arthritis or osteoarthritis who took daily therapeutic doses of aspirin and ibuprofen equal to or higher than those used for over-the-counter indications. Slight increases in these indicators occurred in about 5% of the patients. However, these were considered to be clinically significant in only three (<1%) patients, each of whom was receiving concomitant diuretic therapy. None of the changes led to adverse clinical consequences.


“Congesting” nasal decongestants

United Kingdom — Writing in the British Medical Journal, L. H. Capel and A. R. Swanston issue a reminder regarding the long-recognized damage to the nasal mucosa caused by long-term use of topical “decongestants” (vasoconstrictors) which remain widely prescribed, are prominently displayed in chemists’ shops, and are extensively advertised on posters and television. This contrasts with advice offered in the British National Formulary which says that if decongestants are needed, ephedrine is the drug of choice and it should be used for short periods only.

The vasoconstrictors are mostly sympathomimetic amines. The α-adrenergic agonists constrict subepithelial precapillary sphincters, arterioles and venous sinuses, and the β-agonists mediate vasodilatation.

Out of 460 new patients seen in the rhinitis clinic of the Royal National Throat, Nose and Ear Hospital in London in 1985, 60 (13%) had used vasoconstrictor nose drops for more than two months to relieve persistent nasal obstruction. However, in reality, their symptoms were aggravated and sustained by such treatment.
The authors suggest that nasal decongestant sprays and drops should not be advertised to the public and that a warning, "Use of these drops for more than five days becomes increasingly harmful", should be printed prominently on the containers.


Drug interference in thyroid testing

United Kingdom — Because an increasing number of drugs has been shown to interfere with the standard tests of thyroid function both in vivo and in vitro the assessment of thyroid status is becoming more complex. The following drugs are among those that cause serious interference:

- Amiodarone induces antithyroid antibodies.
- Fenclofenac, by displacing thyroxine from binding sites, causes an apparent reduction in the total thyroxine concentration.
- Fenoprofen increases the free triiodothyronine concentration.


Electrical stimulation devices to treat scoliosis

United States of America — The Food and Drug Administration has approved an electrical device consisting of a two-channel stimulator and dual sets of electrodes which conduct electrical impulses to selected muscles, causing contractions that gradually correct abnormal curvatures of the spine in children. Electrical stimulation must be used until the child's spine is mature. The devices are not approved for use in infants or adults or for patients with structural spinal deformities.


Sugar in oral liquid medicines

United Kingdom — The British Pharmacopoeia Commission is hoping to discourage the use of sugar in medicines by allowing "BP" preparations to be formulated using alternative substances when this is considered desirable. Rather than making specific recommendations for replacements, the relevant monograph will specify the use of a "suitable vehicle".

Certain of the current sugar-based formulae will be retained for extemporaneous preparations since these are rarely supplied for long-term use.


Cardiac pacemaker registry

United States of America — The Food and Drug Administration and the Health Care Financing Administration have published a regulatory proposal providing for the establishment of a national cardiac pacemaker registry (Federal Register of 15 May 1986). The proposed registry is designed to provide information that will assist the Secretary of Health and Human Resources in determining when Medicare payments for pacemaker devices may properly be made, in studying the use of the devices, and in monitoring their performance.


Oxybutynin prescribing "unusually high"

United Kingdom — Tillots Laboratories, which is
one of the two companies developing oxybutynin for the UK market under the name Cystrin®, has alerted doctors that the prescribing of the drug has reached an "unusually high" level under the named-patient exemption and is creating administrative problems both for pharmacists and for the company. The product is not yet licensed in the UK and it is supplied only on a named-patient basis. It is expected that it will become generally available within the next two years and, in the meantime, the prescriber must assume full responsibility for the use of the drug. Smith & Nephew is also developing oxybutynin, as Ditropan®.

Oxybutynin is not a new drug. It has been marketed for several years in many countries, including the United States of America. It has anticholinergic properties and a direct antispasmodic effect on the smooth muscle of the bladder.


United Kingdom — The efficacy and safety of oxybutynin have been reviewed in the Drug Newsletter of the Northern Regional Health Authority. In incontinent children with spina bifida, continence was achieved in 70-80%, although intermittent catheterization remained necessary. However, these studies were not controlled and the contribution of the drug to the outcome is regarded as difficult to assess.

Two placebo-controlled studies of the use of oxybutynin to reduce bladder contraction following transurethral surgery were contradictory in their findings and inadequately documented. The reviewer concludes that oxybutynin seems effective in some patients but that it is associated with a high incidence of adverse effects, including dry mouth, impaired vision, tachycardia and nausea.

The relevant published studies are considered to be of poor quality and those which compare oxybutynin with propantheline are dismissed as of little value. In all, it is felt that the merits of oxybutynin therapy have yet to be established.

Reference: Drug Newsletter of the Northern Regional Health Authority, No. 38, June 1986.

Benzodiazepine dependence

David Nutt, writing in the November 1986 issue of Trends in Pharmacological Sciences, examines the basis of the public concern that has arisen within the past decade over possible "addiction" or "dependence" to the widely prescribed benzodiazepines.

Benzodiazepines were introduced in the early 1960s and were quickly shown to be effective anxiolytics and hypnotics. In the mid-1970s it became clear that tolerance develops extremely rapidly to their anticonvulsant and sedative effects. Indeed, it was shown that patients taking overdoses of benzodiazepines would commonly leave hospital with plasma (and therefore most certainly brain) levels of the drug greater than those at the time they were comatose.

Dependence upon benzodiazepines may be evident from clinical observation of withdrawal symptoms or dose escalation. A plethora of symptoms has been attributed to curtailment of benzodiazepine therapy. However, the mechanisms of benzodiazepine tolerance, dependence and withdrawal remain ill understood.

The symptoms of withdrawal are highly variable and many patients do not experience any disturbance. Among the important determinants are the rate of withdrawal (both fast and slow discontinuation may present problems), and the pharmacokinetics of the drug being withdrawn (diazepam and other long-acting drugs tend to be easier to stop). Intrinsic characteristics of the patient are probably of great importance: individuals who are markedly dependent and inadequate in their personalities do badly. Previous or co-existent depression may also prejudice the prognosis.

There are at least 250,000 chronic users of benzodiazepines in the UK. Opinion varies on the extent to which they should be encouraged to stop.

Amitriptyline in diabetic neuropathy

United States of America — In a randomized, double-blind cross-over clinical trial conducted by the National Institute of Dental Research, amitriptyline was shown to provide effective relief of the pain of diabetic neuropathy, without any evidence of elevation in mood. Patients received a single nightly dose ranging from 25 mg to 150 mg (mean dose 90 mg) for six weeks.


A review of clinical risks

United Kingdom — Clinical practice, in virtually every speciality, involves the acceptance of calculated risks. Bernie O'Brien of the Health Economics Research Group at Brunel University considers the nature of these risks and how they are perceived both by doctors and patients. As pointed out in an introductory message by George Teeling Smith, the health professions, the consumerist organizations and the media need to develop a more sophisticated awareness of the ways in which patients can be helped to appreciate the relative risks of illness and treatment. This booklet should help to promote this all-important awareness.


Barbiturate anaesthetics and termination of pregnancy

United States of America — The New York City Bureau of Maternity Services and Family Planning has reported that, since 1980, seven deaths have been associated with the administration of an ultrashort-acting barbiturate anaesthetic (Brevital®) prior to termination of pregnancy. In all seven cases cardiorespiratory arrest occurred either during induction, during the surgical intervention, or in the recovery room.

Short-acting barbiturates are the intravenous anaesthetics of choice for most anaesthesiologists. They are commonly used to induce general anaesthesia and sometimes for maintenance during procedures lasting no more than 15-20 minutes. These deaths underscore the need for care in calculating dosage on a weight basis, supervision of administration by a qualified anaesthesiologist and adequate recovery room monitoring.


Nicardipine, a new calcium antagonist

United Kingdom — The Drugs Newsletter of the Northern Regional Health Authority has recently reviewed published comparative trials of the new calcium antagonist nicardipine (Cardene®, Syntex) with nifedipine. These indicate that nicardipine is useful in the treatment of both hypertension and angina, although trials in hypertension have been of relatively short duration. No adequate comparisons with verapamil or diltiazem have yet been published. As is the case with other calcium antagonists, nicardipine can be used in combination with beta-blockers to obtain a more potent hypotensive effect. The adverse effects of nicardipine are similar to those of nifedipine, and include dizziness, headache and oedema of the feet.

Reference: Drug Newsletter, Northern Regional Health Authority, No. 40, October 1986.

Biotechnology patents for pharmaceuticals

United States of America — Of 1,232 US patents issued in the field of biotechnology last
year, 673, or 54.6%, were directly related to pharmaceuticals and other healthcare products. The greatest number was accorded to Syntex (15), followed by Merck (13), Miles Laboratories and Eli Lilly (12 each).


Standardization of rabies immunoglobulin

WHO is initiating a collaborative study to resolve problems that have arisen in the potency testing of rabies immunoglobulin and anti-rabies sera. Until further notice, the International Standard of rabies immunoglobulin should be considered only as a reference reagent of unknown potency.


World Federation of Associations of Clinical Toxicology Centres and Poison Control Centres

At its General Assembly in October 1985 the Federation focused its attention on industrial toxicology, particularly on packaging and labelling of pesticides, and on the training of nurses and others in clinical toxicology and veterinary toxicology.

Prospects for vaccines and antiviral therapy

In the six years since AIDS was first described, the causative retrovirus (human immunodeficiency virus, HIV) has been isolated, identified and cultured. (1). Methods have been devised for detecting antibodies raised against the organism (2, 3) which can virtually eliminate the risk of contracting AIDS through blood transfusion, and the task of developing a vaccine has begun. Many genetic variants of the virus exist that form a continuum of related strains (4-6). Moreover, since the disease attacks the immunological defence system responsible for cellular immunity (particularly T cells and macrophages) and invokes only a weak humoral antibody response, a successful vaccine will need to boost both reactions immediately and vigorously if it is to offer an effective defence against subsequent infection.

Nonetheless, an impressive amount of fundamental research has already been accomplished that has direct bearing upon the development of a vaccine. Specific glycoprotein components of the virus envelope have been identified as having biological significance both as major antigens (2, 8-11) and as foci that react with specific receptors on target cells of the immune system (12, 13). The United States Food and Drug Administration anticipates that at least two applications will be made this year to test candidate vaccines in human subjects. Meanwhile, preliminary results have already been published of a study undertaken in Zaire in which volunteers were immunized with a recombinant vaccinia virus expressing envelope glycoprotein derived from a defined strain of HIV (14). Whereas the primary immune response resulted in neutralizing antibodies that exhibited specificity for the strain from which the vaccine was derived, the investigators claim that selected cell-mediated responses were stimulated, in different degree, by an antigenically distinct strain of virus. Some of these volunteers have now received second, boosting doses of the vaccine to determine whether this results in an augmented immune response associated with neutralizing antibodies against different strains of HIV. This vaccine, however, contains live vaccinia virus as the carrier which, it has been suggested, could trigger AIDS in a previously infected person by placing an additional stress on an already compromised immune system (15).

There is, however, a general consensus among the experts involved — and expressed during the Third International Conference on AIDS in Washington in June 1987 — that, even if the development of an effective vaccine proves to be feasible, it is unrealistic to expect a marketable product to become available within the next five years. In the interim, fundamental knowledge already acquired on the mechanism of replication of the virus has identified approaches to the treatment, as opposed to the prevention of the disease, that could exert a significant influence on its management within a much shorter time-frame. Already, zidovudine (azidothymidine, Retrovir® Wellcome), the first compound to have been shown in a controlled setting to attenuate the progress of the disease, has been approved for marketing in seven countries in Europe and North America, and the United States Food and Drug Administration has announced that 16 other products are under consideration for clinical testing (see table p. 64).

Zidovudine

Zidovudine (azidothymidine) is a synthetic thymidine analogue that is metabolized in mammalian cells but which frustrates the construction of nucleic acid chains because it does not provide for the formation of the necessary phosphodiester linkages. It is presumed to act by preventing production of viral DNA during the process of reverse transcription on which its replication within the cells depends (16). The clinical basis of this claim resides in the findings of a preliminary open study (17) and of a single unpublished double-blind placebo-controlled study which
started in February 1986 involving 282 patients who had either recovered from a recent episode of *Pneumocystis carinii* pneumonia or who had advanced AIDS-related complex and were at risk of developing opportunistic infections (18).

In the initial study, which involved 19 patients, zidovudine was first administered intravenously for two weeks and then orally for one month during which time the compound was shown to be efficiently absorbed. Most patients gained weight and improved both clinically and in their immune status. Similar improvements soon became evident within the controlled study and the placebo control was discontinued after eight months when an interim analysis revealed that 19 deaths had occurred among the 137 control patients but only one among the 145 patients who has received zidovudine. More recently, a preliminary review has been undertaken of the progress of 3247 patients in the United States of America who had received zidovudine prior to mid-January 1987 on a compassionate use basis. Thus far, 97 deaths have been recorded in this group, only 21 of which occurred in patients who had received the drug for more than three weeks (18). Some of these patients have received zidovudine continuously for more than 18 months and reports of their progress suggest not only that their life-expectancy is increased but that associated neurological signs, ranging from peripheral neuropathy to profound dementia — and which are now recognized to constitute an important complication of the disease — may partially regress (16, 19).

Although, *in vitro*, the reverse transcriptase of HIV is much more susceptible to the inhibitory effects of zidovudine than the analogous mammalian enzyme (20, 21), this specificity is reduced *in vivo* (17, 22). This has important implications for the toxicity of the compound. Overall, 25% of the patients who took zidovudine in the controlled study developed severe anaemia due to bone marrow suppression which was considered, in some degree, to be drug-induced (23, 24). Treatment had to be interrupted in about one-fifth of these and many others required repeated transfusions even after reduction of the initial dosage. Approximately half of the patients complained of headache, sometimes associated with nausea and vomiting, and sporadic cases of more serious central nervous system toxicity have been reported (25, 26).

These problems underscore the fact that clinical experience with zidovudine is still limited. Optimal dosage regimens have yet to be defined. The long-term sequelae of treatment remain uncertain, yet demonstration of the rapid return of circulating HIV antigen following reduction or cessation of treatment (27) suggests it may be needed for life. The results of ongoing trials must be awaited before any assessment can be made of the potential toxicity of the compound in less severely infected individuals. It has even been suggested that the myelotoxic effects of treatment in these groups might exacerbate the disease process by imposing an additional stress on the immune system (23).

Much attention is inevitably being devoted to the possibility of attenuating the adverse effects of treatment by concomitant use of other agents. A case has been made for the physiological stimulation of formed blood elements by haematopoietins (28) as well as for the synergistic use of other immuno-modulating agents, such as acyclovir which has been claimed to potentiate the action of zidovudine *in vitro* (21). However, an apparent case of neurotoxicity, confirmed by rechallenge, in a patient that received the latter combination (29) underscores the need for caution in multiple drug therapy.

The advent of zidovudine has created optimism, where none existed before, that an effective and safe means may eventually be developed for holding the disease in check indefinitely. However, it cannot be regarded as an end in itself: in those countries where the drug has been registered it is as yet available only to subgroups of infected patients, not primarily on grounds of cost which at current prices has recently been estimated at about US$ 7000 a year, but on considerations of safety. Other agents, including a related pyrimidine analogue, dideoxycytidine, are already being subjected to clinical evaluation and it is reasonable — even in the current state of knowledge — to anticipate significant, if not spectacular, progress in discovering less toxic alternatives.
**Products under consideration for clinical testing**

**Immuno-modulating agents**
- Thymopentin (Ortho Pharmaceutical Corp.)
- Thymostimulin (Serono Laboratories Inc.)
- Inosine pranobex (Newport Pharmaceuticals)

**Anti-viral agents**
- Ansymycin (Adria Laboratories)
- Ribavin (Viratex/ICN Pharmaceuticals)
- Dideoxycytidine or DDC (National Cancer Institute)
- Antimoniotungstate or HPA-23 (Rhône-Poulenc)
- AL 721 (Matrix Laboratories)
- Foscarnet sodium (National Institute of Allergy & Infectious Diseases)

**Biological products**
- Interferon alfa (Hoffmann-La Roche, Inc.)
- Interferon gamma (Genetech, Inc.)
- Imreg-I (IMREG, Inc.)
- Interleukin-2 (Hoffmann-La Roche, Inc.)
- Poly IC12U (HEM Research)
- Immune globulin IG-IV (Sandoz Pharmaceuticals Corp. and Alpha Therapeutics)

**References**

29. Bach, M. C. Possible drug interaction during therapy...
Keeping the AIDS virus out of blood supplies

United States of America — Participants in a Consensus Conference organized by the National Institutes of Health concluded that autologous blood transfusion offers the safest option for blood replacement for a person facing elective surgery. It was recommended that blood banks and blood centres should provide this facility whenever possible; the donation process should be simplified to the fullest possible extent, and physicians and patients should be informed about the advantages and mechanics of this approach.

By 14 July 1986, 422 people in the United States had developed AIDS as a consequence of receiving infected blood or blood products. This number, which does not include haemophiliacs, represents less than 2% of all the people who have developed AIDS, and this proportion is expected to fall as a result of the introduction of routine blood screening in 1985.

It was emphasized that the currently used ELISA tests for antibodies to the AIDS virus occasionally yield a “false negative” result, particularly in the case of recently infected individuals who have very low blood levels of antibodies. An effective solution to this problem demands the development of more sensitive antibody tests, or tests that measure the virus or its proteins directly.


AIDS: condoms on prescription?

United Kingdom — To encourage their use in combating the transmission of AIDS, the Council of the Pharmaceutical Society has urged that condoms be made available on prescription and that they should qualify in the same way as oral contraceptives for exemption from prescription charges.


Safety of factor VIII and IX concentrates

United States of America — The effects of exposure to blood factor concentrates containing donations from identified AIDS patients have been reviewed in a recent paper by Janine Jason and others. The authors compared recipients of eight lots of factors VIII and IX subsequently withdrawn from distribution because of suspected contamination with AIDS virus with a nonexposed cohort matched by age, sex, and factor use.

None of these cohorts differed in HIV antibody prevalence or in any other tests of immune function, but both the exposed and non-exposed cohorts had high rates of HIV seroprevalence (>70%). It is concluded that this type of regulatory control offers insufficient means of limiting the spread of the AIDS virus in the haemophiliac population.

Wet or dry heat treatment which appears to be effective in inactivating HIV and related viruses is recommended as a mandatory precaution in the manufacture of all blood-factor concentrates.


Autologous blood transfusion

United States of America — The Council on Scientific Affairs of the American Medical Association has endorsed guidelines on the use of "autologous blood" (blood collected for retransfusion at a later time into the same individual). It provides assurance that safe matched blood is readily available, and it eliminates the risk of
alloimmunization or transmission of infectious disease from transfusion.

Several hospitals have already developed successful transfusion programmes on this basis, and the Council believes autologous blood transfusions to be the safest form of transfusion therapy.


**Australia** — Autologous blood transfusion in one of its three major forms — preoperative collection and storage, and acute perioperative collection with haemodilution — has been advocated for many years as a safe and appropriate means for providing blood for selective surgical procedures.

Although there is little, if any, risk for the recipient, there are potential risks to surgeons, anaesthetists and ancillary staff members if the donor happens to be hepatitis B surface antigen (HBsAg) positive. This risk can be avoided if autologous donations are grouped as a routine and screened appropriately for potential infections in exactly the same way as isologous donations.


The physician must also provide periodic patient progress reports to the company which will provide supplies, initially free of charge, to patients with AIDS who have recovered from one or more episodes of *Pneumocystis carinii* pneumonia and who do not have AIDS-associated conditions that require chemotherapy (such as Kaposi's sarcoma).

Patients must have a total granulocyte count $\geq 1000/mm^3$, haemoglobin $\geq 9.0$ g/dl, platelet count $\geq 50,000$, SGOT $\leq 3$ times the upper limit of normal value, serum creatinine $\leq 1.5$ mg/dl and positive antibody for HIV confirmed by any federally licensed ELISA test kit. They must also have a Karnofsky performance status of at least 60 (defined as requiring occasional assistance but able to care for most of their needs). Patients should not be younger than 12 years of age. Pregnant women, nursing mothers, fertile women not using barrier contraception and patients receiving any myelosuppressive, nephrotoxic or cytotoxic drug are also excluded from the controlled trial.


**AIDS, condoms and spermicides**

**United Kingdom** — Evidence is emerging not only to demonstrate that the HIV retrovirus cannot permeate the condom membrane but that it is inactivated by commercially available spermicides. A recent study showed that HIV is inactivated *in vitro* in 60 seconds by 0.05% nonoxylol-9, an ingredient present at concentrations of 5-12.5% in several spermicides widely used in Britain. There is, however, no proof that spermicides offer effective protection in practice, nor can many available brands of condoms be relied upon to provide the degree of mechanical protection required particularly during anal sex. Manufacturers are only now beginning to produce condoms specifically designed for prophylactic use.

Pharmaceutical Products Approved

Benzodiazepine antagonist

The first benzodiazepine antagonist, flumazenil (Anexate® Roche), a competitive receptor-blocking agent, may shortly become commercially available. Its potential clinical applications include rapid reversal of benzodiazepine-induced anaesthesia and diagnosis and treatment of benzodiazepine overdosage. It may also assist in the differential diagnosis of drug overdosage where an unknown mixture of substances has been taken.

In a double-blind trial in 40 patients premedicated with diazepam for outpatient gastroscopy it has been reported that patients given flumazenil were fully alert 30 minutes after the procedure.


Diagnostic assay for hepatitis delta agent

United States of America — The Food and Drug Administration has approved an in vitro radio-immunoassay for antibody to hepatitis D antigen in human serum or plasma (Anti-Delta®, Abbott). The hepatitis D virus, or delta agent, is an incomplete RNA virus that requires coinfection with the hepatitis B virus for survival and replication. Chronic hepatitis D infection is associated with chronic active hepatitis, cirrhosis, and fulminant hepatitis. The test is indicated as an aid in the diagnosis of hepatitis D virus infection in patients who have severe hepatitis B virus infections; patients with non-A, non-B hepatitis; persons who are hepatitis B surface-antigen positive; chronic carriers of hepatitis B virus; intravenous drug users; patients undergoing haemodialysis; individuals from the Mediterranean region and other areas where hepatitis is endemic; and others who are exposed to high risk of contracting hepatitis B infections.


Biotechnology: a new hepatitis B vaccine

A new recombinant DNA vaccine against hepatitis B has been approved for marketing in Belgium (Engerix-B®, SmithKline Biologicals). This vaccine will compete directly with a similar recombinant DNA vaccine produced by Merck (Recombivax H-B®) and already approved by the Food and Drug Administration in the United States of America. Both companies are synthesizing the vaccines in yeast cells. Small double-stranded rings of Escherichia coli DNA are used to transfer the portion of the gene which codes for the surface protein of the hepatitis B virus into the genetic code of yeast cells.

The new vaccine has now been tested on 6,000 volunteers. It effectively boosts immunity conferred by the plasma-derived vaccine with which it appears to be equi-effective. Four doses may be necessary to produce a protective degree of immunity which, it is anticipated, will persist for about ten years (1).

The price for both the new genetically engineered vaccines and the plasma-derived vaccines will initially be similar, but the cost of the newer vaccines is expected to fall as production capacity increases (2).

References
Other products approved

**Australia** — The following products have been approved for marketing:

**Misoprostol** (Cytotec®, Searle) 200 µg tablets. A synthetic prostaglandin E1 analogue and the first of a new class of antisecretory, cytoprotective agents to be approved for the treatment of acute duodenal and gastric ulcer.

**Leuprorelin** (Lucrin® Injection, Abbott). A synthetic analogue of naturally-occurring luteinizing hormone releasing hormone (LHRH) approved for the palliative treatment of advanced prostatic cancer. Its role in the long-term management of the disease has yet to be established.

**Terfenadine** (Teldane® Merrel Dow). The first of a number of long-acting antihistamines to be approved for the management of seasonal allergic rhinitis. Terfenadine is claimed to have little or no effect on the central nervous system. Whether this claim can be sustained will depend on more extensive experience of its use.


**United States of America** — The Food and Drug Administration has approved a 250 mg tablet formulation of acetohydroxamic acid (Lithostat®, Uro-Research) for use as palliative adjunctive therapy in patients with chronic urinary infections due to urea-splitting organisms. The drug should not be used in lieu of curative treatment. The recommended starting dose is 12 mg/kg/day, administered in divided doses at 6-8 hour intervals between meals. This dose should be reduced in patients with impaired renal function and the drug is contraindicated in patients with advanced renal insufficiency (i.e., serum creatinine 3.0 mg/dl).


United States of America — The Food and Drug Administration has approved a transdermal preparation of the antihypertensive agent clonidine (Catapres-TTS®, Boehringer Ingelheim) available in sizes of 3.5, 7.0, or 10.5 cm$^2$ to deliver *in vivo* 0.1, 0.2 or 0.3 mg clonidine per day for 7 days.

Reference: Food and Drug Administration, New Drug Application No. 18-891.

United States of America — The Food and Drug Administration has approved for marketing buspirone hydrochloride (Buspar®, Mead Johnson & Co.), an antianxiety agent chemically and pharmacologically unrelated to benzodiazepines or barbiturates.

The mechanism of action is unknown. It differs from benzodiazepines because it is devoid of anticonvulsant and muscle relaxant activity. Indications include management of anxiety disorders and short-term relief of the symptoms of anxiety. Buspirone is contraindicated in patients with severe hepatic or renal impairment. Adverse effects include dizziness, nausea, headache, nervousness, light-headedness, and excitement. There is no evidence of tolerance or physical or psychological dependence.

Reports from Regulatory Agencies

Aminophenazone

Brazil — The Division of Medicines decided to withdraw aminophenazone from medicinal products as from 23 May 1986. Manufacturers were granted a period of 90 days to remove products from the market.

Reference: Portaria No. 09 of 23 May 1986 sent to WHO under cover of a letter from the Division of Medicines of the National Health Secretariat of Brazil, dated 24 July 1986.

Anticholinergic drugs

United States of America — The Food and Drug Administration has decided in the course of its ongoing review of “over-the-counter” products, that anticholinergic drugs used for the symptomatic treatment of hay fever, rhinitis and the common cold may continue to be marketed after 10 November 1986 only if a full application for registration has been approved by the Agency.


Barbiturates

New Zealand — The Division of Clinical Services of the Ministry of Health has proposed that the use of barbiturates be further restricted, having regard to continued reports of fatal overdosage (five in 1985). The approval of the Ministry of Health is likely to be required for each individual prescription and supplies will be available from hospital pharmacies only. Practitioners are asked to review the possibility of transferring patients to alternative sedatives. Phenobarbital, which is used primarily as an anticonvulsant, is exempted from these measures.


Bepridil

France — The Minister of Health has reminded physicians that the vasodilator agent bepridil may induce burst dysrhythmia (torsades de pointe or clusters of brief episodes of ventricular tachycardia), particularly in elderly patients receiving other drugs that predispose to dysrhythmias. The product information has been amended to recommend a reduced dose of 200 mg daily for patients over 70 years of age. Concurrent treatment with quinidine-like dysrhythmic agents, sotalol, amiodarone, fenoxedil, lidoflazine, pencyamine and vincamine must be avoided. Monitoring of the electrocardiogram is recommended, particularly with respect to the length of the Q-T segment. Hypokalaemia should be corrected before treatment is instituted and serum potassium levels monitored during treatment.


Bucetin

Federal Republic of Germany — Further to its decision to withdraw products containing phenacetin from the market, the Federal Office of Health has now also withdrawn products containing the phenacetin analogue, bucetin.


Bupivacaine

Egypt — The Drug Organization of the Ministry of Health has restricted the approved indications of the local anaesthetic bupivacaine. Its use is now contraindicated in regional intravenous anaesthesia and paracervical block, and it is indicated for use in obstetric practice only in concentrations of 0.25% and 0.5%. Doctors are also warned that use
of higher concentrations in epidural anaesthesia has resulted in cardiac arrest.


Captopril

Federal Republic of Germany — The Federal Health Office has revised the product information for preparations containing the angiotensin-converting enzyme blocking-agent, captopril. A warning is added that treatment of patients with cardiac insufficiency should start under close medical supervision with 2-3 daily dosages of 6.25 mg. Blood pressure must be monitored for 60 minutes after the first dose. Patients with severe renal impairment must be carefully assessed before treatment is started and renal function should be monitored throughout treatment. The maintenance requirement should be reached by cautiously increasing the dose and should not exceed the minimum effective amount.


Carbamazepine

France — The Directorate of Pharmacy and Drugs has informed WHO that products containing the anticonvulsant carbamazepine (Tegretol®, Ciba-Geigy) are now additionally indicated for the treatment of manic or hypomanic excitement and for the prevention of recurrent episodes of manic depression, particularly in patients resistant to or intolerant of lithium.


Flunitrazepam

Turkey — In view of its frequent abuse by drug addicts, the Ministry of Health and Social Assistance has subjected flunitrazepam to controls equivalent to those applied to drugs in Schedule II of the 1971 Convention on Psychotropic Substances.


Hydrocortisone (topical preparations)

Canada — The Health Protection Branch of the Ministry of Health and Welfare has amended the Food and Drug Regulations to permit non-prescription pharmacy-only sale of monocomponent products for external use containing hydrocortisone or hydrocortisone acetate at a concentration of no more than 0.5%. Indications must be limited to temporary relief of minor skin irritation associated with symptoms of redness, itching, dryness and scaling. Products intended for ophthalmic, otic or buccal use remain under prescription control. The package size must be limited to 15 g for ointments, creams and gels and 30 ml for lotions.

The package insert must include the following warnings:

• For external use only.
• Do not use in children aged 2 years or younger, unless directed by a physician.
• Do not use in or around eyes.
• Do not apply to large areas of the body.
• Do not use to treat vulvar itching associated with a vaginal discharge.
• Do not use for more than 7 days. If symptoms persist after this time, or return after discontinuing use of the product, consult a physician.
• Do not apply to the affected area more than 3 or 4 times daily.


Mefloquine

Brazil — In order to prevent, as far as is possible, the development of mefloquine-resistant strains of Plasmodium falciparum, the Division of Medicine of the National Health Secretariat has decided, in conformity with the recommendations of the WHO
Working Group on Chemotherapy of Malaria, to restrict the use of mefloquine as follows:

- purchase, distribution and use of medicinal products containing mefloquine have been placed under the direct control of the Ministry of Health;
- the indication for these products should state that use should be restricted to radical treatment of infections caused by multi-resistant *Plasmodium falciparum*;
- having regard to the lack of conclusive evidence on the safety and efficacy of mefloquine-containing products in pregnant women and in children, they are contraindicated during pregnancy (unless their use is regarded as imperative) and in children of less than two years of age.

Reference: Portaria No. 5 of 24 April 1986, sent under cover of letter to WHO from the Division of Medicines of the National Health Secretariat of Brazil dated 24 July 1986.

**Mianserin**

**United Kingdom** — The Licensing Authority has requested that the product information for pharmaceuticals containing the antidepressant mianserin (Bolvidon® Organon; Norval® Beecham) should include reference to the risk of bone marrow depression as follows:

“Bone marrow depression, usually presenting as granulocytopenia or agranulocytosis, has been reported. These reactions have occurred most commonly after 4-6 weeks of treatment. A full blood count is recommended every four weeks during the first three months of treatment. In addition, monitoring of the patient’s clinical condition should continue and if fever, sore throat, stomatitis or other signs of infection develop, treatment should be stopped and a full blood count obtained. These adverse reactions have been observed in all age groups but appear to be more common in the elderly.”


**Metformin**

**France** — The Minister of Health has decided that data sheets for products containing the oral antihyperglycaemic agent metformin should include a warning that their use is associated with severe lactic acidosis, and that the risk is of the order of 1 case in 40,000 treatment years.


**Nifedipine**

**Japan** — Having regard to reports of cases of gingival hyperplasia associated with the use of the antihypertensive calcium-channel blocking-agent nifedipine, the Pharmaceutical Affairs Bureau of the Ministry of Health and Welfare has recommended that the precautions contained in the product information be extended to include the following statement:

“Oral cavity: gingival hyperplasia may occur in patients receiving long-term treatment with nifedipine. In this event the drug should be discontinued.”


**Paracetamol**

**Chile** — The Institute of Public Health has decided that product information for pharmaceutical preparations containing paracetamol should include:

- advice that the dosage for children must be adapted to their age and that a doctor should be consulted if fever persists for more than two days when paracetamol is used in the treatment of febrile children;
- warnings that allergic reactions and hepatic damage are important adverse effects;
- a statement that these products are contraindicated in persons with hepatic or renal disease, and
• a caution that the duration of use should not exceed 10 days.


Phenacetin

Oman — The Ministry of Health has prohibited the import and marketing of products containing phenacetin as from 1 January 1987 having regard to their potential to cause hepatic and renal damage.


Spironolactone

United Kingdom — Because of concern regarding the possible carcinogenic risk associated with long-term use of spironolactone, the Committee on Safety of Medicines has decided that the indications for all spironolactone-containing products should be limited to:

• cirrhosis with ascites and oedema,
• malignant ascites,
• nephrotic syndrome,
• diagnosis and treatment of primary hyperaldosteronism, and
• congestive cardiac failure.

Reference: Telex from the Medicines Division, Department of Health and Social Security, 9 October 1986.

Sulpiride

Federal Republic of Germany — The Federal Health Office proposes to restrict the approved indications for products containing sulpiride to neurotic and exogenous depression that fails to respond to other antidepressants, and to acute and chronic schizophrenia in adults. It also proposes to amend the product information by deleting recommendations for paediatric use and by emphasizing that:

• the product is contraindicated in children and patients with prolactin-dependent tumours and mammary tumours;

• the maximum daily dose in schizophrenia should not exceed 100 mg.


Tartrazine

Egypt — The Drug Organization of the Ministry of Health has decided that products containing tartrazine as a colouring agent should bear a warning on the package insert that ingestion may evoke allergic reactions.


Other decisions

Egypt — The Egyptian Technical Committee for Drug Control has announced the following regulatory decisions:

• Domperidone (anti-emetic) - Injectable preparations containing domperidone have been withdrawn from the market following reports of cardiotoxicity, sometimes fatal. Other dosage forms will remain available.

• Buprenorphine (analgesic) - Preparations containing this substance will no longer be considered for registration to avoid the possibility of abuse.

• Etretinate - Preparations containing this substance will be available only for the treatment of hospitalized patients with acute psoriasis causing psychological disturbances. The approved product labelling must indicate that cardiac function should be monitored carefully before and during treatment and that blood lipids and blood coagulation indices should be estimated periodically, as the drug has occasionally been associated with myocardial ischaemia and infarction.

Regulatory Matters

The future of regulatory affairs in Europe

The first meeting of the Council for European Regulatory Affairs (CERA) was organized in Brussels on 14 and 15 October 1986 by the British Institute of Regulatory Affairs to promote communication between regulatory affairs personnel throughout Europe.

Professor P. Juul, Chairman of the Danish Regulatory Registration Committee, discussed the occasional difficulties faced by Denmark in trying to comply with approaches to harmonization both with the European Economic Community (EEC) and the Nordic Council. Differences of principle between the two groups of countries exist in several particulars, including attitudes towards fixed combination products, and the need for placebo-controlled clinical studies.

Professor D. Poggiolini, Director General, Pharmaceutical Department, Italian Ministry of Health, said that compliance with EEC directives had resulted in a substantial reduction in the number of pharmaceutical manufacturers in Italy as well as in the number of registered products.

Dr P. Klein, Head of the Registration Department within the Swiss Intercantonal Office for the Control of Medicines explained that the “Scheme for the Mutual Recognition of Evaluation Reports on Pharmaceutical Products” (PER Scheme) had been revised in June 1986 to provide for the use of an alternative reporting format developed within the European Economic Community (EEC). The PER Scheme, which is administered by the European Free Trade Association (EFTA) Secretariat in Geneva, continues to gain adherants, the latest country to join being the Federal Republic of Germany.

Pharmaceuticals in the European Community

The results of twenty years of working towards harmonization of pharmaceutical regulation in Europe have been reviewed by Fernand Sauer, Principal Administrator, Commission of the European Communities, Brussels, in Industrie Santé. The rules governing pharmaceuticals now comprise seven basic directives, one Council Recommendation and various other texts which apply to most newly-registered medicinal products, excluding immunological, blood and radioactive products, and homoeopathic medicines. By 1990 it is intended that each of these provisions will be applied to longer-established medicines.

In discussing the EEC Multistate Procedure for Drug Registration in Europe, the author concedes that only if a single body is created with powers to act for the Community as a whole, will discrepancies which still arise between national decisions be eliminated. However, support for a decentralized system remains strong within most Member States, among Members of the European Parliament and among representatives of the pharmaceutical industry.

Several initiatives taken by the Community are presented as having operated to the benefit of the biotechnology industry in Europe. These include the development of a four-year programme costing 55 million ECU (European Currency Unit, 1 ECU = approx. US$ 1.2) that embraces training, promotion of fundamental research, protection of biotechnological innovation, access to the necessary agricultural raw materials at world prices (particularly sugar and starch), and creation of a stable regulatory environment as a prerequisite to a large and unified European market.

Proposals for a variety of legislative measures have been submitted to the Council, including provision for prior consultation at Community level.

on applications relating to products derived from bioengineering and other high-technology processes. If adopted, these proposals would also require each Member State to notify the Commission of any draft national regulations affecting the manufacture, marketing or use of such products before their adoption in an attempt to obviate further fragmentation of domestic markets.

Other planned initiatives include:

- extension of the harmonization programme to include immunological products and substitutes for blood products by 1987;
- proposals on the transparency measures governing pricing and reimbursements of medicinal products; and
- harmonization of rules governing the information supplied by manufacturers to doctors and patients, and on the controls applied to the supply of prescription medicines to patients.


### Controlled studies not essential for “home medicines”

**United Kingdom** — The Committee on the Review of Medicines, which is evaluating all products marketed before the implementation of the 1968 Medicines Act, says in its annual report:

“The products awaiting review under the Medicines Act have been available for at least 15 years and many of them for much longer. Any major safety problems arising from their use would probably (though not definitely) have come to light by now. As to quality, the licensing authority and the Committee consider the ingredients and the manufacturing process very carefully to ensure that they comply with modern standards.

“The main problem with these medicines is to establish satisfactory criteria for judging efficacy. The distinction between claims for treating major and for treating minor conditions is central to our approach. The Committee has advised that when manufacturers claim for the treatment of major conditions the claims must be capable of substantiation by the results of clinical trials in the same way as would claims for new medicines. If, however, claims are restricted to the symptomatic relief of self-limiting conditions, the Committee has advised the licensing authority that it may be unreasonable to demand controlled trials.

“Nevertheless, the Committee does expect a pharmacological rationale and bibliographical evidence of efficacy. Many old products contain illogical combinations, and considerable modifications, often including the omission of unjustified ingredients, may be necessary before the Committee and the licensing authority will be satisfied. Herbal medicines are being dealt with the same way as orthodox medicines. Provided the claims are restricted to the relief of minor self-limiting conditions, bibliographical evidence may be acceptable. For herbal preparations, as for all products, concern over quality or safety may override otherwise acceptable indications for use and prevent the grant of a full licence.

“Self-medication plays a vital and growing role in health care as members of the public become better informed about their ailments and increasingly conscious of the need not to take up their doctor's time with self-limiting conditions.”


### Exports of unapproved drugs: new legislation

**United States of America** — Pharmaceutical and biological products may now be exported in precisely defined circumstances without necessarily having been approved for domestic use by the US Food and Drug Administration. Stringent criteria for the exportation of such pharmaceutical products are defined in the recently passed Drug Export Amendment Act of 1986. After applying to the federal government for permission, a manufacturer of an unapproved “new drug” or an
unlicensed biological product intended for human or animal use may export the product to another country recognized to possess a sophisticated health care regulatory system provided:

- the manufacturer is actively pursuing approval of the product in the United States;

- the receiving country has approved the importation of the product;

- the product was manufactured in the United States in accordance with officially approved standards of good manufacturing practices and is labelled for export, and

- the Secretary of Health and Human Services has determined that the manufacture of the drug for export is not contrary to the public health and safety of the United States.

The Secretary may revoke an application for export if either the manufacturer of the product no longer meets the criteria for approval or if the product is being trans-shipped to a country not on the approved list.

The Act lists 21 countries recognized as having a sophisticated drug regulatory system:

- Australia
- Austria
- Belgium
- Canada
- Denmark
- Federal Republic of Germany
- Finland
- France
- Iceland
- Ireland
- Italy
- Japan
- Luxembourg
- The Netherlands
- New Zealand
- Norway
- Portugal
- Spain
- Sweden
- Switzerland
- United Kingdom

The Secretary may add other countries to the list provided that their drug regulatory systems meet certain stringent criteria, as specified in the Act, to ensure that drugs used in their countries are safe and effective.

The Act also includes special provisions for the export of unapproved drugs (and biologicals) for the treatment or prevention of tropical diseases, provided the Secretary finds that the scientific evidence, including the clinical investigations, establish that the drug is safe and effective for use in the country to which it is to be exported.


Carcinogenicity studies

Ireland — The National Drugs Advisory Board requires the results of carcinogenicity studies to be included in marketing applications for new drugs in the following circumstances:

- If the drug substance bears a close chemical analogy to substances known to have carcinogenic or cocarcinogenic activity, or if it is a hormone or has hormonal effects.

- If the drug substance is likely to be used over long periods of time in man, either by continuous dosing or frequent intermittent use, particularly if it is likely to be administered regularly to infants, children, or pregnant women.

- If standard studies suggest that the drug substance is mutagenic, or affects the immune mechanisms.

- If evidence has emerged from other studies to suggest a potential carcinogenic effect.

- If evidence from other tests indicates that the drug or its metabolites are retained or sequestered for long periods in the body.

The Board acknowledges that many corticosteroids, in particular, were introduced long before the above requirements were formulated. To some extent their widespread use over this period has provided an epidemiological indication of freedom from carcinogenic potential. None the less many corticosteroids are known to interfere with immune responsiveness and to disturb endocrine equilibrium. The Board consequently requires carcinogenicity studies in all applications to market new products containing corticosteroids and it is
encouraging similar testing of all marketed cortico-steroid substances.


Mutual recognition of toxicological data

France and the United States of America have agreed to accept toxicological data generated in each other’s countries and submitted in support of applications for pharmaceutical products, provided the tests have been conducted in accordance with nationally-prescribed Good Laboratory Practices (GLP). This agreement will eliminate the need for costly, time-consuming repetition of toxicological tests and the number of laboratory animals required for these purposes.


Good Laboratory Practices

Italy — A Ministerial Decree issued on 26 June 1986 provides the regulatory basis for establishing Good Laboratory Practices in accordance with the recommendations of the Organization for Economic and Commercial Development (OECD). In order to assure the quality of the data included in marketing applications for pharmaceutical products, whether they are submitted to the Italian Ministry of Health or to foreign regulatory bodies, all toxicological tests performed in Italy are now required to conform to these regulations.

Reference: Gazzetta Ufficiale No. 76, Suplemento Ordinario, 27 August 1986, Rome, Italy.

Proprietary medicinal products

Nordic guidelines for evaluation reports

The Nordic Council on Medicines has issued guidelines on the compilation of Evaluation Reports on Proprietary Medicinal Products. Evaluation reports are used in national registration procedures in all Nordic countries. The guidelines were thus prepared to conform to the requirements of each of the national authorities within the region and, in particular, to provide a check-list to assist each national authority on whether a product should be approved — or not. The report should not exceed 15 pages and should provide:

- a summary of the product documentation,
- a commentary on the documentation prepared by the regulatory authority; and
- conclusions and recommended regulatory action.


Over-the-counter drug (OTC) review

A difficult and time-consuming process

United States of America — The OTC drug review process was initiated by the Food and Drug Administration in 1972. The aim was to complete a comprehensive review of the safety, efficacy and labelling of marketed OTC drug products in order to establish general conditions for the marketing of products in each therapeutic class that would provide assurance that they are safe, effective and “not misbranded”.

Originally estimated to be completed in three to five years, it is now apparent that the programme will not be fully completed until the mid-1990s. Although proposed monographs have been published for all 26 therapeutic categories, only one substantive final OTC monograph (for antacid products) has been issued to date. As each stage provides for an opportunity to submit additional data and comments, development of final monographs has proved to be a very difficult and time-consuming process.

Good Manufacturing Practices for medical devices

The Food and Drug Administration of the United States of America and the Department of Health and Social Security of the United Kingdom have signed an agreement to accept each other's inspection reports as providing formal evidence that manufacturers of medical devices have complied with Good Manufacturing Practices.

Reference: *FDA Consumer, 20:32 (1986).*

Sterility testing of parenteral drugs

Canada — The Health Protection Branch of the Ministry of Health and Welfare has recently issued new regulations for assuring the sterility of parenteral drugs. A representative sample of each lot of the drug taken from the final container must be found to be sterile when tested by an acceptable method, except:

- in the case of living vaccines, and
- where the manufacturer has submitted evidence to prove that processing controls ensure the sterility of the drug in its final container.


Approved veterinary drugs

United States of America

- A List of Approved Veterinary Drugs will shortly be published by the Food and Drug Administration providing, as a minimum, the following information:
  - Chemical name of primary active ingredient(s)
  - Trade name
  - Sponsor's name
  - New Drug Application (NDA) number
  - Availability (Rx or OTC)
  - Approval date
  - Species in which the product is approved for use.

- The Veterinary Drug Adverse Reaction Reporting Center is currently developing a computerized data file containing details of all notified adverse reaction reports. The Center solicits these reports within the context of its surveillance of animal drug performance under field conditions. All information that could be used to identify the source of these reports is held in strict confidence.


Mutual recognition of inspection certificates between Japan and the Federal Republic of Germany

A bilateral agreement has been signed by Japan and the Federal Republic of Germany that provides for the exchange of certificates of inspection of pharmaceutical manufacturing premises. The certificates will be written in English and endorsed by the competent regulatory authority. Circumstances are specified in which either side may request additional information.

All such inspections must conform to mutually acceptable standards and, in every case, the criteria established by the World Health Organization for Good Practices in the Manufacture and Quality Control of Pharmaceutical Products will apply.

A similar agreement has already been signed by the two countries concerning Good Laboratory Practice.

Labelling and advertising of new animal drugs

United States of America — The Federal Food, Drug and Cosmetic Act specifically prohibits a manufacturer of a drug intended for human use from using approval of the Food and Drug Administration (FDA) for promotional purposes. No similar prohibition applies to new animal drugs.

An FDA policy guide regarding the use of FDA approval statements in labelling and advertising of new animal drugs is now available which provides guidance to drug sponsors interested in voluntarily placing FDA approval information on labels or package inserts or in advertising and promotional material for approved drugs.


Generic drugs for animals

United States of America — The Drug Price Competition and Patent Term Restoration Act of 1984 authorized abbreviated premarketing approvals for generic versions of innovative drugs for human use approved after 1982, and restored a portion of the patent protection time lost due to premarketing requirements. Animal drugs were not included in this legislation.

Legislation referring to generic drugs for animal use has now been introduced in both the Senate and the House of Representatives. Both versions of the legislation would eliminate the necessity for full safety and effectiveness testing for generic versions of most post-1982 animal drugs. As with human drugs, the Food and Drug Administration would provide a list of products for which abbreviated new animal drug applications may be submitted.


Product liability and its implications for the practice of pharmacy and medicine

United Kingdom — The recent Directive of the European Economic Community (EEC) on Strict Product Liability states that if a product is defective, the producer shall be liable, except when:

- its provenance is unknown,
- the retailer has attached his own name or trademark or other distinguishing feature to the product, or
- it has been imported from outside into the European Community.

In these instances it is emphasized that the retailer or the importer will be liable without proof of negligence (2). Thus, whenever a product is dispensed in a container other than the original pack, the retailer might well be strictly liable for a defect rather than the manufacturer.

Under the Directive, the test of liability will be based upon "reasonable expectation" of the safety of the product when it was put into circulation. However, any evidence of negligence by the claimant will also be taken into account.

The principal defences to an action arising from a claim that a product is defective are as follows:

- Assumption of risk — A patient, having been given all relevant information, assumes the risk of taking the product. For instance, a patient who assumes the risk of baldness following chemotherapy for cancer would not be able to claim damages for a defect in this regard.

- Tampering — If the retailer, e.g. the pharmacist, tampered with the original product by covering or obliterating manufacturers' labels or warnings, or by removing the patient information leaflet, the liability of the retail supplier would be considerably increased.

If an individual is to assume the risk of using a medicinal product, he must be given the necessary information leaflets and warnings. Failure of the
pharmacist to provide these could create a legal liability.

In a commentary in the *British Medical Journal* (3) it is pointed out that many doctors could be affected by a Consumer Protection Bill now being introduced in the UK, in that:

- a doctor could become a producer if he mixes a preparation of his own or dilutes a liquid preparation or cream;

- a general practitioner is called upon from time to time to supply his patients with drugs, particularly in emergencies. As a supplier he will need to keep detailed records of the sources of supply of every drug he dispenses for at least 10 years. Drugs used in premarketing clinical trials are likely to be exempted from these requirements.

**References**


**Drug Regulatory Index**

The WHO Collaborating Centre for Drug Information and Quality Assurance in Budapest, Hungary, periodically issues the "Drug Regulatory Index".

This title has acquired a broad connotation since many different types of documents are covered, ranging from laws to explanatory leaflets that provide information on drug policy, drug registration or the drug control practices of individual countries.

The first issue of the Index (No. 1, 1984, as revised in 1985) dealt with clinical guidelines irrespective of their origin. The second issue (No. 2) was devoted to documents relating to drug regulation promulgated by international organizations.

Index No. 3, which is now published, lists documents issued by individual European countries.

**Reference**: Drug Regulation Index No. 3 - Documents issued by national agencies, 1986 - WHO Regional Office for Europe, Scherfigsvej 8, 2100 Copenhagen Ø, Denmark.
Advisory Notices

Pregnancy warnings in data sheets

United Kingdom — All officially-required drug data sheets must now include a statement about the safety of the product in pregnancy. Ideally the statement should summarize evidence from animal studies and experience in man. In practice, however, only the former is generally available since very few drugs have been proven to be human teratogens. These include thalidomide; cytotoxic drugs, particularly alkylating drugs and methotrexate; and retinoids (etretinate, isotretinoin).

The Committee on Safety of Medicines and the Committee on Review of Medicines consider that data sheets providing the following elements of information should enable a doctor to make a balanced assessment between the potential risks to the fetus and the benefits to the mother:

- Animal data — Any positive evidence of animal teratogenicity, embryotoxicity, or other adverse effects on reproductive behaviour, including the nature of the abnormality or risk, the animal species, and the timing and dose-relationships.

- Human experience — Factual statements on any human population studies and any anecdotal reports.

- Interpretation — While it is always appropriate to advise against the use of drugs in pregnancy unless there is an overriding clinical need, more specific advice should be given, both for use during pregnancy and in women of childbearing potential.

Three categories of products are specified:

- use during pregnancy is acceptable,
- use during pregnancy is advisable only if the disease itself carries significant risks for the mother or child,
- use is contraindicated during pregnancy.


Clinical evaluation of non-steroidal anti-inflammatory drugs

United States of America — The Food and Drug Administration has issued a revised draft Guideline for the Clinical Evaluation of Nonsteroidal Anti-inflammatory Drugs. The first edition, published in 1977, was concerned exclusively with nonsteroidal anti-inflammatory drugs (NSAIDs). In this edition additional guidelines are presented for disease modifying anti-rheumatic drugs (DMARDs) in adults and children.

Responsibility for updating this information lies with the FDA Arthritis Advisory Committee which approved the revised guidelines in May 1986.

In a separate statement it also discussed the use of dimethyl sulfoxide (DMSO) in scleroderma and it concluded that the available information did not provide adequate evidence of efficacy.


Allergen extracts and anaphylaxis

United Kingdom — The Committee on Safety of Medicines issued a letter to all doctors on 8 October 1986 informing them that severe anaphylactic reactions have occurred following treatment with desensitizing vaccines (allergen extracts).

Since 1957, in the UK alone, 26 patients are known to have died from anaphylaxis caused by these products. 11 of these patients, most of whom were young, have died within the past six years, 5 in the
last 18 months. In most of these cases adequate facilities for cardio-respiratory resuscitation were not available. The frequency of anaphylaxis, both fatal and non-fatal, may vary from 1 in 500 to 1 in 28,000 courses of treatment, according to the nature of the extract. Patients with asthma appear to be particularly susceptible.

It is important that doctors always carefully balance the known risks of desensitizing vaccines against their potential benefits. They should only be administered where facilities for full cardio-respiratory resuscitation are immediately available, and patients should be kept under medical observation for at least 2 hours after treatment.

Reference: Committee on Safety of Medicines, United Kingdom, letter to WHO dated 8 October 1986.

Sweden — The National Board of Health and Welfare has requested producers of all marketed allergen extracts to file registration applications. Extracts currently available may remain on the market until a final decision has been taken. However, having regard to recently reported adverse reactions, preparations derived from mites (Dermatophagoides pteronyssinus or D. farinae), moulds (Alternaria or Cladosporium) and certain animals (horse, dog, cat) may no longer be used except on special licence or within the framework of a clinical trial.


Adverse effects of anti-infective drugs

United Kingdom — The Committee on Safety of Medicines (CSM) has reviewed all reported adverse effects of anti-infective drugs notified between 1964 and 1985. These constitute about 19% of the 150,000 "yellow card" reports received during this period. The highest proportion (20%) relate to skin reactions. However blood dyscrasias of all types (including aplastic anaemia, agranulocytosis, and haemolytic anaemia) are also represented and these have been the subject of several warnings by the Committee.

- The penicillins account for the greatest single number of cases — 2,502, of which 54 were fatal. The majority of these reactions were rashes, associated principally with ampicillin and amoxycillin. Nearly 200 cases of diarrhoea were reported: 42 were diagnosed as pseudomembranous colitis (13 of them fatal) and 26 as colitis (4 fatal).

- Sulfonamides — The fact that only 322 adverse reactions were reported (11 fatal) is interpreted as offering evidence of substantial under-reporting.

- Cefalosporins — Thirteen different cefalosporins accounted for 788 cases (28 fatal), the most serious being 46 cases of pseudomembranous colitis, 12 of which were fatal. 65 reports (7 deaths) of haemorrhage and coagulation defects were attributed to latamoxef.

- Antituberculosis drugs prompted 799 reports (52 fatal cases). Blood dyscrasias accounted for 59 of these (6 fatal) and jaundice or hepatitis 161 (22 fatal). The latter were associated mainly with rifampicin and isoniazid. There were 58 reports of optic neuritis, most of them associated with ethambutol, and 42 of renal impairment or failure, usually following treatment with rifampicin (4 fatal).

- Aminoglycosides — Of the 299 reported reactions, 30 were associated with deafness, 16 with renal impairment (2 fatal), and 7 with pseudomembranous colitis (2 fatal).

- Metronidazole was implicated in 589 reports, 7 of them fatal (one case of anaphylaxis and two of blood dyscrasias). There were also 20 reports of neuropathy and 13 of paraesthesia.

- Antimalarial prophylaxis — Several reports received in the period 1984-1986 cited Maloprim®, Fansidar® and amodiaquine. Each of these drugs has been associated with agranulocytosis, and some cases have been fatal. Amodiaquine is no longer recommended for prophylaxis because of the frequency of this reaction. Fansidar® has also been associated with Stevens-Johnson syndrome and renal failure.
• Co-trimoxazole (trimethoprim and sulfadoxine) has been responsible for fatal aplastic anaemia more frequently in patients aged over 65 than in those under 40.


Anabolic steroids and athletic performance

United States of America — It has been estimated that athletes spend nearly $100 million annually to obtain anabolic steroids in an endeavour to enhance their athletic performance.

Numerous approved and unapproved drug products have been used for this purpose, most of which are obtained through illicit channels. They include ethylestrenol, fluoxymesterone, metandienone, various testosterone esters, oxandrolone and nandrolone esters. Such treatment carries substantial health risks and the Food and Drug Administration has asked manufacturers and distributors to assist in curbing unlawful diversion of supplies. It has also appealed to health professionals to report suspected improper use of these drugs.

Essential Drugs

“River blindness” affects 18 million people

Onchocerciasis or “river blindness”, which affects almost 18 million people, is most prevalent in tropical Africa, particularly along the rivers of the savanna south of the Sahara. The endemic area extends into the south-west Arabian peninsula and foci also exist in Central and South America.

The disease is caused by a filarial nematode, *Onchocerca volvulus*. Larval forms are transmitted when man is bitten by an infected blackfly (*Simulium damnosum* and related species). These mature into adult worms or “macrofilariae” over a period of one to two years, usually in subcutaneous tissue, where they form nodules.

The major symptoms of the disease, intense itching and progressive visual impairment, are caused by large numbers of migratory microfilariae shed by female worms. These lodge preferentially in the dermis where they may be picked up by the blackfly vectors and in the eye where they subsequently degenerate causing local inflammation and scarring.

Prevention

Control is primarily dependent upon the use of insecticides to reduce the vector population at their breeding sites and teaching the communities at risk how to avoid contact with the blackfly.

Aerial spraying with larvicial compounds, including temephos, chlorphoxim and permethrin has been effective in the savanna regions of the Volta River Basin and the campaign is being extended to other areas of West Africa. However, spraying is difficult in forested areas, and too costly to use in lesser endemic foci. In Guatemala, effective larvicial control of *S. ochraceum* is possible but more information on breeding habits of other *Simulium* vectors is needed before effective control measures can be devised in other parts of the Americas. Control of the vectors by the specific microbial larvicide, *Bacillus thuringiensis* H-14 holds promise if more effective formulations can be developed.

Essential drugs

The drugs now generally used to treat the disease, and which are currently featured in WHO’s Model List of Essential Drugs, are unsuited for mass chemotherapy.

Diethylcarbamazine is more active on the microfilariae while suramin destroys the macrofilariae, an action which is essential to the radical cure of the disease. The manifest deficiencies of these drugs are evident from model prescribing sheets recently prepared by WHO which are set out on the following pages.

However, new hope of a more effective and less toxic approach to the treatment of this disease has resulted from the development of new larvicidal compounds by Ciba Geigy in Switzerland and Merck, Sharp & Dohme in the United States of America. Prospects are now bright that a suitable preparation of the MSD compound, ivermectin (see p. 43), can be made available, at least for limited use, before the end of 1987.

Diethylcarbamazine

tablet 50 mg (citrate)

A larvicidal piperazine derivative which is readily absorbed following oral administration and is widely distributed in non-fatty tissues. It is excreted, largely as urinary metabolites, within 48 hours. In onchocerciasis, it is effective only against microfilariae. However, in lymphatic filariasis and loiasis,
it kills both the microfilariae and adult worms.

**Uses**

As a microfilaricide in onchocerciasis, diethylcarbamazine is used:

- in *curative treatment* at low initial doses under steroid cover before and after the macrofilaricide, suramin, initially to reduce the microfilarial load and, subsequently, to kill residual microfilariae; and

- in *suppressive treatment* at intermittent low dosage, to preserve sight and relieve pruritus by reducing the microfilarial load.

**Dosage**

**Curative treatment**

*Prior to suramin therapy in heavily infected patients:*

- 25 mg initially, doubled on successive days to 100 mg twice daily on day 4. Then 200 mg (4-5 mg/kg) in two divided doses for 5-7 days until the microfilarial load in the skin approaches zero;

- a course of dexamethasone 80 µg/kg daily is started two days before the first dose of diethylcarbamazine to prevent a severe reaction resulting from the death of microfilariae (Mazzotti reaction). This dosage should be maintained for 5 days before gradual withdrawal is attempted.

*After suramin therapy:*

- 200 mg daily for three days, repeated monthly, until no Mazzotti reaction occurs. Steroid cover and low initial dosage are rarely necessary in patients pretreated with diethylcarbamazine.

**Suppressive treatment**

- 50-200 mg given each month in a single dose following a full course of treatment may keep skin and eyes virtually clear of microfilariae despite the presence of many fertile female worms. Periodic ophthalmic examinations are essential.

**Contraindications and precautions**

The drug should always be given under medical supervision and systemic corticosteroids should only be administered in a hospital or a special treatment centre.

- Pregnant women should not be treated until after delivery.

- Patients with malaria should first receive a course of antimalarial therapy since diethylcarbamazine may provoke a severe attack.

- Pulmonary tuberculosis and other contraindications to steroid therapy must be excluded or treated before dexamethasone or other corticosteroids are administered.

**Adverse effects**

The Mazzotti reaction, which most patients experience following their first dose of diethylcarbamazine, results from the death of microfilariae. Its intensity depends upon the dose and the microfilarial load. Less severe reactions are confined to the skin, but severe ophthalmic and systemic effects can occur.

**Cutaneous component:**

- An intensely irritant urtico-papular rash develops 1-24 hours after administration.

* Depending on the distribution of microfilariae this may be confined to one limb or cover the whole body.

* Regional lymph nodes become swollen and tender.

**Ophthalmic complications:**

- If microfilariae are present in the conjunctiva, cornea or anterior chamber of the eye, lachrymation, photophobia, conjunctivitis and acute iridocyclitis occur.
Symptomatic treatment may be necessary to prevent formation of synechiae.

Prolonged administration of diethylcarbamazine may result in inflammatory and subsequent degenerative changes in the optic disc and retina, which classically cause peripheral field loss, tunnel vision and night-blindness.

**Systemic component:**

- Postural hypotension, collapse, respiratory distress, vertigo, fever, joint pains, muscular aches and headache may occur.

- These effects can be severe and may persist for several days.

**Overdosage**

Adverse dose-related effects, including nausea, vomiting, headache, dizziness and drowsiness, occur only when the daily dose exceeds 30 mg/kg.

**Storage**

Store in tightly closed containers.

**Note on other microfilaricides:** Other drugs with microfilaricidal activity include metrifonate, mebendazole, and levamisole. All are less effective than diethylcarbamazine. However, evidence from ongoing clinical studies indicates that a single dose of ivermectin (see p. 43) kills microfilariae gradually without evoking a severe Mazzotti reaction and that a low microfilarial density is maintained for at least 12 months.

**Suramin sodium**

powder for injection 1 g vial

Suramin in adequate doses kills the adult worms responsible for onchocerciasis. Microfilariae are somewhat more resistant.

Because it forms stable complexes with protein, suramin must be administered intravenously. It enters the extracellular space but does not penetrate into the CSF.

It dissociates slowly from plasma proteins and is detectable unchanged in the urine for up to three months after the last dose.

**Uses**

As a macrofilaricide in the *curative treatment* of severe onchocerciasis. In heavily infected patients suramin is better tolerated if it is preceded by an oral course of diethylcarbamazine to reduce the microfilarial load. Subsequently, further short courses of diethylcarbamazine may be needed to kill residual microfilariae.

**Dosage**

Suramin is administered by slow intravenous injection of a 10% aqueous solution.

A total of 66.7 mg/kg is administered in six successive increasing weekly doses apportioned as follows:

<table>
<thead>
<tr>
<th>Week</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mg/kg</td>
<td>3.3</td>
<td>6.7</td>
<td>10.0</td>
<td>13.3</td>
<td>16.7</td>
<td>16.7</td>
</tr>
</tbody>
</table>

**Precautions for the first injection** (0.2 g in 2 ml water for a 60 kg adult): because collapse has occasionally occurred, this should be administered with particular caution:

- Wait at least one minute after injecting the first few µl.
- Inject the next 0.5 ml over 30 seconds and wait one minute.
- Inject the remainder over several minutes.
Contraindications and precautions

Suramin is an extremely toxic drug. It should always be given under medical supervision. To avoid unacceptable toxicity in heavily infected patients at risk of reinfection, it is often preferable to reduce the parasite load with diethylcarbamazine rather than to attempt a radical cure.

The general condition of the patient should first be improved as far as possible and a satisfactory food and fluid intake maintained throughout treatment. Treatment should be discontinued immediately in patients who develop serious adverse effects including heavy albuminuria with casts.

Suramin should not be administered to:

- old or infirm individuals or patients with severe hepatic or renal disease who may not be strong enough to withstand its effects;
- totally blind patients, unless they require relief from intensely irritant skin lesions;
- lightly to moderately-infected subjects who have no symptoms and whose eyes are not at risk; and
- pregnant women who should be treated after delivery.

Adverse effects

Adverse effects result either from the innate toxicity of the drug or its filaricidal action.

Direct toxic effects

- Toxic effects that call for immediate withdrawal of treatment include rare cases of potentially fatal collapse during the first injection, heavy albuminuria, stomal ulceration, exfoliative dermatitis, severe diarrhoea, prolonged high fever and prostration.
- Less severe symptoms, which are common, include tiredness, anorexia, malaise, polyuria, increased thirst and tenderness of the palms and soles.

Indirect reactions attributable to the death of the parasites include:

- urticaria, swelling, tenderness and abscess formation around adult worms;
- painful immobilization of the hip resulting from an inflammatory reaction around worm bundles against the joint capsule;
- an intensely irritant urtico-papular rash associated with death of microfilariae;
- inflammatory and subsequent degenerative changes in the optic nerve and retina resulting from the death of intraocular microfilariae; and
- swollen painful joints, particularly in the hands and feet, possibly due to the formation of immune complexes.

Storage

Store in well-closed containers protected from light.

Note on other macrofilaricides: Suramin is the only drug in routine use. Another compound, CGP 6140, is now at an early stage of clinical evaluation.

Accelerated stability studies under simulated tropical conditions

Many pharmaceutical substances are known to deteriorate during distribution and storage, particularly in the hot, humid climates that prevail in many developing countries. The World Health Organization has commissioned a systematic survey of the stability of many widely used substances contained within its Model List of Essential Drugs and has developed simplified tests to detect or exclude gross degradation of the least
stable substances. As well as providing information on stability this report provides detailed information on which substances are degradable and which are resistant to degradation.


Sensitivity of *Plasmodium falciparum* to quinine and mefloquine in Thailand

Thailand — Between 1982 and 1984 a regimen of quinine and tetracycline was routinely used in Thailand to treat outpatients with microscopically confirmed falciparum malaria. Due in part to inadequate compliance with the 7-day multiple-dose regimen, the recrudescence rate was as high as 30%. Epidemiologically-based studies undertaken in four areas of Thailand also indicated that the sensitivity of *P. falciparum* to quinine was decreasing significantly with time. A less marked reduction in sensitivity to the structurally-related drug mefloquine was also detected. These findings emphasize the urgent need for an effective, acceptable, single-dose treatment for falciparum malaria.


Nigeria adopts an essential drugs list

Nigeria — The Federal Minister of Health, Prof. Olikoye Ransome-Kuti, announced at a meeting held in Lagos in December 1986 that the country has adopted an Essential Drugs List (EDL). The list, which is adapted from the WHO model list, comprises 205 essential drugs. Only listed drugs will be used in government hospitals and other institutions and it is anticipated that this will both rationalize prescribing and at the same time eliminate ineffective, overpriced, unsafe medicines and irrational combinations.

The editor of the *Pharmacy World*, Ifeanyi Atueyi, says that since these drugs will be identified only by their generic names, some resentment will be evoked in drug manufacturers who are implicitly required to “trail the simple and common path towards primary health care goals”. He anticipates that the change to generic prescribing will lower drug costs because investment in brand name promotion will be reduced and because prices of products sold under the same generic name will be more responsive to market forces.

The author also acknowledges that experience in other countries has shown that manufacturers invariably resist the introduction of essential drugs lists and that, in some instances, they have attempted to undermine governmental efforts through litigation. He expresses confidence, however, that any adverse financial effect this decision may have on private industry will be more than compensated by the advantages of the Essential Drugs List to the nation.

Lastly, he expresses the hope that manufacturers will demonstrate social conscience by voluntarily withdrawing any hazardous and irrational drugs from the market and by directing their efforts to respond to health needs.

The introduction of the Essential Drugs List calls for understanding and committed cooperation from the pharmaceutical industry and, not least, strong political will on the part of the government.

Sudan’s new drug policy and essential drugs list

Sudan — The national health authorities, with the assistance of the World Health Organization and the United Nations Industrial Development Organization, have formulated both a national drug policy and a list of essential drugs. The list, which was first published in 1983, and is currently being revised, contains about 400 active substances and 600 dosage forms.

It is claimed that since the list came into use shortages of essential drugs have been fewer and less severe and that the selection, procurement, management, distribution, registration and control of drugs has become more efficient. Another less predictable consequence of the policy is that the contribution of the indigenous drug industry to total sales has increased from 5% to about 20%. The list has apparently left the country’s manufacturers in no doubt about the types and quantities of drugs that are principally needed.

Recent Publications

Essential malarialiology

**United Kingdom** — The second edition of this book by Leonard Jan Bruce-Chwatt is more broadly-based than the first. The world's malaria situation has deteriorated in recent years. Because of adverse social and economic conditions many developing countries have been unable to implement an effective strategy for malaria control (which is now accepted as a more realistic objective than malaria eradication).

Some 1600 million people throughout the world remain exposed to considerable risk of infection. The message is emphasized that any country that institutes a malaria control campaign must organize it as a component of its primary health care system, keeping in mind the need for a nucleus of specialized professional expertise.

In addition to providing a scientific account of recent advances in the parasitology, entomology, epidemiology and immunology of malaria, the new edition contains a detailed description of prevention, diagnosis, treatment and control of malaria in both developing and developed countries.

The text and illustrations are so clearly presented that the book serves not only as a standard work for malarialologists but also as an effective primer in the subject for all health personnel.


Treatment of cardiac tachyarrhythmias

The Swedish Drug Information Committee has recently reviewed the treatment of tachyarrhythmias. It advises that in *paroxysmal supraventricular tachycardia*, vagal stimulation should be tried first; if the tachycardia continues, verapamil in doses of 5 mg to a total of 50 mg should be administered intravenously under close ECG- and blood surveillance. In *atrial flutter and fibrillation*, electroconversion should be considered in cases of fibrillation/flutter of no more than a few days' standing. Digitalis remains the treatment of first choice to normalize ventricular rates in patients with chronic atrial fibrillation/flutter. Prophylactic treatment with quinidine may be used to maintain rhythm following electroconversion. In *ventricular tachycardia and fibrillation* that has persisted for more than 30 seconds, immediate defibrillation is indicated. Failing this, lidocaine is the drug of choice.


Medicinal products for use in self-medication

The WHO Regional Office for Europe has issued guidelines for the assessment of medicinal products used in self-medication. The term "assessment" is used rather than "clinical evaluation" since the guidelines are concerned with the review of existing data and experience rather than the generation of new data through clinical investigation, though the latter may on occasion be necessary. The document is not intended as a basis for regulation, nor is it intended to set an administrative or legal standard. It is hoped that it will promote research, constructive discussion and the development of a more rational approach to the principle of self-medication.

Reference: *Guidelines for the Assessment of Medicinal Products for Use in Self-Medication*, World Health Organization Regional Office for Europe, Copenhagen, Denmark.
Drugs in hospitals

The WHO Regional Office for Europe has issued the report of the 14th European Symposium on Clinical Pharmacological Evaluation in Drug Control held in November 1985. The introduction discusses general aspects of drug use in hospitals and the body of the report describes the objectives of hospital drug and formulary committees, reviews the problems of drug supply in hospitals and analyses the relationship of hospital drug therapy to general practice.


Pharmaceutical regulation in Italy

Italy — A book in English entitled "Pharmaceutical Regulatory Activities in Italy" and edited by Duilio Poggiolini, Director-General of the Pharmaceutical Department of the Ministry of Health, provides a comprehensive overview of the drug regulatory process. Information is included on economic aspects of pharmaceutical production in Italy as well as details of current requirements for drug registration. Space is also devoted to international activities, particularly within the EEC.


A handbook of pharmaceutical excipients

The Pharmaceutical Society of Great Britain and the American Pharmaceutical Association have issued a joint publication on pharmaceutical excipients. It is widely assumed that excipients are inert substances, but they can, on occasion, interfere with active ingredients in drug dosage forms. Preformulation studies always need to be undertaken to identify potential interactions, both chemical and physical, and to ensure appropriate selection of excipients.

The handbook, which has taken 11 years to produce, involves 200 contributors and contains 148 monographs on the most commonly used excipients in pharmaceutical formulations.


Drug information for the health care provider

United States of America — The 6th edition of this two-volume series has recently been published by the United States Pharmacopeial Convention.

Volume I provides drug information for doctors, pharmacists, nurses and other health care personnel. Each drug or drug combination is presented as a monograph which includes concise sections on pharmacological properties, clinical indications, chemistry, pharmacokinetics, precautions, adverse effects as well as information on dosage and dosage forms. It is supplemented regularly as part of a continuing subscription service.

Volume II contains a parallel series of monographs which are intended to provide answers to patients' concerns about the medicines they are receiving.


Pharmaceutical administration in Japan

The 3rd Edition of Pharmaceutical Administration in Japan has just been published under the aegis of the Pharmaceutical Affairs Bureau, Ministry of Health and Welfare. In particular, it provides, both in English and Japanese, information on the whole
range of governmental pharmaceutical services. In particular it describes the mechanisms of pharmaceutical administration, the Pharmaceutical Affairs Law, the procedure for approval of drugs and related products, and other activities aimed at ensuring drug safety and for providing compensation to drug-induced injury. Many tables and charts are included in the book.


Treatment of sexually transmitted diseases

Sweden — The Drug Information Committee of the National Board of Health and Welfare publishes, from time to time, comprehensive “state-of-the-art” reviews on the therapeutic management of specific diseases. The latest booklet in this series reviews the treatment of sexually transmitted diseases and particularly of infections caused by the gonococcus, Chlamydia trachomatis, herpes simplex virus and human papilloma viruses as well as non-specific bacterial genital infections.


Cancer pain relief

A “three-step ladder” approach to treatment of cancer pain has been proposed in a booklet published by the World Health Organization. It is based upon the sequential use of increasingly potent oral analgesics ranging from non-opioids (paracetamol and acetylsalicylic acid) to mild (codeine) and then strong (morphine) opioids with the aim of keeping the patient free from pain.

It is emphasized that analgesics need to be given every four to six hours, and not “as required”. The practicability of this approach has been demonstrated in studies carried out in both Japan and Italy. The booklet includes sections on the comprehensive management of cancer pain, education and training of health personnel, legal considerations and the abuse potential of analgesics.


Human experimentation: legal and ethical aspects

United States of America — Alexander M. Capron of the Law Center, University of Southern California, has undertaken a comprehensive review of the legal and ethical aspects of human experimentation. His book begins with an examination of terminology and presents a justification for research using human subjects. It provides an historical survey of major developments and concludes with a description of the system now in use in the United States. The final section explores a number of currently relevant ethical and social issues including specific problems in surgical experimentation; the degree to which commercial pressures contribute to the demand for comparative drug testing; problems in social and psychological studies; difficulties in performing potentially valuable but intrinsically risky experiments; and the barriers to conducting research on vulnerable subjects, including children and the unborn.


Drug consumption in Norway

Norway — The Norwegian Medicinal Depot has published its sixth yearbook which provides information on drug consumption in Norway from 1981 to 1985. An original feature of this publication is the inclusion of commentaries on the statistical material which focus on issues of current therapeutic importance.

Reference: The Drug Consumption in Norway 1981-1985, Norwegian Medicinal Depot, P. O. Box 100, Veitvet, 0518 Oslo 5, Norway.
Drug information bulletin from Chile

Chile — The Drug Control Department of the National Institute of Public Health publishes a drug information bulletin on a regular basis that includes updates on approved information sheets for selected drugs. The July 1986 issue features amiodarone, domperidone and interferon. Another section, which is intended to maintain doctors' awareness of drug-related risks and to engage their collaboration in reporting them, deals with the monitoring of adverse reactions to drugs.

Reference: **Boletin Informativo sobre Medicamentos,** Departamento Control Nacional, Ministerio de Salud Pública de Chile, Avda. Marathon N° 1000, Santiago, Chile.

A magazine for physicians and pharmacists from the German Democratic Republic

German Democratic Republic — A quarterly magazine entitled *Medicamentum* and published by the national health authority in English, French, Spanish and Russian is distributed free of charge. No. 77, 1986, contains reviews on new non-glycoside cardiotonic substances, hormonal contraception, the efficacy of carbamazepine and a listing of new drugs developed within the pharmaceutical industry of the GDR.

Reference: **Medicamentum,** Glienicker Weg 125/127, 1199 Berlin-Adlershof, German Democratic Republic.

An international society of editors of drug bulletins

India — In the latest issue of its *Drugs Bulletin* the Department of Pharmacology of the Postgraduate Institute of Medical Education and Research in Chandigarh provides a commentary on the first meeting of Editors of Drug Bulletins held in Madrid in May, 1985 at which the International Society of Drug Bulletins was inaugurated. The establishment of the Society is regarded as an important milestone in the dissemination of independent information on drugs especially in developing countries — which are in greatest need of such services — and in the promotion of rational and economic use of drugs.

Reference: **Drugs Bulletin,** Vol. 9, No. 4, Department of Pharmacology, Postgraduate Institute of Medical Education and Research, Chandigarh, India.
International Nonproprietary Names for Pharmaceutical Substances

In accordance with article 5 of the Procedure for the Selection of Recommended International Nonproprietary Names for Pharmaceutical Substances, notice is hereby given that the following names are under consideration by the World Health Organization as Proposed International Nonproprietary Names.

Comments on, or formal objections to, the proposed names may be forwarded by any person to the Pharmaceuticals unit of the World Health Organization within four months of the date of their publication in WHO Drug Information, e.g., for List 57 Prop. INN not later than 31 October 1987.

Proposed International Nonproprietary Names (Prop. INN): List 57

<table>
<thead>
<tr>
<th>Proposed International Nonproprietary Name (Latin, English)</th>
<th>Chemical Name or Description, Molecular and Graphic Formulae</th>
<th>Chemical Abstracts Service (CAS) registry number</th>
</tr>
</thead>
<tbody>
<tr>
<td>adibendanum</td>
<td>5,7-dihydro-7,7-dimethyl-2-(4-pyridyl)pyrrolo[2,3-f]benzimidazol-6(3H)-one</td>
<td>100510-33-6</td>
</tr>
<tr>
<td>adibendan</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The inclusion of a name in the lists of proposed international nonproprietary names does not imply any recommendation for the use of the substance in medicine or pharmacy.

Comprehensive information on the INN programme can be found in: WHO Technical Report Series, No. 581, 1975 (Nonproprietary Names for Pharmaceutical Substances. Twentieth Report of the WHO Expert Committee), ISBN 92 4 120581 4 (price: Sw. fr. 6.–); an account of this publication will be found in Annex 2 of the present List. All names from Lists 1-47 of Proposed International Nonproprietary Names, together with a molecular formula index, will be found in International Nonproprietary Names (INN) for Pharmaceutical Substances. Cumulative List No. 6, 1982, World Health Organization, Geneva (ISBN 92 4 056013 0) (price: Sw. fr. 55.–). This publication consists, in the main, of a computer printout which groups together all the proposed and recommended international nonproprietary names (INN)—in Latin, English, French, Russian, and Spanish—published up to April 1982. The printout also indicates in which of the 47 individual lists of proposed names and 21 lists of recommended names each INN was originally published, and gives references to national nonproprietary names, pharmacopoeia monographs, and other sources. In addition, the list contains molecular formulae and Chemical Abstracts Service registry numbers. For easy reference, national nonproprietary names that differ from INN molecular formulae, and Chemical Abstracts Service registry numbers are indexed in a series of annexes. A final annex describes the procedure for selecting recommended INN and outlines the general principles to be followed in devising these names. All the textual material published in this volume appears in both English and French.

These publications may be obtained, direct or through booksellers, from the sales agents listed on the back cover of WHO Drug Information. Orders from countries where sales agents have not yet been appointed may be addressed to: World Health Organization, Distribution and Sales Service, 1211 Geneva 27, Switzerland.

1 See Annex 1.
2 Other lists of proposed and recommended international nonproprietary names can be found in Cumulative List No. 6, 1982.
Proposed International Nonproprietary Name
Chemical Name or Description, Molecular and Graphic Formulae
Chemical Abstracts Service (CAS) registry number

aloxistatinum
aloxistatin

ethyl (+)-(2S,3S)-2,3-epoxy-N-[(S)-1-(isopentylcarbamoyl)-3-methylbutyl]succinamate
C_{17}H_{30}N_{2}O_{5} 88321-09-9

anaritidum
anaritide

C_{112}H_{175}N_{39}O_{35}S_{3} 95896-08-5

argatrobanum
argatroban

(2R,4R)-4-methyl-1-[(S)-N^{2}-[(RS)-1,2,3,4-tetrahydro-3-methyl-8-quinolyl]-sultonyl]arginyl]pipecolic acid
C_{23}H_{36}N_{6}O_{5}S 74863-84-6

bemarinonum
bemarinone

5,6-dimethoxy-4-methyl-2(1H)-quinazolinone
C_{11}H_{12}N_{2}O_{3} 92210-43-0
benexatum
benexate

benzyl salicylate; trans-4-(guanidinomethyl)cyclohexanecarboxylate
$C_{23}H_{24}N_4O_4$ 78718-52-2

beperidii iodidum
beperidium iodide
cis-1-ethyl-4-hydroxy-1-methylpiperidinium iodide
$C_{23}H_{34}IN_3O_3$ 86434-57-3

bermoprofenum
bermoprofen
$(\pm)$-10,11-dihydro-$\alpha$,8-dimethyl-11-oxodibenz[b,f]oxepin-2-acetic acid
$C_{18}H_{16}O_4$ 72619-34-2

bifeprofenum
bifeprofen
$(\pm)$-2$'$-chloro-$\alpha$-methyl-4-biphenylacetic acid, ester with 1-glycoloyl-$4$-$\alpha$-methylpiperazine
$C_{22}H_{25}ClIN_2O_3$ 108210-73-7

bisfentidinum
bisfentidine
$N$-isopropyl-$N'$-[p-(2-methylimidazol-4-yl)phenyl]formamidine
$C_{14}H_{16}N_4$ 96153-56-9
Proposed International Nonproprietary Name (Latin, English)
Chemical Name or Description, Molecular and Graphic Formulae
Chemical Abstracts Service (CAS) registry number

**Proposed International Nonproprietary Name**

<table>
<thead>
<tr>
<th>Chemical Name or Description</th>
<th>Molecular and Graphic Formulae</th>
<th>Chemical Abstracts Service (CAS) registry number</th>
</tr>
</thead>
<tbody>
<tr>
<td>cefepimum</td>
<td>1-[(6R,7R)-7-2-(2-amino-4-thiazolyl)glyoxylamido]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl-1-methylpyrrolidinium hydroxide, inner salt, 7(^{2})-(Z)-(O-methyloxime)</td>
<td>C(<em>{19})H(</em>{24})N(_{6})O(_5)S(_2) 88040-23-7</td>
</tr>
<tr>
<td>cefepime</td>
<td></td>
<td></td>
</tr>
<tr>
<td>cefempidium chloride</td>
<td></td>
<td></td>
</tr>
<tr>
<td>celpodoximum</td>
<td>(±)-1-hydroxyethyl (±)-(6R,7R)-7-2-(2-amino-4-thiazolyl)glyoxylamido]-3-(methoxymethyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate, 7(^{2})-(Z)-(O-methyloxime), isopropyl carbonate (ester)</td>
<td>C(<em>{21})H(</em>{27})N(_5)O(_9)S(_2) 87239-81-4</td>
</tr>
<tr>
<td>celpodoxime</td>
<td></td>
<td></td>
</tr>
<tr>
<td>clopidogrelum</td>
<td>methyl (±)-α-(o-chlorophenyl)-6,7-dihydrothieno[3,2-c]pyridine-5(4H)-acetate</td>
<td>C(<em>{16})H(</em>{16})CINO(_2)S 94188-84-8</td>
</tr>
<tr>
<td>clopidogrel</td>
<td></td>
<td></td>
</tr>
<tr>
<td>daltrobanum</td>
<td>[p-(2-(p-chlorobenzesulfonyl)ethyl]phenyl]acetic acid</td>
<td>C(<em>{18})H(</em>{16})CINO(_2)S 79094-20-5</td>
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<tr>
<td>daltroban</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Proposed International Nonproprietary Name (Latin, English)</th>
<th>Chemical Name or Description, Molecular and Graphic Formulae</th>
<th>Chemical Abstracts Service (CAS) registry number</th>
</tr>
</thead>
<tbody>
<tr>
<td>datelliptii chloridum</td>
<td>2-[2-(diethylamino)ethyl]-9-hydroxy-5,11-dimethyl-6H-pyrido[4,3-b]-carbazolium chloride</td>
<td>C$<em>{23}$H$</em>{28}$ClN$<em>3$O$</em>{10}$ 105118-14-7</td>
</tr>
<tr>
<td>datellium chloride</td>
<td>2-[2-(diethylamino)ethyl]-9-hydroxy-5,11-dimethyl-6H-pyrido[4,3-b]-carbazolium chloride</td>
<td>C$<em>{23}$H$</em>{28}$ClN$<em>3$O$</em>{10}$ 105118-14-7</td>
</tr>
<tr>
<td>dexamethasoni acefuras</td>
<td>9-fluoro-11ß,17,21-trihydroxy-16a-methylpregna-1,4-diene-3,20-dione 21-acetate 17-(2-fluorate)</td>
<td>C$<em>{29}$H$</em>{33}$FO$_8$ 83880-70-0</td>
</tr>
<tr>
<td>dexamethasone acefurate</td>
<td>9-fluoro-11ß,17,21-trihydroxy-16a-methylpregna-1,4-diene-3,20-dione 21-acetate 17-(2-fluorate)</td>
<td>C$<em>{29}$H$</em>{33}$FO$_8$ 83880-70-0</td>
</tr>
<tr>
<td>dobuturidum</td>
<td>4-amino-2-butoxy-5-chloro-N-[1-(1,3-dioxolan-2-ylmethyl)-4-piperidyl]benzamide</td>
<td>C$<em>{20}$H$</em>{30}$ClN$_3$O$_4$ 106707-51-1</td>
</tr>
<tr>
<td>dobutride</td>
<td>4-amino-2-butoxy-5-chloro-N-[1-(1,3-dioxolan-2-ylmethyl)-4-piperidyl]benzamide</td>
<td>C$<em>{20}$H$</em>{30}$ClN$_3$O$_4$ 106707-51-1</td>
</tr>
<tr>
<td>dramedilotum</td>
<td>acetone (±)-[6-[(3,4-dimethoxyphenethyl)amino]-2-hydroxypropoxy]-3-pyridazinylhydrazone</td>
<td>C$<em>{20}$H$</em>{26}$N$_4$O$_4$ 76953-65-6</td>
</tr>
<tr>
<td>dramedilot</td>
<td>acetone (±)-[6-[(3,4-dimethoxyphenethyl)amino]-2-hydroxypropoxy]-3-pyridazinylhydrazone</td>
<td>C$<em>{20}$H$</em>{26}$N$_4$O$_4$ 76953-65-6</td>
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<tr>
<td>droxidopa</td>
<td>(-)-threo-3-(3,4-dihydroxyphenyl)-1-serine</td>
<td>C$<em>{9}$H$</em>{11}$NO$_5$ 23651-95-8</td>
</tr>
<tr>
<td>droxidopa</td>
<td>(-)-threo-3-(3,4-dihydroxyphenyl)-1-serine</td>
<td>C$<em>{9}$H$</em>{11}$NO$_5$ 23651-95-8</td>
</tr>
<tr>
<td>Proposed International Nonproprietary Name (Latin, English)</td>
<td>Chemical Name or Description, Molecular and Graphic Formulae</td>
<td>Chemical Abstracts Service (CAS) registry number</td>
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<td>------------------------------------------------------------</td>
<td>----------------------------------------------------------</td>
<td>-----------------------------------------------</td>
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<tr>
<td>ebrotidine</td>
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<td></td>
</tr>
<tr>
<td>eltoprazinum</td>
<td>1-(1,4-benzodioxan-5-yl)piperazine</td>
<td>98224-03-4</td>
</tr>
<tr>
<td>eltoprazone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>elziverinum</td>
<td>6,7-dimethoxy-4-[[4-(o-methoxyphenyl)-1-piperazinyl]methyl]-1-veratrylisoquinoline</td>
<td>95520-81-3</td>
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<tr>
<td>elziverine</td>
<td></td>
<td></td>
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<tr>
<td>eprovafenum</td>
<td>5-(3-phenylpropyl)-2-thiophenevaleric acid</td>
<td>101335-99-3</td>
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<tr>
<td>eprovaten</td>
<td></td>
<td></td>
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<tr>
<td>epsiprantelum</td>
<td>(+)-2-(cyclohexylcarbonyl)-2,3,6,7,8,12b-hexahydropyrazino[2,1-a][2]benzazepin-4(1H)-one</td>
<td>98123-83-2</td>
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<tr>
<td>epsiprantel</td>
<td></td>
<td></td>
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<tr>
<td>Proposed International Nonproprietary Name (Latin, English)</td>
<td>Chemical Name or Description, Molecular and Graphic Formulae</td>
<td>Chemical Abstracts Service (CAS) registry number</td>
</tr>
<tr>
<td>-----------------------------------------------------------</td>
<td>-------------------------------------------------------------</td>
<td>------------------------------------------------</td>
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<tr>
<td>etanidazolum</td>
<td>N-(2-hydroxyethyl)-2-nitroimidazole-1-acetamide</td>
<td>22668-01-5</td>
</tr>
<tr>
<td>etanidazole</td>
<td></td>
<td></td>
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<tr>
<td>etofenproxum</td>
<td>α-[(p-ethoxy-β,β-dimethylphenethyl)oxy]-m-phenoxyltoluene</td>
<td>80844-07-1</td>
</tr>
<tr>
<td>etofenprox</td>
<td></td>
<td></td>
</tr>
<tr>
<td>exametazimum</td>
<td>(±)-(3RS, 3′RS)-3,3′-[(2,2-dimethyltrimethylene)diimino]di-2-butanone dioxime</td>
<td>105613-48-7</td>
</tr>
<tr>
<td>exametazime</td>
<td></td>
<td></td>
</tr>
<tr>
<td>fotemustine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>guaisteinum</td>
<td>thioacetic acid, S-ester with (±)-3-(mercaptoacetyl)-2-[(o-methoxyphenoxy)methyl]thiazolidine</td>
<td>103181-72-2</td>
</tr>
<tr>
<td>guaisteine</td>
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<td></td>
</tr>
</tbody>
</table>

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Proposed International Nonproprietary Name (Latin, English)

Chemical Name or Description, Molecular and Graphic Formulae

Chemical Abstracts Service (CAS) registry number

ibacitabinum
ibacitabine

2'-deoxy-5-iodocytidine
C₉H₁₄IN₃O₄  611-53-0

indolidanum
indolidan

3,3-dimethyl-5-(1,4,5,6-tetrahydro-6-oxo-3-pyridazinyl)-2-indolinone
C₄H₆N₃O₂  100643-96-7

iobenguanum (¹³¹I)
iobenguane (¹³³I)

(m-iodo-¹³¹I-benzyl)guanidine
C₈H₁₀¹³¹IN₃  77679-27-7

lacidipinum
lacidipine

4-[o-[(E)-2-carboxyvinyl]phenyl]-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylic acid, 4-tert-butyl diethyl ester
C₂₆H₃₃NO₆  103980-78-4

levocarnitinum
levocarnitine

(L-3-carboxy-2-hydroxypropyl)trimethylammonium hydroxide, inner salt
C₇H₁₅NO₃  541-15-1
Proposed International
Nonproprietary Name (Latin, English)  Chemical Name or Description, Molecular and Graphic Formulae  Chemical Abstracts Service (CAS) registry number
levofenfluraminum  levofenfluramine  \((-\))-(R)-N-ethyl-\(\alpha\)-methyl-\(m\)-(trifluoromethyl)phenethylamine  \(C_{12}H_{16}F_{3}N\)  37577-24-5

\begin{center}
\text{\includegraphics[width=0.3\textwidth]{levofenfluramine.png}}
\end{center}

lixazinonum  lixazinone  \(N\)-cyclohexyl-\(N\)-methyl-4-\([\text{1,2,3,5-tetrahydro-2-oxoimidazo[2,1-b]quinazolin-7-yl} \text{oxy}]\)butyramide  \(C_{21}H_{28}N_{4}O_{3}\)  94192-59-3

\begin{center}
\text{\includegraphics[width=0.3\textwidth]{lixazinone.png}}
\end{center}

iodaxaprinum  lodaxaprine  1-\([6\text{-}(\text{o-chlorophenyl})\text{-}3\text{-pyridazinyl}]\)-4-piperidinol  \(C_{15}H_{16}ClIN\)  93181-81-8

\begin{center}
\text{\includegraphics[width=0.3\textwidth]{iodaxaprin.png}}
\end{center}

loperamidum oxidum  loperamide oxide  \(\text{trans-4-}[(\text{p-chlorophenyl})\text{-}4\text{-hydroxy-}N,N\text{-dimethyl-}\alpha,\alpha\text{-diphenyl-1-piperidinebutyramide 1-oxide}}\)  \(C_{29}H_{33}ClN_{2}O_{3}\)  106900-12-3

\begin{center}
\text{\includegraphics[width=0.3\textwidth]{loperamideox.png}}
\end{center}
<table>
<thead>
<tr>
<th>Nonproprietary Name (Latin, English)</th>
<th>Chemical Name or Description, Molecular and Graphic Formulae</th>
<th>Chemical Abstracts Service (CAS) registry number</th>
</tr>
</thead>
<tbody>
<tr>
<td>lorcinadolum</td>
<td><strong>(E)-3-chloro-6-(4-cinnamyl-1-piperazinyl)pyridazine</strong></td>
<td>104719-71-3</td>
</tr>
<tr>
<td>lorcinadol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>lovastatinum</td>
<td><strong>(S)-2-methylbutyric acid, 8-ester with (4R,6R)-6-[2-[(1S,2S,6R,8S,8aR)-1,2,6,7,8,8a-hexahydro-8-hydroxy-2,6-dimethyl-1-naphthyl]ethyl]tetrahydro-4-hydroxy-2H-pyran-2-one</strong></td>
<td>75330-75-5</td>
</tr>
<tr>
<td>lovastatin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>loxiglumidum</td>
<td><strong>(±)-4-(3,4-dichlorobenzamido)-N-(3-methoxypropyl)-N-pentylglutaramic acid</strong></td>
<td>107097-80-3</td>
</tr>
<tr>
<td>loxiglumide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mafoprazinum</td>
<td><strong>4’-[3-4-(o-fluorophenyl)-1-piperazinyl)propoxy]-m-acetanisidide</strong></td>
<td>80428-29-1</td>
</tr>
<tr>
<td>mafoprazine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>midaglizolum</td>
<td><strong>(±)-2-[α-(2-imidazolin-2-ylmethyl)benzyl]pyridine</strong></td>
<td>66529-17-7</td>
</tr>
<tr>
<td>midaglizole</td>
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<td></td>
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</tbody>
</table>
Proposed International Nonproprietary Name (Latin, English)

Chemical Name or Description, Molecular and Graphic Formulae

Chemical Abstracts Service (CAS) registry number

molfarnatum
molfarnate

3,7,11-trimethyl-2,6,10-dodecatrienyl 4,8,12-trimethyl-3,7,11-tridecatrienoate

\[
\text{C}_{31}\text{H}_{50}\text{O}_{2}
\]

\[
\begin{align*}
\text{CH}_3 & \quad \text{CH}_3 \\
\text{C} & \quad \text{CH} = \text{CH} - \text{CH}_3 \\
\text{CH} & \quad \text{C} = \text{CH} - \text{CH}_3 \\
\text{CH}_3 & \quad \text{C} = \text{CH} - \text{CH}_2 \text{CH}_2 - \text{C} - \text{O} - \text{CH}_2 - \text{CH}_2 - \text{CH}_2 - \text{CH} = \text{C} - \text{CH}_3 \\
\end{align*}
\]

niguldipinum
niguldipine

\((\pm)-3-(4,4\text{-diphenylpiperidino})\text{propyl methyl 1,4-dihydro-2,6-dimethyl-4-(m-nitrophenyl)-3,5-pyridinedicarboxylate}

\[
\text{C}_{36}\text{H}_{39}\text{N}_{3}\text{O}_{6}
\]

\[
\begin{align*}
\text{H}_2\text{C} & \quad \text{C} \\
\text{N} & \quad \text{H} \\
\text{C} & \quad \text{O} - \text{CH}_2 - \text{CH}_2 - \text{CH}_2 - \text{CH}_2 - \text{CH}_2 - \text{CH}_2 - \text{CH} = \text{C} - \text{CH}_3 \\
\text{NO}_2 & \quad \text{C} \\
\end{align*}
\]

nuclomedonum
nuclomedone

\((\pm)-6-(p\text{-chlorobenzyl})\text{-2,3-dihydro-5H-thiazolo[3,2-a]pyrimidine-5,7(6H)-dione}

\[
\text{C}_{13}\text{H}_{11}\text{CIN}_{2}\text{O}_{2}
\]

\[
\begin{align*}
\text{Cl} & \quad \text{C} \\
\text{H}_2\text{CO} & \quad \text{C} \\
\text{C} & \quad \text{O} - \text{CH}_2 - \text{CH}_2 - \text{CH}_2 - \text{N} \quad \text{S} \\
\text{N} & \quad \text{O} \\
\text{S} & \quad \text{N} \\
\end{align*}
\]

orbutoprilum
orbutopril

\((2\text{S,3aS,7aS})-1-\{(S)-\text{N-}\{(S)-1\text{-carboxypentyl}\text{alanyl}\}\text{hexahydro-2-indoline-carboxylic acid, 1-ethyl ester}

\[
\text{C}_{20}\text{H}_{34}\text{N}_{2}\text{O}_{5}
\]

\[
\begin{align*}
\text{H}_2\text{C} & \quad \text{CH}_2 \quad \text{CH}_2 \quad \text{CH}_2 \quad \text{C} \quad \text{H}_2\text{CO} \\
\text{H}_2\text{C} & \quad \text{CH}_2 \quad \text{CH}_2 \quad \text{CH}_2 \quad \text{C} \quad \text{H}_2\text{CO} \\
\text{N} & \quad \text{C} \\
\text{H} & \quad \text{H} \\
\text{H} & \quad \text{H} \\
\text{H} & \quad \text{H} \\
\text{H} & \quad \text{H} \\
\text{H} & \quad \text{H} \\
\text{H} & \quad \text{H} \\
\end{align*}
\]

parodilolum
parodilol

\((\pm)-1-\{(2\text{-indol-3-yl-1,1-dimethyl} \text{ethyl} \text{amino})\text{-3-(indol-4-ylxylo)-2-propanol}

\[
\text{C}_{25}\text{H}_{27}\text{N}_{2}\text{O}_{2}
\]

\[
\begin{align*}
\text{O} & \quad \text{CH}_2 - \text{CH}_2 - \text{NH} - \text{C} - \text{CH}_2 \\
\text{C} & \quad \text{CH}_3 \\
\text{H} & \quad \text{H} \\
\text{H} & \quad \text{H} \\
\end{align*}
\]

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Proposed International Nonproprietary Name (Latin, English)  
Chemical Name or Description, Molecular and Graphic Formulae  
Chemical Abstracts Service (CAS) registry number

pelanserinum  
pelanserin  
3-[3-(4-phenyl-1-piperazinyl)propyl]-2,4(1H,3H)-quinazolinedione  
\(C_{21}H_{24}N_2O_2\)  
2208-51-7

![Pelanserin](image)

pimonidazolum  
pimonidazole  
(±)-α-[2-nitroimidazol-1-yl]methyl]-1-piperidineethanol  
\(C_{11}H_{18}N_4O_3\)  
70132-50-2

![Pimonidazole](image)

pirtenidinum  
pirtenedine  
1,4-dihydro-1-octyl-4-(octylimino)pyridine  
\(C_{21}H_{38}N_2\)  
103923-27-9

![Pirtenedine](image)

pravastatinum  
pravastatin  
(±)-(3R,5S,8R,1S,2S,6S,8aR)-1,2,6,7,8,8a-hexahydro-P,8,6,8-tetrahydroxy-2-methyl-1-naphthaleneheptanoic acid, 8-[2R)-2-methylbutyrate]  
\(C_{23}H_{36}O_7\)  
81093-37-0

![Pravastatin](image)

ramoplaninum  
ramoplanin  
factor A\(_2\) of the antibiotic complex A/16686 produced by Actinoplanes sp. ATCC 33076  
empirical molecular formula \(C_{119}H_{154}ClIN_{20}O_{40}\)

![Ramoplanin](image)

ranolazinum  
ranolazine  
(±)-4-[2-hydroxy-3-(o-methoxyphenoxy)propyl]-1-piperazineaceto-2',6'-xylidide  
\(C_{24}H_{33}N_2O_4\)  
95635-55-5

![Ranolazine](image)
Proposed International Nonproprietary Name (Latin, English)

<table>
<thead>
<tr>
<th>Chemical Name or Description, Molecular and Graphic Formulae</th>
<th>Chemical Abstracts Service (CAS) registry number</th>
</tr>
</thead>
<tbody>
<tr>
<td>retelliptinum retelliptine</td>
<td>1-[[3-(diethylamino)propyl]amino]-9-methoxy-5,11-dimethyl-6H-pyrido[4,3-b]-carbazole</td>
</tr>
<tr>
<td></td>
<td>C_{25}H_{32}N_{8}O 72238-02-9</td>
</tr>
<tr>
<td>rilmenidinum rilmenidine</td>
<td>2-[[dicyclopropylmethyl]amino]-2-oxazoline</td>
</tr>
<tr>
<td></td>
<td>C_{10}H_{16}N_{2}O 54187-04-1</td>
</tr>
<tr>
<td>risperidonum risperidone</td>
<td>3-[[4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidino]ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-alpyrimidin-4-one</td>
</tr>
<tr>
<td></td>
<td>C_{23}H_{27}FNO_{2} 106266-06-2</td>
</tr>
<tr>
<td>rocastinum rocastine</td>
<td>(+)-2-[2-(dimethylamino)ethyl]-3,4-dihydro-4-methylpyrido[3,2-f]-1,4-oxazepine-5(2H)-thione</td>
</tr>
<tr>
<td></td>
<td>C_{13}H_{19}N_{3}O_{3} 91833-77-1</td>
</tr>
<tr>
<td>ronactololum ronactolol</td>
<td>(+)-4′-[2-hydroxy-3-(isopropylamino)propoxy]-p-anisanilide</td>
</tr>
<tr>
<td></td>
<td>C_{26}H_{32}N_{8}O_{4} 90895-85-5</td>
</tr>
</tbody>
</table>
**Proposed International Nonproprietary Name**

**Latin, English**

<table>
<thead>
<tr>
<th>Chemical Name or Description, Molecular and Graphic Formulae</th>
<th>Chemical Abstracts Service (CAS) registry number</th>
</tr>
</thead>
<tbody>
<tr>
<td>rotraxatum rotraxate</td>
<td>$p$-[(trans-4-(aminomethyl)cyclohexyl)carbonyl]hydrocinnamic acid C$<em>{17}$H$</em>{23}$NO$_3$ 92071-51-7</td>
</tr>
<tr>
<td></td>
<td><img src="image1" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>rufloxacinum rufloxacin</td>
<td>9-fluoro-2,3-dihydro-10-(4-methyl-1-piperazinyl)-7-oxo-7H-pyrido[1,2,3-de]-1,4-benzothiazine-6-carboxylic acid C$<em>{17}$H$</em>{18}$FN$_3$O$_3$S 101363-10-4</td>
</tr>
<tr>
<td></td>
<td><img src="image2" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>seglitidum seglitide</td>
<td>cyclo(N-methyl-L-alanyl-L-tyrosyl-D-tryptophyl-L-lysyl-L-valyl-L-phenyl-alanyl) C$<em>{44}$H$</em>{56}$N$_8$O$_7$ 81377-02-8</td>
</tr>
<tr>
<td></td>
<td><img src="image3" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>sibutraminum sibutramine</td>
<td>(+)-1-(p-chlorophenyl)-α-isobutyl-N,N-dimethylcyclobutanemethylamine C$<em>{17}$H$</em>{26}$ClN 106650-56-0</td>
</tr>
<tr>
<td></td>
<td><img src="image4" alt="Chemical Structure" /></td>
</tr>
</tbody>
</table>
sizofiranum  sizofiran

Schizophyllan or Poly[3→(O→β-D-glucopyranosyl-(1→3)-O→β-D-glucopyranosyl-(1→6)-O→β-D-glucopyranosyl-(1→3)-O→β-D-glucopyranosyl)] (C_{24}H_{40}O_{20})_{n}  9050-67-3

somatorelinum  somatorelin

growth hormone-releasing factor (human)
C_{215}H_{336}N_{72}O_{66}S  83930-13-6

tameridonum  tameridone

7-[2-(4-indol-3-ylpiperidino)ethyl]theophylline
C_{22}H_{26}N_{6}O_{2}  102144-78-5

tifuracum  tifurac

7-\{\text{[p-\{methylthio\}benzoyl]-5-benzofuranacetic acid}\}
C_{18}H_{14}O_{4}S  97483-17-5

tigemonamum  tigemonam

[[[Z]-\{2-amino-4-thiazolyl\}]\{\{(3S)-1-hydroxy-2,2-dimethyl-4-oxo-3-azetidinyl\}carbamoyl\}methylene\}amino\}oxy\}acetic acid hydrogen sulfate (ester)
C_{12}H_{13}N_{2}O_{9}S_{2}  102507-71-1
Proposed International Nonproprietary Name (Latin, English)  

Chemical Name or Description, Molecular and Graphic Formulae

Chemical Abstracts Service (CAS) registry number

---

tilisololum  
(tilisolol)  

$\pm$-4-[3-(tert-butylamino)-2-hydroxypropoxy]-2-methylisocarbostyril  
$\text{C}_{17}\text{H}_{24}\text{N}_{2}\text{O}_{3}$  
85136-71-6

---

tilmicosinum  
(tilmicosin)  

4A-O-de(2,6-dideoxy-3-C-methyl-\(\alpha\)-\(\alpha\)-ribo-hexopyranosyl)-20-deoxo-20-(\(\text{cis}\)-3,5-dimethylpiperidino)tylosin  
$\text{C}_{46}\text{H}_{80}\text{N}_{2}\text{O}_{13}$  
108050-54-0

---

tiospironum  
(tiospirone)  

N-\{4-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]butyl\}-1,1-cyclohexanediacetimide  
$\text{C}_{24}\text{H}_{32}\text{N}_{4}\text{O}_{2}\text{S}$  
87691-91-6

---

tiprotimodum  
(tiprotimod)  

2-\{(3-carboxypropyl)thiol\}-4-methyl-5-thiazoleacetic acid  
$\text{C}_{16}\text{H}_{13}\text{NO}_{2}\text{S}_{2}$  
105523-37-3

---

topiramatum  
(topiramate)  

2,3,4,5-di-O-isopropylidene-\(\beta\)-\(\alpha\)-fructopyranose  
$\text{C}_{12}\text{H}_{12}\text{NO}_{4}\text{S}$  
97240-79-4

---
<table>
<thead>
<tr>
<th>Proposed International Nonproprietary Name (Latin, English)</th>
<th>Chemical Name or Description, Molecular and Graphic Formulae</th>
<th>Chemical Abstracts Service (CAS) registry number</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>urofollitropinum</strong></td>
<td>a preparation of menopausal gonadotrophin extracted from human urine, but possessing negligible luteinising hormone (LH) activity</td>
<td></td>
</tr>
<tr>
<td><strong>urofollitropin</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>vadocainum</strong></td>
<td>(±)-6'-methoxy-2-methyl-1-piperidinepropiono-2',4'-xylidide</td>
<td>72005-58-4</td>
</tr>
<tr>
<td><strong>vadocaine</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>vesnarinonum</strong></td>
<td>1-(1,2,3,4-tetrahydro-2-oxo-6-quinolyl)-4-veratroylpiperazine</td>
<td>81840-15-5</td>
</tr>
<tr>
<td><strong>vesnarinone</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>vinorelbinum</strong></td>
<td>3',4'-didehydro-4'-deoxy-8'-norvincaleukoblastine</td>
<td>71486-22-1</td>
</tr>
<tr>
<td><strong>vinorelbine</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Supplement to Vol. 32, No. 9, 1978

Proposed International Nonproprietary Names (Prop. INN): List 40

p. 7 cinoquidoxum
    cinoquidox

replace graphic formula by:

\[
\begin{align*}
\text{NH} - \text{CH}_2 - \text{CH}_2 - \text{CN} \\
\text{O} \\
\text{C} \\
\text{O} \\
\text{CH}_3
\end{align*}
\]

Supplement to Vol. 34, No. 9, 1980

Proposed International Nonproprietary Names (Prop. INN): List 44

p. 8 ciadoxum
    ciadox

replace graphic formula by:

\[
\begin{align*}
\text{N} \\
\text{O} \\
\text{C} \\
\text{O} \\
\text{CH}_3
\end{align*}
\]

Supplement to Vol. 38, No. 2, 1984

Proposed International Nonproprietary Names (Prop. INN): List 51

p. 2 ademetionum
    ademetionine

replace chemical name, graphic formula and CAS reg. no. by the following:

(+)\text{-}S\text{-}\{(R')\text{-}\{(R')\text{-}3\text{-}amino\text{-}3\text{-}carboxypropyl\text{methylsultonio}\}\text{-}\text{deoxy}\text{-}adenosine hydroxide, inner salt

17176-17-9

\[
\begin{align*}
\text{NH}_2 \\
\text{N} \\
\text{OOC} \\
\text{C}_2 \text{H}_4 - \text{CH}_2 - \text{CH}_2 \\
\text{CH}_2
\end{align*}
\]
Proposed International Nonproprietary Names (Prop. INN): List 55

p. 2  ardacinum  
ardacin  

add the following graphic formula:

\[
\text{Side chain}
\]

p. 17  tetronasnum  
tetronasin  

replace molecular formula by: C_{35}H_{54}O_{8}

p. 20  omoconazolum  
omoconazole  

delete 4991 rev. and insert the following CAS reg. no.: 105102-19-0
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 Organization1 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;

(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 substitut 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 registration of the name as a trade-mark or trade-name.


The title of this publication was changed to WHO Chronicle in January 1959. From 1967 onwards lists of INNs are published in WHO Drug Information.

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 designing 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.

7. To facilitate the translation and pronunciation of INN, "1" 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>anti-inflammatory agents of the ibufenac group</td>
</tr>
<tr>
<td>-actidum</td>
<td>synthetic polypeptides with a corticotrophin-like action</td>
</tr>
<tr>
<td>-adol-</td>
<td>anti-asthmatic, anti-allergic substances not acting primarily as antihistaminics</td>
</tr>
<tr>
<td>-astum</td>
<td>antihistaminics</td>
</tr>
<tr>
<td>-astinum</td>
<td>substances of the diazepam group</td>
</tr>
<tr>
<td>-azepamum</td>
<td>1-lactamase inhibitors</td>
</tr>
<tr>
<td>-bactamum</td>
<td>steroids, anabolic</td>
</tr>
<tr>
<td>-bol</td>
<td>anti-inflammatory analoges of the phenylbutazone group</td>
</tr>
<tr>
<td>-buzonum</td>
<td>analgesics</td>
</tr>
<tr>
<td>-cain-</td>
<td>antifibrillant substances with local anaesthetic activity</td>
</tr>
<tr>
<td>-cainum</td>
<td>local anaesthetics</td>
</tr>
<tr>
<td>-cef-</td>
<td>antibiotics, derivatives of cefalosporanic acid</td>
</tr>
<tr>
<td>-cillinum</td>
<td>antibiotics, derivatives of 6-aminopenicillanic acid</td>
</tr>
<tr>
<td>-conazolum</td>
<td>systemic antifungal agents of the miconazole group</td>
</tr>
<tr>
<td>-cort</td>
<td>corticosteroids, except those of the prednisolone group</td>
</tr>
<tr>
<td>-dipinum</td>
<td>calcium antagonists of the nifedipine group</td>
</tr>
<tr>
<td>-fibratum</td>
<td>substances of the clofibrate group</td>
</tr>
<tr>
<td>-gest</td>
<td>steroids, progestogens</td>
</tr>
<tr>
<td>-gli-</td>
<td>sulfonamide hypoglycemics</td>
</tr>
<tr>
<td>-io-</td>
<td>iodine-containing contrast media</td>
</tr>
<tr>
<td>-iium</td>
<td>quaternary ammonium compounds</td>
</tr>
<tr>
<td>-metacinum</td>
<td>anti-inflammatory substances of the indometacin group</td>
</tr>
<tr>
<td>-mycinum</td>
<td>antibiotics, produced by Streptomyces strains</td>
</tr>
<tr>
<td>-nidazolum</td>
<td>antiprotozoal substances of the metronidazole group</td>
</tr>
<tr>
<td>-olol</td>
<td>1-adrenergic blocking agents</td>
</tr>
<tr>
<td>-oxacinum</td>
<td>antibacterial agents of the nalidix acid group</td>
</tr>
<tr>
<td>-pridum</td>
<td>sulphiride derivatives</td>
</tr>
<tr>
<td>-pril(at)um</td>
<td>angiotensin-converting enzyme inhibitors</td>
</tr>
<tr>
<td>-profenum</td>
<td>anti-inflammatory substances of the ibuprofen group</td>
</tr>
<tr>
<td>-prost</td>
<td>prostaglandins</td>
</tr>
<tr>
<td>-relinum</td>
<td>hypophyseal hormone release-stimulating peptides</td>
</tr>
<tr>
<td>-terolum</td>
<td>bronchodilators, phenylethylamine derivatives</td>
</tr>
<tr>
<td>-tidinum</td>
<td>H₂-receptor antagonists</td>
</tr>
<tr>
<td>-trexatum</td>
<td>folic acid antagonists</td>
</tr>
<tr>
<td>-verinum</td>
<td>spasmyloics with a papaverine-like action</td>
</tr>
<tr>
<td>-vin-</td>
<td>vinca type alkaloids</td>
</tr>
<tr>
<td>-vin-</td>
<td></td>
</tr>
</tbody>
</table>

1 A more extensive listing of stems is contained in the working document Pharm S/Nom 15 which is regularly updated and can be requested from Pharmaceuticals, WHO, Geneva.
In its twentieth report¹ 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 recent 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. Also reported is the intention to change the practice with regard to the nomenclature of individual members of polymeric series.

Other sections of the report concern instructions to be followed by bodies making application for international nonproprietary names, the availability of computer-printed cumulative lists of international nonproprietary names, information supplied by WHO Member States concerning their official use of national or international names for pharmaceutical products, and proposals relative to the withdrawal of international nonproprietary names allocated to substances that are no longer in use.

The official texts relating to the procedures for selecting, and general guidance for devising, international nonproprietary names are reproduced in two annexes to the report. Other annexes give examples of international nonproprietary names that incorporate selected stems, the most frequently used initial groups of letters in international nonproprietary names, a historical review of the programme of selecting international nonproprietary names, some useful literature references, and a model of the form to be used in all applications for international nonproprietary names.
