WHO Drug Information

Contents

General Policy Topics

ICDRA: an influential forum for drug regulators

The biennial International Conference of Drug Regulatory Authorities (ICDRA) has become firmly established as a forum that offers officials from every country the opportunity to exchange information, views and ideas. Doubts have long been dissipated as to whether enough common ground exists between regulators operating in diverse settings around the world to sustain a truly global conference. The attendance figures for the seventh conference that was hosted by the Ministry of Health of the Netherlands in April this year provide proof enough of success: more than 160 participants from almost one hundred national authorities attended. Countries represented ranged from the most highly evolved in north America, Europe and the western Pacific, to some of the smallest in Africa and the Caribbean, and included most of the countries now in transition in eastern Europe.

For the local organizers this was a triumph; for WHO it confirmed that its normative responsibilites remain one of its unique strengths; and, for the participants, it inspired a sense of solidarity in their need to confront changing circumstances. Drug control is no longer concerned simply with the regulation of a reasonably ordered industry. Every country now needs to protect itself from an insurgence of fraudulently represented counterfeit products and other criminally-inspired and potentially substandard medicines. Introduced illicitly into the distribution chain, these products readily escape every modality of control. Recently confirmed examples include generic versions of antibiotics and antimalarials containing grossly subtherapeutic amounts of the active ingredient — a counterfeit proprietary antibiotic that contained a pyschoactive substance as the only active ingredient; and paediatric syrups of paracetamol made up in a toxic solvent — diethylene glycol instead of propylene glycol. The latter products alone are known to have resulted in the deaths of several hundreds of young children from acute renal failure.

Regulators are aware that there are no easy remedies to assuring protection against such activities. The solution resides in the development of effective and comprehensive drug registration systems complemented by a strong drug inspectorate that serves as the enforcement arm of the regulatory apparatus, and vigilance among consumers and health professionals at every level. This requires investment that many countries are reluctant to contemplate. The reality has to be faced, however, that the circulation of medicines of uncertain and sometimes inadmissible quality undermines the basic objectives of drug regulation and, in some countries, it threatens to erode confidence in the health care system.

Over the past few years, circulation of counterfeit medicines has been reported from more than 40 countries. One highly-developed country with a particularly strong tradition in drug regulation now reports some 20 to 30 separate instances of counterfeiting each year. It has responded by substantially augmenting its drug inspectorate to include medicines inspectors and "enforcement investigators", who are now occupied full time on the investigation of cases. They receive a great deal of collaboration from pharmaceutical manufacturers, who have conceded — in the face of increasing criminal competition — to the need to protect their commercial interests and their reputations.

Counterfeiting is no longer restricted to finished pharmaceutical products. Complex commodity trading in raw and starting materials facilitates the infiltration of illicit substances into supply channels. It has even been suggested that a confidential system of chemical "fingerprinting" of a company's starting materials and, particularly, of expensive active ingredients, might be explored as a means of detecting falsification.

A key recommendation of the Conference, which has inescapable funding implications for governments, is the application of WHO's guiding principles for small regulatory authorities; its Certification Scheme on the Quality of Pharma-

ceutical products moving in international commerce; its guidelines of good manufacturing practices; and implementation of other aspects of quality assurance as set out in various reports of the WHO Expert Committees on Pharmaceutical Specifications and Biological Standardization.

Awareness of the prevalence of counterfeiting, the Conference concluded, needs to be increased among politicians and all health care professionals. It must be generally recognized that, without the increased funding necessary to strengthen enforcement capacity, and particularly to substantially upgrade the pharmaceutical inspectorate and analytical facilities, the majority of national drug regulatory authorities — which were not originally intended to undertake criminal investigations — will not have the capacity to tackle the problem effectively.

This implies that considerably more information about detected cases of manufacture of substandard and counterfeit products should be circulated between drug regulatory authorities and, when possible, brought into the public domain. WHO, it was emphasized, should serve as a clearinghouse for this information, it should establish a data base of starting materials and products known to be counterfeited, and it should collaborate with national authorities and nongovernmental organizations in any way that facilitates their work at international level.

Two resolutions adopted subsequently during the Forty-seventh World Health Assembly held in May this year reflect these concerns and propose tangible responses. The first of these defines the role of the pharmacist (WHA47.12). In doing so, the resolution "calls upon pharmacists and their professional associations everywhere, through their contributions to regulatory control, pharmaceutical manufacture and community service, to support WHO's policies as embodied in WHO's revised drug strategy and develop the profession at all levels...., in particular:

- "to provide the oversight necessary to assure the quality of pharmaceutical products and services at the time of manufacture, importation or exportation and at all stages of the distribution chain;

- "to manage drug procurement and supply systems and, in so doing, to cooperate in efforts to detect and prevent the distribution of falsely labelled, spurious, counterfeit or substandard pharmaceutical preparations."

The second resolution (WHA47.17), concerned specifically with the safety, efficacy and quality of pharmaceuticals notes that:

"... pharmaceutical trade is becoming more complex as more countries manufacture and export pharmaceutical and biological products and active ingredients, and as new technologies are applied to their production;

"... countries need to develop the capability to assure the quality of all such products — both brand name and generic and both domestically manufactured and imported — on their national markets;

"... an unacceptable prevalence of substandard and counterfeit pharmaceutical products in international trade threatens to erode confidence in the health care system because such products may be inefficacious or toxic."

Accordingly, in two of its operative paragraphs, the resolution "reaffirms the principles embodied in WHO's Guiding Principles for small regulatory authorities and the WHO Certification Scheme on the Quality of Pharmaceutical Products moving in International Commerce", and "urges Member States to provide the resources and manpower needed to strengthen their national regulatory capacity."

This is not an easy proposition to sell to governments often anxious to disengage from direct central budgetary support of public services. Nor, at a time of widespread political strife and instability, has it captured the attention of the general public and the media to the extent that it undoubtedly deserves. We should not forget that every one of us has need of medicines at some time in our lives. We expect them to work. We certainly expect them to be safe. We can only hope that few dramatic incidents are allowed to occur before energetic steps are taken at every level and within every administration to surmount the threat of illicit substandard medicines. The latter are ubiquitous. No individual or government can regard themselves as immune to the risk that they present.

Reports on Individual Drugs

Antiplatelet therapy: enthusiasm tempered by caution

Started promptly in the acute phase of cardiac infarction, antiplatelet therapy can save many lives. This was the central finding in a large randomized trial published in 1988 that involved over 17 000 patients who were admitted in emergency with cardiac infarction to some 400 hospitals in 16 countries (1). The greatest benefit was obtained by patients treated within 4 hours of infarction. Streptokinase alone (1.5 million units infused intravenously over 1 hour) reduced mortality over the subsequent 5 weeks by 35%. For acetylsalicylic acid alone (160 mg daily for 1 month) the reduction was 25% and, for the two drugs combined it was 53%. Marked but lesser benefit was obtained even when 13 to 24 hours elapsed before treatment was started.

Whether prolonged, non-emergency daily use of acetylsalcylic acid is of similar value in the primary and secondary prevention of vascular disease is more difficult to assess, simply because the risk of vascular death in these patients is much lower. Some 10% of patients who survive the immediate consequences of acute myocardial infarction die from a cardiovascular complication within the next 4 weeks. Among adult men who have recovered from a previous infarction, the death rate drops to 10% over any 2-year period, while among men with no risk factors for atherosclerotic disease the risk of death is at least 10-fold lower (2).

At such low levels of risk, very large cohorts of patients are required to demonstrate even a substantial protective effect associated with sustained antiplatelet therapy. In the 1980s two such studies directed to assessing the value of daily use of acetylsalicylic acid among healthy doctors in the USA (3) and the United Kingdom (4) produced conflicting results. The uncertainty generated by these studies has lent particular interest to a recently published overview of 145 randomized trials of prolonged antiplatelet therapy involving observation over 1–3 years of about 70 000 patients with clinical evidence of atherosclerotic disease and about 30 000 apparently healthy subjects (2). On the basis of these data, acetylsalicylic acid was estimated to reduce vascular events by about one-quarter in both high- and low-risk patients. It appeared to be as effective as any other single antiplatelet agent (including dipyridamole, sulfinpyrazone and ticlopidine) at doses as low as 75 mg daily, and the response was independent of sex, age, blood pressure and presence of diabetes (5).

Among patients at high risk of vascular disease, sustained antiplatelet therapy offered worthwhile protection against myocardial infarction, stroke and death. This benefit was apparent not only among patients with unstable angina, a past history of myocardial infarction, stroke, or transient ischaemic attack, but also among other categories of high-risk patients, including those undergoing vascular surgery and those with stable angina or peripheral vascular disease.

Whereas it is estimated that one non-fatal case of myocardial infarction is prevented among high-risk patients by some 100 patient-years of treatment, at least 1000 patient-years of treatment are required to produce the same effect among patients without specific risk factors (6). Prolonged use of acetylsalicylic acid, however, is not free from risk, and it may well have contributed to a few cases of cerebral haemorrhage recorded in these trials. In patients with least expectation of benefit, the advantages of taking acetylsalicylic acid is thus offset in uncertain degree by risk of haemorrhage (6). One of the most important conclusions of this overview is that the routine use of antiplatelet treatment for primary prevention of vascular disease cannot be recommended on the basis of firm statistical evidence: the data now available suggest that maintenance of a healthy life-style, attention to diet, exercise, and avoidance of smoking provide more tangible protection. It is a conclusion that revives the need to caution against the widespread use of drugs to prevent disease until the benefits and associated risks have been clearly established (6–8).

References

1. ISIS-2 (Second international study of infarct survival) Collaborative Group. Randomized trial of intravenous streptokinase, oral aspirin, both, or neither among 17 187 cases of suspected myocardial infarction. *Lancet*, **2:** 349-360 (1988).

2. Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet treatment. I. Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. *British Medical Journal*, **308:** 81-106 (1994).

3. Steering Committee of the Physicians' Health Study Research Group. Preliminary report: findings from the aspirin component of the ongoing physicians' health study. *New England Journal of Medicine*, **318:** 262-264 (1988).

4. Peto, R., Gray, R., Collins, R. et al. Randomised trial of prophylactic daily aspirin in British male doctors. *British Medical Journal*, **296:** 313-316 (1988).

5. Underwood, M., More, R. The aspirin papers. *British Medical Journal*, **308:** 71-72 (1994).

6. Davey-Smith, G., Egger, M. Who benefits from medical interventions? *British Medical Journal*, **308:** 72-74 (1994).

7. Oliver, M. Risks of correcting risks of coronary disease and strokes with drugs. *New England Journal of Medicine*, **306:** 297-298 (1982).

8. Rose, G., Sick individuals and sick populations. *International Journal of Epidemiology*, **14:** 32-38 (1985).

BCG vaccine: a reappraisal of efficacy

Bacille Calmette-Guérin (BCG) vaccines are lyophilized preparations of a live, laboratory-attenuated strain of *Mycobacterium bovis*. The finished products are prepared from various substrains, all derived from the same original culture, but differing in their DNA structure, immunogenicity and biochemical characteristics. Widely distributed BCG preparations induce a state of tuberculin sensitivity in a high proportion of previously non-reactive individuals. This immune response confers substantial protection against severe forms of tuberculosis of infancy and childhood, including miliary tuberculosis and tuberculous meningitis (1). However, having regard to the documented incidence of severe local complications, including suppurative adenitis and osteomyelitis (2, 3), vaccination of infants is routinely practised when there is tangible risk of infection.

Unfortunately, the protective effect of BCG in older children and adults is less consistent. Confidence was undermined when the largest prospective study of BCG vaccination ever conducted provided no evidence of a protective effect against pulmonary tuberculosis (4-7). This was a randomized controlled trial undertaken in Madras, India during the 1970s. The intention was to compare the protective efficacy of various doses of vaccines from different seed lots. Some 200 000 children and adults, most of whom were demonstrated to be tuberculin-negative, were involved in the study. However, no evidence was obtained, either overall or within any subgroup, to suggest that vaccination reduced susceptibility to subsequent pulmonary tuberculosis.

These findings contrasted remarkably from positive results obtained in 12 of 14 previously published and independently executed smaller trials undertaken in developed countries. These had indicated that BCG provides significant protection against clinical tuberculosis (with relative risks ranging from 0.20 to 0.80) (8). Only one study of meaningful size had failed to demonstrate a protective effect against subsequent disease (9). Because of this inconsistency, the Madras study had little effect on prevailing national policies regarding use of BCG — which in some countries still remains compulsory (10, 11).

Instead, attention was directed to explaining the negative results obtained in Madras in terms of methodological flaws (12) or potential confounding variables (13, 14). Among the many that have been discussed are inadequate immunogenic potency of different preparations of BCG (15–19), variability in the protective potential of these preparations against different clinical forms of tuberculosis, variability in the virulence of different strains of *Mycobacterium tuberculosis* (20), coexistence of other immunogenic mycobacterial species within the study population (21, 22), and demographic or genetic factors.

Failure to provide a satisfactory explanation for the atypical results obtained in Madras created a stimulus to amass more information on the effects of BCG vaccination in countries where the incidence of the disease is relatively high (23). Case-control studies have now been undertaken in many different settings. The advantage of this approach is that information is generated within the context of routine practice. The disadvantage is the difficulty — and often the impossibility — of eliminating bias introduced by confounding variables. Of over 1200 relevant studies reported in the literature, only 70 were considered worthy for potential inclusion in a meta-analysis designed to test the hypothesis that rates of tuberculosis are different in vaccinated and unvaccinated control

populations (8). Over two-thirds of these studies were in turn excluded from consideration, most frequently because the criteria for inclusion of cases and controls were inadequately defined, or because potential for bias was introduced when controls, but not cases, were identified from a tuberculin screened population.

Information derived from ten of the largest case-control studies — which collectively involved over 1200 pulmonary tuberculosis cases — is presented in some detail in the published report of the meta-analysis. Five of these studies were conducted in widely-dispersed developing countries (24–28). Five were conducted in developed countries (29–33), but in three cases these focused exclusively on specific ethnic minorities. Eight of the studies focused on patients vaccinated as infants, while two related to school-age vaccination programmes.

In essence, the results provide an overall estimate of reduction of risk of pulmonary tuberculosis subsequent to BCG vaccination in infancy that approaches 50%. Within independent studies this estimate ranged from 5-fold to two-thirds (odds ratio range: 0.17 to 0.63). In three of these studies (27–29) data were also generated on protection against disseminated tuberculosis of childhood: in this regard vaccination appeared to be somewhat more effective (overall odds ratio: 0.17; 95% confidence limits: 0.12 to 0.42). Notably less protection was demonstrated in the two studies directed to children vaccinated after they had attained school age (odds ratios: 0.79 and 0.84) (25, 32).

On this evidence, BCG vaccination during infancy offers demonstrable and substantial protection against disseminated and pulmonary tuberculosis later in childhood in settings where the disease is most prevalent. What remains uncertain is information relating to the incidence of severe local reactions. Until these data are generated in a variety of socioeconomic settings, national policies on BCG vaccination in populations at marginal risk of tuberculosis cannot be made with the necessary objectivity.

Unfortunately, a new risk factor — HIV infection — has emerged that has not been discussed in studies published thus far. The attenuated BCG vaccine carries an unacceptable risk of generalized infection in immunosuppressed subjects. In some countries, adults targeted for BCG vaccination are now first tested for HIV antibodies (34, 35). For analogous reasons, BCG vaccination at birth is withheld when the mother is HIV-seropositive. Infection in the child cannot be confirmed for some 15 months, by which time passively transferred maternal antibodies are unlikely still to be detectable. Children who are seronegative at this time may then receive the vaccine at normal dosage. Those who remain seropositive should not be vaccinated since they must be assumed to be immunodeficient (36).

References

1. ten Dam, H., Hitze, K. Does BCG vaccination protect the newborn and young infants? *Bulletin of the World Health Organization*, **58:** 37-41 (1980).

2. Bergdahl, S., Felländer, M., Robertson, B. BCG osteomyelitis: experience in the Stockholm region over the years 1961-1974. *Journal of Bone and Joint Surgery*, **58B:** 212-216 (1976).

3. Wasz-Hockert, O., Backman, A., Lotte, A. et al. Osteitis caused by BCG vaccination of the newborn. *Bulletin of the International Union against Tuberculosis*, **54:** 325 (1979).

4. Tuberculosis Prevention Trial. Trial of BCG vaccines in south India for tuberculosis prevention: first report. *Bulletin of the World Health Organization*, **57:** 819-827 (1979).

5. Tuberculosis Prevention Trial, Madras. Trial of BCG vaccines in south India for tuberculosis prevention. *Indian Journal of Medical Research*, **72** (suppl): 1-74 (1980).

6. Editorial. BCG: bad news from India. *Lancet*, **1:** 73-74 (1980).

7. Editorial. BCG vaccination after the Madras study. *Lancet*, **1:** 1309-1310 (1981).

8. Colditz, G., Brewer, T., Berkey, C. et al. Efficacy of BCG vaccine in the prevention of tuberculosis; meta-analysis of the published literature. *Journal of the American Medical Association*, **271:** 698-702 (1994).

9. Comstock, G., Livesay, V., Woolpert, S. Evaluation of BCG vaccination among Puerto Rican children. *American Journal of Public Health*, **64:** 283-291 (1974).

10. von Reyn, C., Clements, C., Mann, J. Human immunodeficiency virus infection and routine childhood immunization. *Lancet*, **2:** 669-672 (1987).

11. World Health Organization. *BCG vaccination policies.* Report of a WHO Study Group. Technical Report Series, No. 652, WHO, Geneva, 1980.

12. Clemens, J., Chuong, J., Feinstein, A. The BCG controversy: a methodological and statistical reappraisal. *Journal of the American Medical Association*, **249:** 2362-2369 (1983).

13. ten Dam, H., Toman, K., Hitze, K., Guld, J. Present knowledge of immunization against tuberculosis. *Bulletin of the World Health Organization*, **54:** 255-269 (1976).

14. Fine, P., Rodrigues, L. Modern vaccines: mycobacterial diseases. *Lancet*, **335:** 1016-1020 (1990).

15. Vallishayee, R., Shasidhara, A., Bunch-Christensen, K. Guld, J. Tuberculin sensitivity and skin lesions in children after vaccination with 11 different BCG strains. *Bulletin of the World Health Organization*, **51:** 489-494 (1974).

16. Ladefoged, A. et al. Tuberculin sensitivity in guinea pigs after vaccination with varying doses of BCG in 12 different strains. *Bulletin of the World Health Organization*, **53:** 435-443 (1964).

17. Dubos, P., Pierce, C. Differential characteristics *in vitro* and *in vivo* of several substrains of BCG. *American Reviews of Tuberculosis and Pulmonary Diseases*, **74:** 699 (1956).

18. Willis, H., Vandiviere, M., Vandiviere, M.R., Melvin, I. Studies in tuberculo-immunity. *American Journal of the Medical Sciences*, **240:** 137-158 (1960).

19. Willis, H., Vandiviere, M. The heterogenicity of BCG. *American Reviews of Tuberculosis and Pulmonary Diseases*, **84:** 288-290 (1961).

20. Mitchison, D. The virulence of tubercle bacilli from patients with pulmonary tuberculosis in India and other countries. *Bulletin of the International Union against Tuberculosis*, **35:** 287-306 (1964).

21. Palmer, C., Long, M. Effects of infection with atypical mycobacteria on BCG vaccination and tuberculosis. *American Reviews of Respiratory Diseases*, **94:** 553-568 (1966).

22. Rook, G., Bahr, G., Stanford, J. The effect of two distinct forms of cell-mediated reponse to mycobacteria on the prospective efficacy of BCG. *Tubercle*, **62:** 63-68 (1981).

23. World Health Organization. *Vaccination against tuberculosis.* Report of an IMCR/WHO Scientific Group. Technical Report Series, No. 651. WHO, Geneva, 1980.

24. Putrali, J., Sutrisna, B., Rahayoe, N. et al. A case-control study of effectiveness of vaccination in children in Jakarta, Indonesia. In: *Proceedings of the Eastern Regional Tuberculosis Conference of IUAT*, Jakarta, 1983, pp. 194–200.

25. Shapiro, C., Cook, N., Evans, D. et al. A case-control study of BCG and childhood tuberculosis in Cali, Colombia. *International Journal of Epidemiology*, **14**: 441-446 (1985).

26. Myint, T., Win, H., Aye, H., Kyaw-Myint, T. Case-control study on evaluation of BCG vaccination of newborns in Rangoon, Burma. *Annals of Tropical Paediatrics*, **7:** 159-166 (1987).

27. Miceli, I., De Kanto, I., Colaiacovo, D. et al. Evaluation of the effectiveness of BCG vaccination using the case-control method in Buenos Aires, Argentina. *International Journal of Epidemiology*, **17:** 629-634 (1988).

28. Sirinavin, S., Chotpitayasunondh, T., Suwanjutha, S. et al. Protective effect of neonatal bacillus Calmette-Guérin vaccination against tuberculosis. *Pediatric Infectious Diseases Journal*, **10:** 350-365 (1991).

29. Young, T., Hershfield, E. A case-control study to evaluate the effectiveness of mass neonatal BCG vaccination among Canadian Indians. *American Journal of Public Health*, **76:** 783-786 (1986).

30. Packe, G., Innes, J. Protective effect of BCG vaccination in infant Asians: a case-control study. *Archives of Diseases of Childhood*, **63:** 277-281 (1988).

31. Houston, S., Fanning, A., Soskoine, C., Frazer, N. The effectiveness of bacillus Calmette-Guérin (BCG) vaccination against tuberculosis. *American Journal of Epidemiology*, **131:** 340-349 (1990).

32. Patel, A., Schofield, F., Siskind, V. et al. Case-control evaluation of a school-age BCG vaccination programme in subtropical Australia. *Bulletin of the World Health Organization*, **69:** 425-433 (1991).

33. Rodrigues, L., Gill, O., Smith, P. BCG vaccination in the first year of life protects children of Indian subcontinent ethnic origin against tuberculosis in England. *International Journal of Epidemiology and Community Health*, **45:** 78-80 (1991).

34. Jewett, J., Hecht, F. Preventive health care of adults with HIV infection. *Journal of the American Medical Association*, **269**: 1144–1153 (1993).

35. Dormont, J. Prise en charge des personnes atteintes d'infection par le VIH. Rapport au ministre. Group of experts chaired by Professor J. Dormont, February 1993. *Préscrire International*, **3**: 47–57 (1994).

36. Mignot, G., Noiry, J.-P. Vaccination of HIV-infected patients. *Préscrire International*, **3**: 87-88 (1994).

Caffeine: a risk factor in pregnancy?

In 1980 the United States Food and Drug Administration advised women to avoid beverages and foods with a substantial content of caffeine during pregnancy (1, 2). Caffeine is less effectively metabolized in the liver during pregnancy (3, 4); it crosses the placenta freely and has been claimed to attain higher concentrations in the fetus which possesses no detoxifying enzymes (5).

Although caffeine is only a weak mutagen (2), it has other properties that could compromise fetal development. Indeed, dose-related embryo-fetal morbidity and mortality have been demonstrated in animal studies (6). Caffeine is structurally related to DNA purine bases and it has been shown to produce chromosomal abnormalities by intercalation in mammalian cells (7). It may also interfere with fetal growth since it increases cyclic adenosine monophosphate in cells (8).

However, some 15 years subsequent to the FDA's warning, doubts have persisted on whether exposure to moderate amounts of caffeine places the human fetus at tangible risk (5). In fact, the field of enquiry has broadened with the suggestion that caffeine consumption may impair fertility (9–12) and concern that, taken in breast milk, it could possibly adversely affect *post partum* neurodevelopment in the infant (13–15) and perhaps induce other long-range adverse effects (16).

One conclusion drawn from the epidemiological evidence, and on which there is general concordance of view, is that a pregnant woman who regularly drinks more than 3 cups of coffee daily (the equivalent of some 300 mg of caffeine) increases her risk of spontaneous abortion and of delivering a low birth-weight baby (17–22). In no study has caffeine intake been estimated to increase these risks more than 2-fold. Smaller risks may be associated with lesser caffeine consumption (22) but most studies have been of insufficient power to detect effects of a lower order with reasonable certainty (23, 24).

Caffeine was never likely to be identified as a potent embryopathic agent. However, it is far from exonerated as such. Given its immediate accessibility and the extent to which it is consumed in coffee and other foods, any tangible risk associated with any aspect of its use has important public health implications. The need is not for restrictive measures, but for well-targeted public information and education, directed particularly to women planning a pregnancy.

References

1. Goyan, J. News Release No. P80-36; Food and Drug Administration, Washington DC, 2 September 1980.

2. Thayer, P., Palm, P. A current assessment of the mutagenic and teratogenic effects of caffeine. *Critical Reviews of Toxicology*, **3:** 345-369 (1975).

3. Aldridge, A., Bailey, J., Neims, A. The disposition of caffeine during and after pregnany. *Seminars in Perinatology*, **5:** 310-314 (1981).

4. Knutti, R., Rothweiler, H., Schlatter, C. The effect of pregnancy on the pharmacokinetics of caffeine. *Archives of Toxicology*, **5:** 187-192 (1982).

5. Eskenazi, B. Caffeine during pregnancy: grounds for concern? *Journal of the American Medical Association*, **270:** 2973-2974 (1993).

6. Dlugosz, L., Bracken, M. Reproductive effects of caffeine: a review and theoretical analysis. *Epidemiological Reviews*, **14:** 83-100 (1992).

7. Tornaletti, S., Russo, P., Parodi, S., Pedrini, A. Studies on DNA binding of caffeine and its derivatives: evidence of intercalation by DNA-unwinding experiments. *Biochimica et Biophysica Acta*, **1007:** 112-115 (1989).

8. Morris, M., Weinstein, L. Caffeine and the fetus: is trouble brewing? *American Journal of Obstetrics and Gynecology*, **140:** 607-610 (1981).

9. Pollard, I., Smallshaw, J. Male mediated caffeine effects over two generations of rats. *Journal of Developmental Physiology*, **10:** 271-281 (1988).

10. Wilcox, A., Weinberg, C., Baird, D. Caffeinated beverages and decreased fertility. *Lancet*, **2:** 1453-1456 (1988).

11. Joesoef, M., Beral, V., Rolfs, R., Aral, S. Are caffeinated beverages risk factors for delayed conception? *Lancet*, **1:** 136-137 (19990).

12. Olsen, J. Cigarette smoking, tea and coffee drinking, and subfecundity. *American Journal of Epidemiology*, **133:** 734-739 (1991).

13. Grimm, V., Frieder, B. Prenatal caffeine causes long-lasting behavioural and neurochemical changes. *International Journal of Neurosciences*, **41:** 15-28 (1988).

14. Jacobson, S., Fein, G. Jacobsen, J. et al. Neonatal correlates of prenatal exposure to smoking caffeine and alcohol. *Infant Behaviour and Development*, **7:** 253-264 (1984).

15. Barr, H., Streissguth, A. Caffeine use during pregnancy and child outcome: a 7-year prospective study. *Neurotoxicology and Teratology*, **13:** 441-448 (1991).

16. Tuomilehto, J., Tuomilehto-Wolf, E., Virtala, E., LaPorte, R. Coffee consumption as a trigger for insulin dependent diabetes mellitus in childhood. *British Medical Journal*, **300:** 642-643 (1990).

17. Srisuophan, W., Bracken, M. Caffeine consumption during pregnancy and association with late spontaneous abortion. *American Journal of Obstetrics and Gynecology*, **154:** 14-20 (1986).

18. Kline, J., Levin, B., Silverman, J. et al. Caffeine and spontaneous abortion of known karyotype. *Epidemiology*, **2:** 409-417 (1991).

19. Fenster, L., Eskenazi, B., Windham, G., Swan, S. Caffeine consumption during pregnancy and spontaneous abortion. *Epidemiology*, **2:** 168-174 (1991).

20. Armstrong, B., McDonald, A., Sloan, M. Cigarette, alcohol and coffee consumption and spontaneous abortion. *American Journal of Public Health*, **82:** 85-87 (1992).

21. Mills, J., Holmes, L., Aarons, J. et al. Moderate caffeine use and the risk of spontaneous abortion and intrauterine growth retardation. *Journal of the American Medical Association*, **269**: 593-597 (1993).

22. Hatch, E., Bracken, M. Caffeine use during pregnancy: what is safe? *Journal of the American Medical Association*, **270:** 46-47 (1993).

23. Eskenazi, B., Fenster, L., Samuels, S., Swan, S. Caffeine use during pregnancy: what is safe? *Journal of the American Medical Association*, **270:** 47 (1993).

24. Infante-Rivard, C., Fernández, A., Gauthier, R. et al. Fetal loss associated with caffeine intake before and during pregnancy. *Journal of the American Medical Association*, **270:** 2940-2943 (1993).

Safer treatments for haemophilia in prospect

The haemophilias are sex-linked, recessive, genetically-determined conditions characterized by a lifelong tendency to excessive haemorrhage and a greatly prolonged blood coagulation time. They are recognized haematologically by specific deficiencies in one of two vital protein coagulation factors, either factor VIII in haemophilia A (classical haemophilia) or factor IX in haemophilia B (Christmas disease). The nucleotide sequences that encode these factors are contained within genes that have been successfully cloned and that are situated in the long arm of the X chromosome (1, 2). Both types of haemophilia are now known to result from a wide range of genetic defects at these loci (3).

Haemophilia A (which is estimated to occur in about 1: 5000 Caucasian males) is more common and more frequently severe than haemophilia B. The clinical severity of the condition correlates with the deficit in expression of the implicated coagulation factor. In the more severe forms, repeated spontaneous bleeding into joints results in chronic synovitis and ultimately, if untreated, in fixed arthroses.

Progression of the disease is prevented for as long as the patient receives supplements of concentrates of clotting factors in amounts sufficient to suppress spontaneous and excessive bleeding. Frequent and regular injections are necessary to maintain normal haemostatis for extended periods. Because of the considerable cost of this replacement therapy and because few countries as yet collect plasma in the considerable amounts required to generate the necessary stocks of concentrates, preventive therapy remains an ideal rather than a practicable option for the vast majority of haemophiliac patients.

For many years the required concentrates have been extracted from pools of plasma prepared from upwards of 3000 units of blood. In the absence of reliable screening tests, there is substantial risk in most countries that one or more of the donors contributing to each pool is infected with hepatitis (4) or HIV (5). This was tragically reflected in the high proportion of deaths from HIV recorded among haemophiliac patients treated in the early 1980s. The subsequent application of reliable methods of selecting and screening potential donors, and of inactivating viruses by heat treatment, virucidal detergents, and use of highly purified monoclonal antibodies has largely eliminated this risk of contamination (6, 7).

Within the past few years, safety has been further advanced by the production of several versions of factor VIII by recombinant technology (8-10). A recombinant version of factor IX may also soon become available (11). These are prepared, not from pools of plasma consisting of several thousands of donations, but from an isolate obtained from a single donor in whom transmissible viral disease has been excluded by meticulous screening.

Further advancement in the management of the haemophilias is now in prospect with the development of gene therapy (11). Provision of the requisite gene through orthotopic liver transplantation is reported to have resulted in successful cure of haemophilia (12), but this technique cannot be undertaken in a routine setting. Less invasive

procedures, it is hoped, will ultimately provide a truly preventive approach to control. Optimism runs high because these diseases should be particularly responsive to such intervention, in that the process of coagulation is not related in a simple quantitative way to the expression of coagulation factors; considerable clinical benefit results from relatively low levels of expression; while over-expression has no known adverse consequence. In general terms, this technology is dependent upon isolation from a healthy donor of genes encoding for the proteins of factor VIII or factor IX and their insertion in a functional state into the genetic apparatus of hepatocytes — or, perhaps, endothelial cells — of recipient patients. It is the latter of these two requirements that continues to pose fundamental scientific problems.

Commonly, but not invariably (13), successful integration of extraneous genetic material into an appropriate target cell has involved use of a viral vector — most commonly a retrovirus — that is capable of penetrating relevant host cells but that has been stripped of genes that confer pathogenic virulence and the ability to replicate (14, 15). Expression of the inserted genetic material then depends upon transcription of viral RNA into DNA (a process described as transduction). Moreover, if this expression is to have therapeutic potential, it must be sustained over a period of time sufficient to provide for effective clinical management.

The simplest method of administration of viral vectors is by injection into the systemic circulation or directly into target tissues. However, two vital conditions must be satisfied for this approach to be successful: the vector should not be immediately inactivated by host antibodies and it should be targeted to cell types with the potential to express the relevant protein. Limited progress has been made in modifying the envelope proteins of retroviral vectors to facilitate their attachment to specific receptors on liver cells (16) but, since transduction occurs only in actively dividing cells (17), the proportion of receptive cells in normal liver tissue remains limited.

As an alternative to the use of viral vectors, several physical and chemical methods have been developed to insert exogenous DNA into target cells either as plasmids or linear fragments that remain separate from the genomic DNA. This approach, which is known as "transfection" has attraction in the genetic modification of non-proliferating cells, including normal hepatocytes. In these cells episomal DNA may remain functional for relatively long periods, whereas it is likely to be lost within a few days or weeks in the course of successive cycles of mitosis in rapidly dividing cells (18). Transfection is readily applied only to target cells maintained in tissue culture. This enables the genetic manipulations to be performed under carefully controlled conditions. This advantage is often nullified, however, by the difficulty in sustaining these cells when they are implanted back into the donor patient (11).

Expression of human factor VIII and factor IX has now been accomplished in various primary cells and cell lines (11). Results thus far have been more encouraging in the case of factor IX. Implantation of transduced fibroblasts into rodents has resulted in detectable circulating levels of the protein for periods extending over several weeks (19-21). Cessation of expression appears to be determined by complex interactions between the transduced cell and the vector (22), but the results of one study in which low levels of canine factor IX was expressed over a period of nine months in mouse myoblasts implanted into syngenic mice (23) suggests that this constraint may soon be overcome.

References

1. Camerino, G., Grzeschik, K., Jaye, M. et al. Regional localization on the human X chromosome and polymorphism of the coagulation factor IX gene (hemophilia B locus). *Proceedings of the National Academy of Sciences, USA*, **81:** 498-502 (1984).

2. Mandel, J., Willard, H., Nussbaum, R. et al. Report of the committee on the genetic constitution of the X chromosome. *Cytogenetics Cell Genetics*, **49:** 107-128 (1988).

3. Lozier, J., High, K. Molecular basis of hemophilia. *Hematologic Pathology*, **4:** 1-26 (1990).

4. Goedert, J., Kessler, C., Aledort, L. et al. A prospective study of human immunodeficiency virus type 1 infection and the development of AIDS in subjects with hemophilia. *New England Journal of Medicine*, **321:** 1141-1152 (1989).

5. Troisi, C., Hollinger, F., Hoots, W. et al. A multicenter study of viral hepatitis in a United States hemophiliac population. *Blood*, **81:** 412-418 (1993).

6. Schimpf, K., Mannucci, P., Kreutz, W. et al. Absence of hepatitis after treatment with a pasteurized factor VIII concentrate in patients with hemophilia and no previous transfusions. *New England Journal of Medicine*, **316:** 918-922 (1987).

7. Schimpf, K., Brackmann, H., Kreutz, W. et al. Absence of anti-human immunodeficiency virus types 1 and 2 seroconversion after treatment of hemophilia A of von Willebrand's disease with pasteurized factor VIII concentrate. *New England Journal of Medicine*, **321:** 1148-1152 (1989).

8. White, G., Campbell, W., Kingdon, H., Shoemaker, C. Use of recombinant antihemophilic factor in the treatment of two patients with classic hemophilia. *New England Journal of Medicine*, **320:** 166-170 (1989).

9. Schwartz, R., Abildgaard, C., Aledort, L. et al. Human recombinant DNA-derived antihemophilic factor (factor VIII) in the treatment of hemophilia A. *New England Journal of Medicine*, **323:** 1800-1805 (1990).

10. Lusher, J., Arkin, S., Abildgaard, C. et al. Recombinant factor VIII for the treatment of previously untreated patients with hemophilia A. *New England Journal of Medicine*, **328:** 453-459 (1993).

11. Lozier, J., Brinkhous, K. Gene therapy and the hemophilias. *Journal of the American Medical Association*, **271:** 47-51 (1994).

12. Lewis, J., Bontempo, F., Spero, J. et al. Liver transplantation in a haemophiliac. *New England Journal of Medicine*, **312:** 1189-1190 (1985).

13. Zhu, N, Liggitt, D., Liu, Y., Debs, R. Systemic gene expression after intravenous DNA delivery into adult mice. *Science*, **261:** 209-211 (1993).

14. Verma, I. Gene therapy. *Scientific American*, **63:** 68-84 (1990).

15. Miller, A. Retrovirus packaging cells. *Human Gene Therapy*, **1:** 5-14 (1990).

16. Salmons, B., Gunzberg, W. Targeting of retroviral vectors for gene therapy. *Human Genetics and Therapeutics*, **4:** 129-141 (1993).

17. Cardosos, J., Branchereau, S., Jeyaraj, P. et al. In situ retrovirus-mediated gene transfer into dog liver. *Human Genetics and Therapeutics*, **4:** 411-418 (1993).

18. Gao, I., Wagner, E., Cotten, M. et al. Direct *in vivo* gene transfer to airway epithelium employing adenovirus-polylysine-DNA complexes. *Human Gene Therapy*, **4:** 17-24 (1993).

19. St Louis, D., Verma, I. An alternative approach to somatic gene therapy. *Proceedings of the US National Academy of Sciences*, **85:** 3150-3154 (1988).

20. Palmer, T., Thompson, A., Miller, A. Production of human factor IX in animals by genetically modified skin fibroblasts: potential therapy for hemophilia B. *Blood*, **73:** 438-445 (1989).

21. Carr-Brendell, V., Lozier, J., Thomas, T. et al. An immuno-isolation device for implantation of genetically engineered cells: long-term expression of factor IX in rats. *Journal of Cellular Biochemistry*, **224:** 17E (1993).

22. Ramesh, N., Lau, S., Palmer, T. et al. High level human adenosine deaminase expression in dog skin fibroblasts is not sustained following transplantation. *Human Gene Therapy*, **4:** 3-7 (1993).

23. Dai, Y., Roman, M., Naviaux, R. Verma, I. Gene expression via primary myoblasts: long-term expression of factor IX protein following transplantation *in vivo*. *Proceedings of the National Academy of Sciences, USA.*, **89:** 10892-10895 (1992).

Hepatitis B vaccines: immunogenicity reappraised

Vaccines to prevent hepatitis B infections became available in many countries during the 1980s. First to be launched was a plasma-derived product, but this was soon superseded by recombinant preparations (1). These vaccines are in greatest need in sub-Saharan Africa and south-east Asia where hepatitis B is hyperendemic, and where children are at high risk of becoming infected during the first few years of life. Subsequently, most of these become chronic carriers of the virus, and many ultimately die from chronic hepatitis, cirrhosis or primary hepatocellular carcinoma.

Vaccination at birth has been shown to be highly effective (2). The recommended schedule of three intramuscular injections results in rates of sero-conversion exceeding 90%, and children have been protected from persistent infection over periods of 10 years and more (3–5).

Also at risk of hepatitis B are older children and adults everywhere who may become infected either through sexual contact, or as a result of transfusion or accidental inoculation of contaminated blood. At particular risk are homosexual men and occupational groups, including health workers, who are frequently exposed to blood and other body fluids (6). The resulting infections sometimes lead to chronic hepatic disease, and typically cause severe and sometimes fulminating acute hepatitis.

Vaccination of young adults at specific risk has hitherto been regarded as highly effective insofar as it results in an immunogenic response whose incidence, intensity and persistence are comparable to that obtained in children (7, 8). In the United States and elsewhere, older persons —

including health workers and others at occupational risk of infection — have been offered special incentives to accept vaccination (9, 10). Routine postvaccination testing for immunogenicity has not been widely practised within these groups (11) and it has been generally assumed that booster doses will not be required within 10 years of initial vaccination (12).

Evidence has now accumulated (13–15), however, that calls the efficacy of adult immunization into question. In particular, recent surveys of the outcome of two large-scale adult vaccination programmes in the United States (14, 15) have confirmed that several factors can attenuate the immunological response. The most evident are increasing age, smoking, extreme obesity (presumably because this creates problems in siting an intramuscular injection) (14, 16), and variations in the immunogenicity of vaccines prepared by different manufacturers (15).

In the populations studied, these factors collectively increased the risk of non-response to the vaccine by some two fold (14, 15). They also tended to reduce the time course of the immunogenic reaction (14). It has been estimated from other studies that 25% to 60% of adults lose all detectable antibody to hepatitis B vaccine within 6 to 10 years (7, 17–18).The clinical implications of this attenuation are unclear. Some experts — noting that loss of detectable antibody to measles vaccine correlates with waning immunity (19) — have reacted by calling for booster doses to be administered to older vaccinees on the basis of their antibody titres (20–22). Others argue that vaccinated persons who have lost detectable antibody are likely to be protected when re-challenged by subsequent exposure by an anamnestic antibody response that is facilitated by the long incubation period of hepatitis B (23).

All agree that adults requiring protection against hepatitis B should be vaccinated at the earliest opportunity; that further studies need to be undertaken to determine the best approach to vaccination in patients likely to respond inadequately; and that provision should be made for open-ended monitoring of possible differences in the immunogenicity of vaccines prepared by different manufacturers.

References

1. Hadler, S. Vaccines to prevent hepatitis B and hepatitis A infections. *Infectious Disease Clinics of North America*, **4:** 29-46 (1990).

2. Viral hepatitis. *WHO Drug Information*, **7:** 128-133 (1993).

3. West, D. Clinical experience with hepatitis B vaccines. *American Journal of Infection Control*, **17:** 172-180 (1989).

4. Szmuness, W., Stevens, C., Harley, E. et al. Hepatitis B vaccine: demonstration of efficacy in a controlled clinical trial in a high-risk population in the United States. *New England Journal of Medicine*, **303:** 833-841 (1980).

5. Coursaget, P., Yvonnet, B., Chotard, J. et al. Seven year study of hepatitis B vaccine efficacy in infants from an endemic area (Senegal). *Lancet*, **2:** 1143-1145 (1986).

6. Shapiro, C., Margolis, H. Hepatitis B epidemiology and prevention. *Epidemiological Reviews*, **12:** 221-227 (1990).

7. Hadler, S., Francis, D., Maynard, J. et al. Long-term immunogenicity and efficacy of hepatitis B vaccine in homosexual men. *New England Journal of Medicine*, **315:** 209-214 (1986).

8. Prinsen, H., Goilav, C., Safary, A. et al. Immunogenicity and tolerance of a yeast-derived hepatitis B vaccine in homosexual men. *Postgraduate Medical Journal*, **63:** 147-149 (1987).

9. Alexander, P., Johnson, R., Williams, W. et al. Hepatitis B vaccination programs for health care personnel in US hospitals. *Public Health Report*, **105:** 610-616 (1990).

10. Department of Labor, Occupational Safety and Health Administration. Occupational exposure to bloodborne pathogens: rules and regulations. *Federal Register*, **56:** 64004-64182 (1991).

11. Immunization Practices Advisory Committee. Protection against viral hepatitis. *Morbidity and Mortality Weekly Report*, **39**: 1-21 (1990).

12. Centers for Disease Control. Hepatitis B virus: a comprehensive strategy for eliminating transmission in the United States through universal childhood vaccination: recommendations of the Immunization Practices Advisory Committee. *Morbidity and Mortality Weekly Report*, **40**(RR-13)**:** 1-20 (1991).

13. Shaw, F., Guess, H., Roets, J. et al. Effect of anatomic injection site, age and smoking on the immune response to hepatitis B vaccination. *Vaccine*, **7:** 425-430 (1989).

14. Roome, A., Walsh, S., Cartter, M., Hadler, J. Hepatitis B vaccine responsiveness in Connecticut public safety personnel. *Journal of the American Medical Association*, **270:** 2931-2934 (1993).

15. Wood, R., MacDonald, K., White, K. et al. Risk factors for lack of detectable antibody following hepatitis B vaccination of Minnesota health care workers. *Journal of the American Medical Association*, **270:** 2935-2939 (1993).

16. Weber, D., Rutala, W., Samsa, G. et al. Obesity as a predictor of poor antibody response to hepatitis B plasma vaccine. *Journal of the American Medical Association*, **254**: 3187-3189 (1985).

17. Wainwright, R., McMahon, B., Bulkow, L. et al. Duration of immunogenicity and efficacy of hepatitis B vaccine in a Yupik Eskimo population. *Journal of the American Medical Association*, **261:** 2362-2366 (1989).

18. Stevens, C., Toy, P., Taylor, F. et al. Prospects for control of hepatitis B virus infection: implications of childhood vaccination and long-term protection. *Pediatrics*, **90**: 170-173 (1992).

19. Centers for Disease Control. Measles prevention: recommendations of the Immunization Practices Advisory Committee. *Morbidity and Mortality Weekly Report*, **38:** S-9 (1989).

20. International Working Group on Hepatitis B Immunization. Immunization against hepatitis B. *Lancet*, **1:** 875-876 (1988).

21. Jilg, W., Schmidt, M., Dienhardt, F. Decline of anti-HBs after hepatitis B vaccination and timing of revaccination. *Lancet*, **335:** 173-174 (1990).

22. Coursaget, P., Yvonnet, B., Gilks, W. et al. Scheduling of revaccination against hepatitis B virus. *Lancet*, **337:** 1180-1183 (1991).

23. Margolis, H., Presson, A. Host factors related to poor immunogenicity of hepatitis B vaccine in adults: another reason to immunize early. *Journal of the American Medical Association*, **270**: 2971-2972 (1993).

Iron supplementation and pregnancy

The United States Public Health Service has recently published a scientific review and a policy statement on routine iron supplementation during pregnancy (1). The basic conclusion is that "although iron supplementation can improve maternal hematologic indexes, controlled clinical trials .... have failed to demonstrate that iron supplementation or changes in hematologic indexes actually improve clinical outcomes for the mother or newborn".

However, the responsible task force qualifies its findings by emphasizing that its conclusions apply to the United States and not to countries where iron deficiency anaemia is common and often severe. It also points to the impossibility of drawing firm conclusions and of formulating definitive advice on the basis of published studies that, in general, are inadequate either in their size or design to demonstrate with reasonable certainty treatment effects that might have therapeutic implications.

In the United States national statistics indicate that some 5% to 10% of pregnant women are iron deficient (2, 3). Each woman requires about 1 g of iron (or some 6 mg iron/day throughout the last 6 months of pregnancy) to replace net losses during pregnancy (4), yet the average diet in the United States provides only about 1.3 mg absorbable iron daily (1).

Given these facts, it is disconcerting that the task force should conclude "few studies of the health effects of iron deficiency have included women". The postulated risks of clinically demonstrable anaemia to the mother during pregnancy are manifold and serious (5–9). They include increased fatigue and impaired work performance; cardiovascular stress; possible increased vulnerability to infection; poor tolerance to heavy blood loss and surgical intervention during delivery coupled with a presumptive increased need for blood transfusion.

The few relevant studies that have been undertaken in developing countries provide firm evidence that severe anaemia during pregnancy is associated with a substantially increased risk of pre-eclampsia, low birth weight, stillbirth and neonatal death (10–14). Similar studies undertaken in developed countries indicate — with one marked exception (15) — that even mild to moderate anaemia is associated with premature delivery, low birth weight, fetal abnormality, and fetal death (16–20).

There is also observational evidence that iron-deficient infants score poorly on tests of mental and psychomotor development (21–26), and it seems that these deficiencies may persist long after anaemia has been corrected (27). However, several studies indicate — again, with one notable exception (28) — that women who are mildly to moderately iron deficient are not at increased risk of delivering an iron-deficient child (29–34). Nor is there evidence of correlation, save in severe anaemia, between intake or storage of maternal iron and the iron content of breast milk (35–37).

It is a basic tenet of good medical practice that clinically significant maternal anaemia needs to be prevented or promptly corrected both in the interest of the mother and of the fetus. This is not challenged by the task force. However, it finds the

data sparse and the conclusions conflicting on whether correction of lesser degrees of anaemia offers tangible benefit (15, 38, 39). Moreover, it questions whether the demonstrated association between anaemia or iron deficiency of moderate degree and adverse obstetric events is necessarily causal. Most of the published studies do not control for other factors, such as smoking, malaria and other parasitic diseases, that are established causes of low birth weight and prematurity.

The task force, in concluding that the evidence is insufficient to recommend either in favour of or against routine iron supplementation during pregnancy within the USA, acknowledges that its findings are not consonant with recommendations supportive of routine supplementation that have been formulated by some other national bodies (40–42). It points, however, to other studies and overviews that have not supported the routine use of iron supplements in healthy, well-nourished women (43–45). Until further evidence is forthcoming it accords to clinicians the responsibility of determining whether and how to screen women for anaemia and iron deficiency and of deciding, on a case-by-case basis, the need for iron supplements.

In countries or population groups in which the incidence of clinically significant iron-deficiency anaemia is higher than in the United States, the case for routine supplementation may well become cost effective (8). The vital consideration is that routine screening should ensure that every pregnant woman who requires iron supplementation should receive them at the earliest opportunity.

References

1. US Preventive Services Task force. Routine iron supplementation during pregnancy. Policy Statement and Review Article. *Journal of the American Medical Association*, **270:** 2846-2854 (1993).

2. Food and drug Administration. *Assessment of the iron nutritional status of the US population based on data collected in the second national health and nutrition examination survey*, 1976-1980. Life Sciences research Office, Bethesda, Md 1984.

3. Centers for Disease Control. CDC criteria for anemia in children and childbearing-age women. *Morbidity and Mortality Weekly Report*, **38:** 400-404 (1989).

4. Institute of Medicine. *Nutrition during pregnancy, Part II: Nutrient supplements* (pp 272-298). National Academy Press, Washington, DC. 1990.

5. Elwood, P. Evaluation of the clinical importance of anemia. *American Journal of Clinical Nutrition*, **26:** 958-964 (1973).

6. Bentley, D. Iron metabolism and anaemia in pregnancy. *Clinical Haematology*, **14:** 613-628 (1985).

7. Worthington-Roberts, B. The role of nutrition in pregnancy course and outcome. *Journal of Environmental Pathology, Toxicology and Oncology*. **5:** 1-80 (1985).

8. Horn, E. Iron and folate supplements during pregnancy: supplementing everyone treats those at risk and is cost effective. *British Medical Journal*, **297:** 1325-1327 (1988).

9. Dallman, P. Iron deficiency: does it matter? *Journal of Internal Medicine*, **226:** 367-372 (1989).

10. Macgregor, M. Maternal anaemia as a factor in prematurity and perinatal mortality. *Scottish Medical Journal*, **8:** 134-140 (1963).

11. Reinhardt, M., Maternal anaemia in Abidjan: its influence on placenta and newborns. *Helvetica Paediatrica Acta*, **33** (suppl 41): 43-63 (1978).

12. Lister, U., Rossiter, C., Chong, H. Perinatal mortality. *British Journal of Obstetrics and Gynaecology*, **92** (suppl 5): 86-999 (1985).

13. Bhargava, M., Kumar, R., Iyer, P. et al. Effect of maternal anaemia and iron depletion on foetal stores, birthweight, and gestation. *Acta Paediatrica Scandinavica*, **78:** 321-322 (1989).

14. Brabin, B., Ginny, M., Sapau, J. et al. Consequences of maternal anaemia on outcome of pregnancy in a malaria endemic area in Papua New Guinea. *Annals of Tropical Medicine and Parasitology*, **84:** 11-24 (1990).

15. Knotterus, J., Delgardo, L., Knipschild, P. et al. Haematological parameters and pregnancy outcome: a prospective cohort study in the third trimester. *Journal of Clinical Epidemiology*, **43:** 461-466 (1990).

16. Klein, L. Premature birth and maternal prenatal anemia. *American Journal of Obstetrics and Gynecology*, **83:** 588-590 (1962).

17. Murphy, J., O'Riordan , J., Newcombe, R. et al. Relation of haemoglobin levels during first and second trimesters to outcome of pregnancy. *Lancet*, **1:** 992-994 (1986).

18. Lieberman, E., Ryan, K., Monson, R. et al. Association of maternal hematocrit with premature labor. *American Journal of Obstetrics and Gynecology*, **157:** 107-114 (1988).

19. Klebanoff, M., Shiono, P., Selby, J. et al. Anemia and spontaneous preterm birth. *American Journal of Obstetrics and Gynecology*, **164:** 59-63 (1991).

20. Scholl, T., Hediger, M., Fischer, R. et al. Anemia vs iron deficiency: increased risk of preterm delivery in a prospective study. *American Journal of Clinical Nutrition*, **55:** 985-988 (1992).

21. Oski, F., Honig, A. The effects of therapy on the development scores of iron-deficient infants. *Journal of Pediatrics*, **92:** 21-25 (1978).

22. Lozoff, B., Brittenham, G., Viteri, F. et al. The effects of short-term oral iron therapy on developmental deficits in iron-deficient anemic infants. *Journal of Pediatrics*, **100:** 351-357 (1982).

23. Walter, T., Kovalskys, J., Stekel, A. Effect of mild iron deficiency on infant mental development scores. *Journal of Pediatrics*, **102:** 519-522 (1983).

24. Grindulis, H., Scott, P., Belton, N. et al. Combined deficiency of iron and vitamin D in Asian toddlers. *Archives of Diseases of Children*, **61:** 843-848 (1986).

25. Lozoff, B., Brittenham, G., Wolf, A. et al. Iron-deficiency anemia and iron therapy effects on infant developmental test performance. *Pediatrics*, **79:** 981-995 (1987).

26. Walter, T., De Andraca, I., Chadud, P. et al. Iron-deficiency anemia: adverse effects on infant psychomotor development. *Pediatrics*, **84:** 7-17 (1989).

27. Lozoff, B., Jimenez, E., Wolf, A. Long-term developmental outcome of infants with iron deficiency anaemia. *New England Journal of Medicine*, **325:** 687-694 (1991).

28. Colomer, J., Colomer, C., Gutierrez, D et al. Anaemia during pregnancy: report from the Valencia Infant Anemia Cohort (VIAC) study. *Paediatric and Perinatal Epidemiology*, **4:** 196-204 (1990).

29. Rios, E., Lipschitz, D., Cook, J. et al. Relationship of maternal and infant iron stores as assessed by determination of plasma ferritin. *Pediatrics*, **55:** 694-699 (1975).

30. Hussain, M., Gaarfar, T., Laulicht, M. et al. Relation of maternal and cord blood serum ferritin. *Archives of Diseases of Children*, **52:** 782-784 (1977).

31. Bratlid, D., Moe, P. Hemoglobin and serum ferritin levels in mothers and infants at birth. *European Journal of Pediatrics*, **134:** 125-127 (1980).

32. Messer, R., Russo, A., McWhirter, D. et al. Serum ferritin in term and preterm infants. *Australian Paediatrics Journal*, **16:** 185-188 (1980).

33. Celada, A., Busset, R., Gutierrez, J. et al. Maternal and cord blood ferritin. *Helvetica Paediatrica Acta*, **37:** 239-244 (1982).

34. Agrawal, R., Tripathi, A., Agrawal, K. Cord blood haemoglobin, iron and ferritin status in maternal anaemia. *Acta Paediatrica Scandinavica*, **72:** 545-548 (1983).

35. Murray, M., Murray, A., Murray, N. et al. The effect of iron status of Nigerian mothers on that of their infants at birth and at six months, and on the concentration of iron in breast milk. *British Journal of Nutrition*, **39:** 627-630 (1978).

36. Vuori, E., Makinen, S., Kara, R. et al. The effects of the dietary intakes of copper, iron, manganese, and zinc on the trace element content of human milk. *American Journal of Clinical Nutrition*, **33:** 227-231 (1980).

37. Celada, A., Busset, R., Gutierrez, J. et al. No correlation between iron concentration in breast milk and maternal iron stores. *Helvetica Paediatrica Acta*, **37:** 11-16 (1982).

38. Taylor, D., Lind, T. Haematological changes during normal pregnancy: iron-induced macrocytosis. *British Journal of Obstetrics and Gynaecology*, **83:** 760-767 (1976).

39. Kullander, S., Kallen, B. A prospective study of drugs and pregnancy. *Acta Obstetrica Gynaecologica Scandinavica*, **55:** 287-295 (1976).

40. Institute of Medicine. *Nutrition during pregnancy, Part II: Nutritional supplements* (pp 272-298). National Academy Press, Washington, DC., 1990.

41. Federation of American Societies for Experimental Biology. *Guidelines for the assessment and management of iron deficiency in women of childbearing age.* Bethesda, Md. 1991.

42. American College of Obstetricians and Gynecologists, American Academy of Pediatrics. *Guidelines for perinatal care.* Washington, DC. 1992.

43. Hemminki, E., Starfield, B. Routine administration of iron and vitamins during pregnancy: review of controlled clinical trials. *British Journal of Obstetrics and Gynaecology*, **85:** 404-410 (1978).

44. Blankson, M. Maternal haematological status and pregnancy outcome. In: Merkatz, I., Thompson, J., Mullen, P., Goldenberg, R. eds. *New Perspectives on Prenatal Care.* Elsevier, New York, NY. 1990, pp. 414-415.

45. Woolf, S., Sox, H. The Expert Panel on Preventive Services: continuing the work of the US Preventive Services Task Force. *American Journal of Preventive Medicine*, **7:** 326-330 (1991).

Zidovudine: lack of effect in asymptomatic patients

The final report has now been published of a study undertaken in various centres within France, Ireland and the United Kingdom with the aim of confirming or rejecting the claim that zidovudine retards the emergence of AIDS in patients teated in the asymptomatic stage of HIV infection (1). This confirms preliminary findings published last year . No significant differences were demonstrated either in deaths or rates of progression of the disease among patients who started taking zidovudine shortly after diagnosis of HIV infection and those who first received it after developing symptoms.

Over 1700 symptomless patients with HIV infection were admitted to the placebo-controlled trial, which was launched in 1988. The double-blind rigour of the trial was subsequently compromised to allow physicians to place patients with low CD+ counts on zidovudine. As a result, almost one quarter of the patients became aware that they were receiving the pharmacologically active treatment. In the view of the trialists this in no way erodes confidence in the conclusions of the study.

The results of the trial are disappointing not only in that they define an important limitation in the therapeutic potential of zidovudine. They also bring into contention the value of monitoring CD+ counts as an indicator of clinical responsiveness to anti-HIV drugs. The administration of zidovudine significantly increased the plasma concentration of CD+ cells in symptomless patients without providing clinical benefit in this phase of the disease. Without a reliable laboratory indicator of immunological or clinical responsiveness, efforts to further elucidate the mechanisms of infection and to assess the potential of candidate anti-HIV drugs and vaccines could be markedly set back.

References

1. Aboulker, J..P., Swart, A.M. Preliminary analysis of the Concorde trial. *Lancet*, **341:** 889-890 (1993).

General Information

Adjuvant therapy in cancer

In the previous issue of this journal some recent evidence was presented to show that whereas metastases of breast carcinoma in soft tissue sites respond significantly to systemic adjuvant therapy, lesions in bone and viscera are largely unresponsive (1).

Many factors influence the prognosis of breast cancer. They include the age of the patient at diagnosis, and particularly whether she is premenopausal or post-menopausal; the degree of lymph node involvement (2, 3); the histologic grade of the tumour (4); the DNA content of the malignant cells (5), their rate of proliferation (6), and the presence or absence of oncogenes (7–10) and other molecular markers in tumour cells (11–14).

Prognosis is also inevitably dependent in operable breast cancer on the supplementary use of radiotherapy, systemic adjuvant chemotherapy, pharmacotherapy involving tamoxifen, other antiestrogen agents, or ovarian ablation. Postmenopausal women with tumours positive for estrogen receptors are particularly responsive to endocrine therapy (15, 16) and tamoxifen has become a standard component in the adjunctive therapy of node-positive cancer in such patients (17, 18). However, the relationship between prognostic factors and the response to adjuvant chemotherapy is less clear (19–21). For more than 20 years multi-agent chemotherapy has been generally favoured for premenopausal women with node-positive breast cancer (24), yet the regimens of cytotoxic drugs that are routinely used have been devised largely on indirect evidence and uncertainty has long prevailed over dosage schedules (22, 23).

A combination of cyclophosphamide, methotrexate, and fluorouracil has been most widely studied (25–28). In recent trials, doxorubicin, which has been successfully used alone in the management of advanced breast cancer, has been either added to this combination or substituted for methotrexate (29, 30). Now that a large prospective randomized study has indicated that survival is significantly prolonged as both dosage and, perhaps, intensity of dosage are increased towards the limit of tolerance (30), these regimens can be prescribed with greater objectivity.

These results have also been interpreted as justifying trials of higher-dose chemotherapy in which haemopoiesis is preserved by bone marrow stimulating factors, progenitor cell support or autologous bone marrow transplantation (30). Cytotoxic chemotherapy, it seems, has not yet attained its full potential. The ground has been prepared for a further round of investigation. Meanwhile, the immediate implication of this study is that, to obtain maximum benefit for women with early breast cancer, cytotoxic drugs need to be used at the highest tolerated dosages.

References

1. Breast cancer relapse: effect of systemic chemotherapy. *WHO Drug Information*, **8:** 22-23 (1994).

2. Carter, C., Allen, .C,. Henson, D. Relation of tumor size, lymph node status, and survival in 24 740 breast cancer cases. *Cancer*, **63:** 181-187 (1989).

3. Identification of breast cancer patients with high risk of early recurrence after radical mastectomy. II. Clinical and pathological correlation: a report of the Primary Therapy of Breast Cancer Study Group. *Cancer:* **42:** 2809-2826 (1978).

4. Henson, D., Ries, L., Freedman, L., Carriaga, M. Relationship among outcome, stage of disease, and histologic grade for 22 616 cases of breast cancer: the basis for a prognostic index. *Cancer*, **68:** 2142-2149 (1991).

5. Hedley, D., Friedlander, M., Taylor, I. Application of DNA flow cytometry to paraffin-embedded archival material for the study of aneuploidy and its clinical significance. *Cytometry*, **6:** 327-333 (1985).

6. O'Reilly, S., Camplejohn, R., Millis, R. et al. Proliferative activity, histological grade and benefit from adjuvant chemotherapy in node positive breast cancer. *European Journal of Cancer*, **26:** 1035-1038 (1990).

7. Barnes, D., Meyer, J., Gonzalez, G. et al. Relationship between c-*erb* B-2 immunoreactivity and thymidine labelling index in breast carcinoma *in situ*. *Breast Cancer Research and Treatment*, **18:** 11-17 (1991).

8. Kallioniemi, O., Holli, K., Visaskorpi, T. et al. Association of c-*erb* B-2 protein in over-expression with high rate of cell proliferation, increased risk of visceral metastasis and poor long-term survival in breast cancer. *International Journal of Cancer*, **49:** 650-655 (1991).

9. Slamon, D., Clark, G., Wong, S. et al. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/*neu* oncogene. *Science*, **235:** 177-182 (1987).

10. Harris, A., Nicholson, S., Sainsbury, R. et al. Epidermal growth factor receptor and other oncogenes as prognostic markers. *Monographs of the National Cancer Institute*, **11:** 181-187 (1992).

11. McGuire, W., Clark, G. Prognostic factors and treatment decisions in axillary-node-negative breast cancer. *New England Journal of Medicine*, **326:** 1756-1761 (1992).

12. Thor, A., Moore, D., Edgerton, S. et al. Accumulation of p53 tumor suppressor gene protein: an independent marker of prognosis in breast cancer. *Journal of the National Cancer Institute*, **84:** 844-855 (1992).

13. Isola, J., Visacorpi, T., Holli, K., Kallioniemi, O. Association of overexpression of tumor suppressor protein p53 with rapid cell proliferation and poor prognosis in node-negative breast cancer patients. *Journal of the National Cancer Institute*, **84:** 1109-1114 (1992).

14. Allred, D., Clark, G., Elledge, R. et al. Association of p53 protein expression with tumor cell proliferation rate and clinical outcome in node-negative breast cancer. *Journal of the National Cancer Institute*, **85:** 200-206 (1993).

15. Early Breast Cancer Trialists' Collaborative Group. Systemic treatment of early breast cancer by hormonal, cytotoxic, or immune therapy: 133 randomised trials involving 31 000 recurrences and 24 000 deaths among 75 000 women. *Lancet*, **339:** 1-15, 71-85 (1992).

16. Tamoxifen: a role in the prevention of breast cancer? *WHO Drug Information*, **8:** 12-16 (1994).

17. Ludwig Breast Cancer Study Group. Randomised trial of chemo-endocrine therapy, endocrine therapy, and mastectomy alone in postmenopausal patients with operable breast cancer and axillary node metastasis. *Lancet*, **1:** 1256-1260 (1984).

18. Fisher, B., Redmond, C., Legault-Poisson, S. et al. Post-operative chemotherapy and tamoxifen compared with tamoxifen alone in the treatment of node-positive breast cancer patients aged 50 years and older with tumors responsive to tamoxifen: results from the National Surgical Adjuvant Breast and Bowel Project B-16. *Journal of Clinical Oncology*, **8:** 1005-1018 (1990).

19. Fisher, E., Redmond, C., Fisher, B. Pathologic findings from the National Surgical Adjuvant Breast Project. VIII. Relationship of chemotherapeutic responsiveness to tumor differentiation. *Cancer*, **51:** 181-191 (1983).

20. Fisher, B., Fisher, E., Redmond, C. Ten-year results from the National Surgical Adjuvant Breast and Bowel Project (NSABP) clinical trial evaluation of the use of L-phenylalanine mustard (L-PAM) in the management of primary breast cancer. *Journal of Clinical Oncology*, **4:** 929-941 (1986).

21. Zambetti, M., Bonadonna, G., Valagussa, P. et al. Adjuvant CMF for node-negative and estrogen receptor-negative breast cancer patients. *Monographs of the National Cancer Institute*, **11:** 77-83 (1992).

22. Canellos, G. The dose dilemma. *Journal of Clinical Oncology*, **6:** 1363-1364 (1988).

23. Henderson, I., Hayes, D., Gelman, R. Dose-response in the treatment of breast cancer: a critical review. *Journal of Clinical Oncology*, **6:** 1501-1515 (1988).

24. Bonnadonna, G. Conceptual and practical advances in the management of breast cancer. *Journal of Clinical Oncology*, **7:** 1380-1397 (1989).

25. Bonnadonna, G., Rossi, A., Valagussa, P. et al. The CMF program for operable breast cancer with positive axillary nodes: updated analysis on the disease-free interval, site of relapse and drug tolerance. *Cancer*, **39** (suppl): 2904-2915 (1977).

26. Carmo-Pereira, J., Costa, F., Henriques, E., Carvalho, V. A randomised trial of two regimens of cyclo-phosphamide, methotrexate, 5-fluorouracil, and prednisone in advanced breast cancer. *Cancer Chemotherapy and Pharmacology*, **17:** 87-90 (1986).

27. Tannock, I., Boyd, N., DeBoer, G. et al. A randomized trial of two dose levels of cyclophosphamide, methotrexate, and fluorouracil chemotherapy for patients with metastatic breast cancer. *Journal of Clinical Oncology*, **6:** 1377-1387 (1988).

28. Engelsman, E., Klijn, J., Rubens, R. et al. "Classical" CMF versus a 3-weekly intravenous CMF schedule in postmenopausal patients with advanced breast cancer: an EORTC Breast Cancer Cooperative Group Phase III Trial. *European Journal of Cancer*, **27:** 966-970 (1991).

29. Buzzoni, R., Bonadonna, G., Valagussa, P., Zambetti, M. Adjuvant chemotherapy with doxorubicin plus cyclophosphamide, methotrexate, and fluorouracil in the treatment of resectable breast cancer with more than three positive axillary nodes. *Journal of Clinical Oncology*, **9:** 2134-2140 (1991).

30. Wood, W., Budman, D., Korzun, A. et al. Dose and dose intensity of adjuvant chemotherapy for stage II, node-positive breast cancer. *New England Journal of Medicine*, **330:** 1253-1259 (1994).

Visceral leishmaniasis: deficiencies in management

Visceral leishmaniasis (kala-azar) is usually reponsive initially to the pentavalent antimonial compounds, meglumine antimoniate or sodium stibogluconate. Both dosage and duration of treatment need to be adjusted according to the clinical response. Patients are considered to be clinically cured when no parasites are detected in splenic or marrow aspirates. However, biopsies should be carried out again after 3 and 12 months since subsequent relapse is frequent. Antimonials combined with either allopurinol, pentamidine or amphotericin B have been used with success in patients in relapse who have become unresponsive to antimonials alone.

The above synopsis encapsulates classical teaching on the management of visceral leishmaniasis (1). However, evidence has been presented over the years, not least from India where the disease is currently epidemic, to indicate that the responsiveness of the protozoal parasite to antimonial compounds is declining. Initial treatment regimens are now commonly based on higher doses than were used a decade ago (2–4). Thus, in the light of disappointing clinical experience, sodium stibogluconate is now generally administered for at least 20 days — and 40 days in the case of relapse — at a dose of some 20 mg/kg daily. This provides more than twice the dose that was generally regarded as curative in the early 1980s (5).

It now seems, however, that there is another explanation for much of this apparent resistance to therapy. A survey of 300 patients with parasitically-proven visceral leishmaniasis living in the heartland of the epidemic in southern India, has indicated that 75% failed to respond to an antimonial. Virtually all these patients, it is claimed, had been undertreated. They had allegedly bought the drug from their own resources and had relied upon unqualified practitioners to administer the injections. Between 5% and 10% had developed cellulitis or abscesses at the injection site.

Moreover, almost half of some 150 patients who received the relatively toxic drug, pentamidine, after failing to respond to antimonial therapy, had received the first drug in subtherapeutic dosage. Amphotericin B, the authors additionally claim, is also being unnecessarily used. Such deficiencies of treatment, they warn, increase the risk of resistance developing to each of the effective antileishmanial drugs now in routine use. Indeed, a report of the parasite developing tolerance to pentamidine has already been published (6).

The authors of the survey conclude, given that this situation is likely to be typical of the management of visceral leishmaniasis elsewhere, that the therapeutic prospects are bleak. The first priority, in their view, is to educate not only the primary health care services, but also the communities at risk, and the government agencies responsible for controlling and preventing the disease, on the need for assuring the provision of effective treatment regimens.

References

1. WHO Model Prescribing Information. Drugs used in parasitic diseases. World Health Organization, Geneva, 1992.

2. Thakur, C., Kumar, M., Pandey, A. Evaluation of efficacy of longer durations of therapy in fresh cases of kala-azar with sodium stibogluconate. *Indian Journal of Medical Research*, **93:** 103-110 (1991).

3. Jha, T., Singh, N., Jha, S. Therapeutic use of sodium stibogluconate on kala-azar from some hyperendemic districts of N. Bihar, India. *Journal of the Association of Physicians of India*, **42:** 868 (1992).

4. Sundar, S., Thakur, B., Tandon, N. et al. Clinico-epidemiological study of drug resistance in Indian kala-azar. *British Medical Journal*, **308:** 307 (1993).

5. World Health Organization. *The leishmaniases: report of a WHO Expert Committee.* WHO Technical Report Series, **701:** 99-109 (1984).

6. Herwaldt, B., Berman, J. Recommendations for treating leishmaniasis with sodium stibogluconate (Pentostam) and review of pertinent clinical studies. *American Journal of Tropical Medicine and Hygiene*, **46:** 296-306 (1992).

More on multidrug-resistant tuberculosis

Within the past 4 years, several outbreaks of multidrug-resistant tuberculosis have been reported from hospitals and other institutions within the United States. These clusters of cases have been characterized by strains of *Mycobacterium tuberculosis* resistant to the two key mycobactericidal compounds, isoniazid and rifampicin, and sometimes also to other first-line antituberculosis drugs (ethambutol, pyrazinamide and streptomycin); by case/fatality rates as high as 70 to 90%;

and by an incidence of co-existing HIV infection in excess of 90% (1–5).

Until recently, however, no general survey of multidrug-resistant tuberculosis had been undertaken within the United States as a whole. A report on an initial nationwide survey has now been published that is based upon the results of drug susceptibility tests for culture-positive cases of tuberculosis reported to the US Centers for Disease Control during the first quarter of 1991 (6). The results hold relevance for everyone concerned with the control of a disease which is increasing dramatically in prevalence in the USA (7) and in the world at large.

In essence, a total of some 4050 culture positive cases of tuberculosis were notified during the three months in question through an established r-porting system involving the health authorities of all 50 States (8). Drug susceptibility data were obtained from isolates provided by 3300 of these patients who were judged to be representative of the larger sample on demographic criteria. Organisms from 14% of these isolates were resistant to one or more first-line drugs, 10% of isolates were resistant to isoniazid and/or rifampicin, and some 3.5% were resistant to both isoniazid and rifampicin. Patients with drug-resistant disease were not dispersed uniformly across the country: over 60% were concentrated in New York City alone and these were less likely to be foreign born than patients with drug resistant disease elsewhere in the United States.

Several important inferences have been derived from these data (9). One of these bears upon the root causes of the deteriorating situation. It now seems clear that multidrug-resistant tuberculosis has not been largely imported into the United States through immigration, as has sometimes been suggested (10, 11), but that the disease is tending rapidly to elude control in the underprivileged social strata of a large metropolis. The causal factors that have been cited are those associated with deprivation: homelessness (12, 13), crowding in sheltered accommodation and in prisons (14, 15), poor compliance with therapy or prophylaxis (11, 16), and the impact of HIV infection (17, 18). Their correction, wherever they are apparent, will depend upon receptiveness to calls for social adjustment as much as upon intensified medical intervention.

Whatever the nature of the intervention, it can be appropriately directed and monitored only in the light of relevant epidemiological information. The USA is now setting a lead in this regard (19), but it is notable that, even here, the data that have been routinely gathered in the past provide information on the incidence and geographical distribution of new cases, but not on outcome of treatment. Notably missing has been information on those patients who fail to complete treatment and who subsequently serve as a reservoir for both transmission and development of drug resistance (9). Also missing is a prospective collaborative effort to monitor — if possible on an international basis — the relationship between the drug concentrations used to establish susceptibility of isolates in laboratory tests and those needed to assure clinical reponse to therapy. Susceptibilities of organisms may change with time; they may differ from location to location, but the need to establish and maintain meaningful correlates between laboratory tests and clinical results is fundamental.

The most immediate message inherent in these data, however, is the need to assure that the basic principles of effective antituberculosis combination chemotherapy are respected. Nearly 10% of cases entered into the survey from New York were resistant either to isoniazid, rifampicin, or to both drugs. The cardinal rule in combination chemotherapy is that, to assure a clinical response and to prevent the emergence of resistant strains, the patient should at all times receive at least two drugs to which the causative bacilli are susceptible (21, 22). Some of the patients now identified as having multidrug-resistant tuberculosis are likely to have been treated previously with a regimen based exclusively upon isoniazid and rifampicin (23). There is now a general consensus, reflected in guidelines issued globally by WHO (20), that treatment should be routinely started with a four-drug regimen (isoniazid, rifampicin, pyrazinamide and either ethambutol or streptomycin) which should be maintained for at least 8 weeks and until the drug susceptibility of isolates has been established (24–27). Equally necessary, it is emphasized, is the need for an effort to find every patient with tuberculosis, and to ensure that prescribed drugs are taken through to the completion of therapy (28).

The emergence of multidrug-resistant tuberculosis is testimony to earlier inadequacies in the treatment and management of the disease. It is a compelling indicator of the urgent need to react. If existing cases are not adequately treated in the short-term, the reservoir of resistant organisms will grow beyond any possiblity of control.

Such efforts will require additional resources, particularly in developing countries where the burden is greatest. Tuberculosis does not respect international boundaries. WHO has consequently called upon all donor governments to provide a minimum of 0.2% of their foreign aid budgets to help poor countries implement prevailing guidelines for controlling the disease (29). This, it is anticipated, would provide an additional US$ 100 million annually for purchasing essential antituberculosis drugs, training health workers in the implementation of the guidelines, and enabling the poorest countries to establish and supervise effective control programmes.

References

1. Centers for Disease Control. Nosocomial transmission of multidrug-resistant tuberculosis among HIV-infected persons — Florida and New York, 1988-1991. *Morbidity and Mortality Weekly Report*, **40:** 585-591 (1991).

2. Beck-Sagué, C., Dooley, S., Hutton, M. et al. Hospital outbreak of multidrug-resistant *Mycobacterium tuberculosis* infections: factors in transmission to staff and HIV-infected patients. *Journal of the American Medical Association*, **268:** 1280-1286 (1992).

3. Dooley, S., Jarvis, W., Martone, W., Snider, D. Multidrug-resistant tuberculosis. *Annals of Internal Medicine*, **117:** 257-259 (1992).

4. Eldin, B., Tocars, J., Grieco, M. et al. An outbreak of multidrug-resistant tuberculosis among hospitalized patients with acquired immunodeficiency syndrome. *New England Journal of Medicine*, **326:** 1514-1521 (1992).

5. Pearson, M., Jereb, J., Friedren, T. et al. Nosocomial transmission of multidrug-resistant *Mycobacterium tuberculosis*: a risk to patients and health care workers. *Annals of Internal Medicine*, **117:** 191-196 (1992).

6. Bloch, A., Cauthen, G., Onorato, I. et al. Nationwide survey of drug-resistant tuberculosis in the United States. *Journal of the American Medical Association*, **271:** 665-671 (1994).

7. Centers for Disease Control and Prevention. Tuberculosis morbidity — United States, 1992. *Morbidity and Mortality Weekly Report*, **42:** 696-704 (1993).

8. Jereb, J., Kelly, G., Dooley, S., et al. Tuberculosis morbidity in the United States: final data, 1990. CDC Surveillance Summaries, December 1991. *Morbidity and Mortality Weekly Report*, **40**(SS-3): 23-27 (1991).

9. Bellin, E. Failure of tuberculosis control: a prescription for change. *Journal of the American Medical Association*, **271:** 708-709 (1994).

10. Powell, K., Brown, E., Farer, L. Tuberculosis among Indo-Chinese refugees in the United States. *Journal of the American Medical Association*, **249:** 1455-1460 (1983).

11. Centers for Disease Control and Prevention. Tuberculosis in Philippine national World War II veterans immigrating to Hawaii, 1992-1993. *Morbidity and Mortality Weekly Report*, **42:** 656-663 (1993).

12. Nardell, E. Tuberculosis in homeless, residential care facilities, prisons, nursing homes and other closed communities. *Seminars on Respiratory Infections*, **4:** 206-215 (1989).

13. Brudney, K., Dobkin, J. Resurgent tuberculosis in New York City: human immunodeficiency virus, homelessness, and the decline of tuberculosis control programmes. *American Reviews of Respiratory Diseases*, **144:** 745-749 (1991).

14. Stead, W. Special problems in tuberculosis: tuberculosis in the elderly and in residents of nursing homes, correctional facilities, long-term care hospitals, mental hospitals, shelters for the homeless and jails. *Clinical Chest Medicine*, **10:** 397-406 (1989).

15. Bellin, E., Fletcher, D., Safyer, M. Association of tuberculosis infection with increased time in or admission to the New York City jail system. *Journal of the American Medical Association*, **269:** 2228-2231 (1993).

16. Alcabes, P., Vossenas, P., Cohen, R. et al. Compliance with isoniazid prophylaxis in jail. *American Reviews of Respiratory Diseases*, **140:** 1194-1197 (1989).

17. Centers for Disease Control. Nosocomial transmission of multidrug-resistant tuberculosis among HIV-infected persons – Florida and New York, 1988-1991. *Morbidity and Mortality Weekly Report*, **40:** 585-591 (1991).

18. Selwyn, P., Sckell, B., Alcabes, P. et al. High risk of active tuberculosis in HIV-infected drug users with cutaneous anergy. *Journal of the American Medical Association*, **268:** 504-509 (1992).

19. Centers for Disease Control and Prevention. Tuberculosis morbidity — United States, 1992. *Morbidity and Mortality Weekly Report*, **42:** 696-697, 703-704 (1993).

20. World Health Organization. *Treatment of tuberculosis: guidelines for national programmes.* WHO, Geneva, 1993.

21. Iseman, M. Treatment of multidrug-resistant tuberculosis. *New England Journal of Medicine*, **329:** 784-791 (1993).

22. Mahmoudi, A., Iseman, M. Pitfalls in the care of patients with tuberculosis: common errors and their association with the acquisition of drug resistance. *Journal of the American Medical Association*, **270:** 65-68 (1993).

23. American Thoracic Society/Centers for Disease Control. Treatment of tuberculosis and tuberculosis infection in adults and children. *American Reviews of Respiratory Diseases*, **134:** 355-363 (1986).

24. American Thoracic Society/Centers for Disease Control. Control of tuberculosis in the United States. *American Reviews of Respiratory Diseases*, **146:** 1623-1633 (1992).

25. Centers for Disease Control and Prevention. Initial therapy for tuberculosis in the era of multidrug-resistance: recommendations of the Advisory Council for the Elimination of Tuberculosis. *Morbidity and Mortality Weekly Report*, **42**(RR-7): 1-8 (1993).

26. Iseman, M., Cohn, D., Sbarbaro, J. Directly observed treatment for tuberculosis: we can't afford not to try it. *New England Journal of Medicine*, **328:** 576-578 (1993).

27. Nardell, E. Beyond four drugs: public health policy and the treatment of the individual patient with tuberculosis. *American Reviews of Respiratory Diseases*, **148:** 2-5 (1993).

28. Frieden, T., Sterling, T., Pablos-Mendez, A. et al. The emergence of drug-resistant tuberculosis in New York City. *New England Journal of Medicine*, **328:** 521-526 (1993).

29. World Health Organization. WHO announces new TB control initiative: adoption of new TB control guidelines could save 12 million lives. Press Release WHO/29, 29 March 1994.

Ambivalence in tobacco control

Smoking-related illness is now recognized to have become the foremost cause of death in the United States (1). The most recent estimates indicate that some 420 000 tobacco-related deaths occur nationwide each year (2). Meanwhile, by the time they finish full-time education, some 17% of US teenagers — of both sexes — are already confirmed daily smokers (3) and, despite increasing regulation, advertising campaigns focusing on young persons (4, 5) still remain a potent inducement to inculcate the habit (6). In the United States alone, 3000 new smokers need to be recruited each day to maintain the smoking population at its current size (7).

Over the past decade, evidence has rapidly accumulated from many independent sources to indicate that smokers do not simply endanger their own health. They can also compromise the health of others. Environmental tobacco smoke has been implicated as a cause of lung cancer, heart disease and respiratory disorders among persons who do not themselves smoke (8–12).

As early as 1978 this hazard had been depicted in a study conducted for the US Tobacco Institute as "the most dangerous development to the viability of the tobacco industry that has yet occurred" (13). "The strategic and long-run antidote to the passive smoking issue", as defined at this time by the tobacco lobby, was vested in "developing and widely publicising the clear-cut, credible medical evidence that passive smoking is not harmful to non-smoker's health" (13). This strategy was pursued in a further position paper issued by the Tobacco Institute in 1986, in which the entire basis of concern regarding the risks associated with environmental exposure to tobacco smoke was challenged as unproven (14). Whereas challenges to the US Environmental Protection Agency's conclusion about the extent of the danger of environmental cigarette smoke have yet to be resolved (15). Meanwhile, symposia convened to examine the evidence — supported directly or indirectly by the tobacco industry — have been criticized as lacking reasonable balance. (16).

Notwithstanding this attempt on the part of the tobacco industry to repudiate the risk to society at large, it seems that most of the 46 million smokers in the United States (17) would like to give up the habit (18, 19). Moreover, they may soon be assisted by pending US legislation that will prohibit smoking in virtually all public places (15). Fortunately, the evidence is now persuasive that some smokers may be assisted towards this goal by nicotine replacement systems, and particularly by transdermal administration using the nicotine patch (20–22). More might be achieved if this pharmacological treatment were combined with more effective counselling (23). However, other initiatives are clearly needed, not least because attitudes within the tobacco industry remain recalcitrant in the face of this modest success. Manufacturers, it seems, commonly add nicotine to cigarettes to satisfy established addiction in their customers (24). Inevitably, this practice also increases the likelihood that new customers will become addicted (15).

On the basis of this evidence, the US Food and Drug Administration has taken an initiative that could well force a showdown on the issue. In the course of litigation, it recalls, manufacturers of cigarettes have described their products as nicotine delivery systems. Taken together with the evolving evidence regarding the efficacy of nicotine replacement systems in overcoming addiction to cigarettes, the FDA suggests that this concept might provide a basis for regulating tobacco products and for removing from the market those products that contain nicotine at levels that cause

or satisfy addiction. The agency is consequently looking to Congress to provide clear direction to resolve "once and for all" the regulatory status of cigarettes under the US Food, Drugs and Cosmetics Act.

References

1. McGinnis, J., Foege, W. Actual causes of death in the United States. *Journal of the American Medical Association,* **270:** 2207-2212 (1993).

2. The Coalition for Smoking OR Health. *A 30-year report card for the Federal Government on tobacco control,* Washington, D.C. 1994.

3. US Department of Health and Human Services. *Preventing tobacco use among young people: a report of the Surgeon-General.* Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health. (In Press).

4. Zimmerman, C. 120 good things about tobacco. *Tobacco Reporter,* pp.56-58, July 1993.

5. Bohner, K. Smoke and mirrors. *Forbes,* No. 316, November 1993.

6. Pierce, J., Lee, L., Gilpin, E. Smoking initiation by adolescent girls, 1944 through 1988: an association with targeted advertising. *Journal of the American Medical Association,* **271:** 608-611 (1994).

7. Pierce, J., Fiore, M., Novotny, T., Hatziandreu, E., Davis. R. Trends in cigarette smoking in the United States. *Journal of the American Medical Association,* **261:** 61-65 (1989).

8. US Environmental Protection Agency. *Respiratory health effects of passive smoking: lung cancer and other disorders.* Indoor Air Division, Office of Atmospheric and Indoor Air Programmes, Office of Air and Radiation, Washington, DC, 1992.

9. US Department of Health and Human Services. *The health consequences of involuntary smoking: a report of the Surgeon General.* DHSS Publication CDC 87-8398 (1986).

10. International Agency for Research on Cancer. *Tobacco smoking.* (IARC Monographs on the Evaluation of carcinogenic risks to humans, No. 38) Lyon, 1986, pp. 163-314.

11. Glanz, S., Parmsley, W. Passive smoking and heart disease. *Circulation,* **83**: 1-12 (1991).

12. Steenland, K. Passive smoking and risk of heart disease. *Journal of the American Medical Association,* **267**: 94-99 (1992).

13. Roper Organization, eds. *A study of public attitudes towards cigarette smoking and the tobacco industry in 1978.* p. 1, as cited in: Bero, L., Galbraith, A., Rennie, D. Sponsored symposia on environmental tobacco smoke. *Journal of the American Medical Association,* **271:** 612-617 (1994).

14. Tobacco Institute. *Tobacco smoke and the non-smoker: scientific integrity at the crossroads.* Washington, D.C., 1986.

15. Editorial. FDA lights smoking fire. *Nature,* **368:** 83-84 (1994).

16. Bero, L., Galbraith, A., Rennie, D. Sponsored symposia on environmental tobacco smoke. *Journal of the American Medical Association,* **271:** 612-617 (1994).

17. Centers for Disease Control and Prevention. Cigarette smoking among adults — United States, 1991. *Morbidity and Mortality Weekly Report,* **42:** 230-233 (1993).

18. Thomas, R., Larsen, M. *Smoking prevalence, beliefs and activities by gender and other demographic indicators.* The Gallup Organization Inc., Princetown, NJ., 1993.

19. Moss, A., Allen, K., Giovino, G., Mills, S. Recent trends in adolescent smoking, smoking uptake correlates, and expectations about the future. *Advance Data from Vital and Health Statistics,* National Center for Health Statistics, Hyattsville, MD., USA, No. 221, 1992.

20. Hurt, R., Dale, L., Fredrikson, P. et al. Nicotine patch therapy for smoking cessation combined with physician advice and nurse follow-up: one year outcome and percentage nicotine replacement. *Journal of the American Medical Association,* **271:** 595-600 (1994).

21. Kenford, S., Fiore, M., Jorenby, D. et al. Predicting smoking cessation: who will quit with and without the nicotine patch? *Journal of the American Medical Association,* **271:** 589-594 (1994).

22. Orleans, C., Resch, N., Noll, E. et al. Use of transdermal nicotine in a state-level prescription plan for the elderly: a first look at "real world" patch users. *Journal of the American Medical Association,* **271:** 601-607 (1994).

23. Foire, M., Epps, R., Manley, M. A missed opportunity: teaching medical students to help their patients successfully quit smoking. *Journal of the American Medical Association,* **271:** 624-626 (1994).

24. Open letter from the Commissioner of Food and Drugs, US FDA, to the Coalition for Smoking or Health dated 25 February 1994.

Regulatory Matters

Alpidem: hepatotoxicity results in withdrawal

France — Alpidem, an imidazopyridine introduced in 1991 as an anxiolytic agent, has been withdrawn from the market on the advice of the French Pharmacovigilance Commission following receipt of 104 reports of hepatic dysfunction in patients receiving the product.

All but 2 of these patients were taking other drug products, and in many instances included some known to be potentially hepatotoxic. A causal association was thought to be probable, having regard to the apparently high incidence of cases among patients receiving alpidem and the unusual severity of some of the reactions.

Alpidem has not been registered in other countries and it is reported that clinical trials undertaken in the USA had previously been suspended.

Source: Agence du Médicament. Pharmacovigilance technical case on Ananxyl® (alpidem), 13 December 1993.

Screening of blood and plasma products for transmissible pathogens

Germany — With a view to reducing the risk of transmission of human immunodeficiency virus (HIV) and hepatitis viruses from blood and plasma products, the following standard operating procedures have been proposed for introduction in blood collection centres and manufacturing facilities throughout Germany (1).

1. Each donation of frozen or lyophilized fresh plasma that has not been subjected to a validated and approved method for virus inactivation, and every cryopreserved cellular blood fraction with a minimum shelf-life of 12 months, may be released only after it (or the source material) has been stored in quarantine for at least 6 months, and if at the end of this period:

- no markers of infection — HIV antibodies, hepatitis B surface antigen, and raised concentration of hepatic transaminases — are detected with agreed test methods in a fresh blood sample obtained from the donor; and
- the donor has no signs or symptoms indicative of such infection.

2. All stocks of fresh frozen plasma should be stored at a temperature at or below – 30 °C to assure stability.

In a separate decision, the Federal Health Office has suspended the product licence of a preparation of albumin derived from human placentas. It is claimed that this starting material could provide a vehicle for transmission of Creutzfeldt-Jakob disease (2).

Sources:

1. Bundesgesundheitsamt. Notice of intent of regulation issued in an open letter to pharmaceutical manufacturers dated 30 July 1993.

2. Arzneimittelkommission der Deutschen Apotheker. *Deutsche Apotheker Zeitung*, **134:** 13 January1994.

Botulinum toxin and severe dysphagia

United Kingdom — Use of botulinum type A toxin to relieve the muscle spasm of persistent torticollis can result in the development of severe and persistent dysphagia some days subsequent to the injection of the product into the neck muscles. The Committee on Safety of Medicines has received reports of four cases in which muscle paralysis induced by the toxin — which can persist for several weeks — resulted in aspiration of gastric contents into the lungs. In one case the patient subsequently died from bronchopneumonia.

The Committee has reminded doctors that botulinum toxin is licensed only for blepharospasm and hemifacial spasm. Injection of the product into the neck is an unlicensed route of administration.

Source: Committee on Safety of Medicines, *Current Problems in Pharmacovigilance*, Vol. 19, 1993.

Clozapine and myocarditis

United Kingdom — It is estimated that some 5000 schizophrenic patients have been treated with clozapine in Britain. Myocarditis has been demonstrated on autopsy in three of these patients who died while taking clozapine. The Committee on Safety of Medicines has received a report of another such case and one of cardiomyopathy among the treated patients. These 5 patients had been treated for periods ranging from 15 days to 1 year before adverse cardiovascular events were noted. Similar cases associated with clozapine or with another antipsychotic drug have been reported in other countries.

The manufacturer of clozapine has collaborated with drug regulatory authorities in creating a system for registering and monitoring schizophrenic patients receiving clozapine because it is also associated with a high risk of agranulocytosis (2). This may increase the frequency with which other adverse effects associated with its use are notified to regulatory authorities. Thus the possibility has previously been raised that clozapine may occasionally induce dose-related convulsive episodes (3).

Doctors are reminded that myocarditis presents in various ways, and that they should immediately withdraw treatment from any patient who develops heart failure, an arrhythmia, or signs of myocardial infarction or pericarditis while taking clozapine or any other antipsychotic drug.

Sources

1. Committee on Safety of Medicines. *Current Problems in Pharmacovigilance*, Vol. 19, November 1993.

2. *WHO Drug Information*, **4**: 23 and 177 (1990).

3. *WHO Drug Information*, **5**: 126 (1991).

Cyproheptadine: no longer promoted as an appetite stimulant

United Kingdom — A syrup formulation of the serotonin and histamine H1 receptor antagonist, cyproheptadine, has been voluntarily withdrawn from sale by the manufacturer in the United Kingdom (1). In addition, the company has deleted reference to the use of this and other formulations of cyproheptadine as appetite stimulants from its product information worldwide. Use of cyproheptadine preparations as antihistamines is unaffected by this decision.

The action was prompted by concerns that the syrup formulation of cyproheptadine was being promoted and used inappropriately as an appetite stimulant in some developing countries. The claim that cyproheptadine is of value in this indication was initially based on some variable results obtained in the management of anorexia nervosa (2). In the longer term, however, cyproheptadine had little effect in promoting weight gain (3) and it is generally agreed that behavioural therapy and nutritional advice offer the best approach to treatment.

References

1. *The Pharmaceutical Journal*, **252:** 136 (1994).

2. Herzog, D., Copeland, P. Eating disorders. *New England Journal of Medicine*, **313:** 295-305 (1985).

3. Kennedy, S., Goldbloom, D. Current perspectives on drug therapies for anorexia nervosa and bulimia nervosa. *Drugs*, **41:** 367-377 (1991).

Postmenopausal estrogen therapy: requirement for concomitant progestogen administration

Germany — The Federal Health Office has issued an order requiring that, as from 1 November 1993, the package inserts of estrogens intended for replacement therapy in postmenopausal women carry a statement that the product should always be used together with a progestogen, except in women who have had a hysterectomy. Unopposed by the action of progestogens, estrogens induce hyperplasia of the endometrium that results in a substantially increased risk of cancerous change.

The Federal Health Office has rejected in the following terms the submission that this risk is overwhelmed by the protective effect of estrogens against ischaemic heart disease, and that simultaneous use of progestogens may be expected to attenuate this protective effect (see *also WHO Drug Information*, **5:** 162–163, 1991):

- "It is not known whether progestogens alone influence the occurrence of cardiovascular diseases as there is no physiological situation in which they are released without simultaneous release of estrogens.

- " No conclusion can be drawn as to the incidence of cardiovascular diseases from progestogen treatment of breast cancer during the menopause as the doses used are too low.

- " Progestogens used in hormone replacement to induce changes in the lipoprotein profile are a very heterogeneous group.

- " A recent investigation of various cardiovascular risk factors in postmenopausal women receiving hormone replacement therapy concluded that: 'the use of estrogen combined with progestin appears to be associated with a better profile than the use of estrogen alone'."

Source: *Medicinal products containing estrogen for hormone substitution.* Open letter from the Federal Health Office to pharmaceutical manufacturers dated August 1993.

Ethylene oxide: limitations on its use in the manufacture of pharmaceuticals

European Commission — The Committee for Proprietary Medicinal Products has issued a note for guidance to advise pharmaceutical manufacturers that ethylene oxide may be used as a sterilant only where safer alternatives cannot be used. As a proven genotoxic carcinogen, it may not be used at concentrations greater than 1 ppm, which is the current limit for detection of the compound, without full justification. Its use in sterilizing raw materials must be justified and validated on a case-by-case basis. Since ethylene oxide is effective only as a surface sterilant, it is proposed that it should be used, in general, only for sterilizing containers and closures.

It is explained that ethylene oxide is an alkylating agent which also reacts with nucleic acids and proteins. Cytotoxicity, carcinogenicity and mutagenicity, which are attributed to these properties, have been demonstrated in many *in vitro* tests. Moreover, epidemiological data from many sources have indicated that workers occupationally exposed to ethylene oxide are at increased risk of leukaemia and other neoplasias.

Source: Committee for Proprietary Medicinal Products. *Limitations to the use of ethylene oxide in the manufacture of medicinal products.* Commission of the European Communities, III/9261/90-EN, Brussels, December 1993.

Homoeopathic products: requirements for registration

United Kingdom — As from 14 February 1994, registration requirements for homoeopathic products that may be purchased over-the-counter and that are intended for either external or oral administration became operative in accordance with European Community requirements. An advisory board will provide expert advice to the licensing authority on the safety and quality of products covered by the new scheme.

Homoeopathic products must now comply with standards of quality and safety comparable to those required for licensed allopathic medicines, but there is no requirement for evidence of efficacy and the products will not be registered for a specific therapeutic indication.

To qualify for a licence, a product must contain no more than one part per 100 000 of the mother tincture, or — should it contain a prescription-only medicine — the homoeopathic dose should not exceed more than one hundredth of the smallest dose used in allopathic medicine. Labelling regulations have been amended to include standard requirements for homoeopathic medicines.

Source: European Community Directive 92/73/EC The Medicines (Advisory Board on the Registration of Homoeopathic Products) Order 1994, SI 1994, No 102. The Medicines (Homoeopathic Medicinal Products for Human Use) Regulations 1994, SI 1994, No 105.

Moxisylyte: dose-related hepatitis

France — A preparation of the alfa-adrenoreceptor blocking agent, moxisylyte, which was first registered in France in 1989 for the symptomatic management of benign prostatic hypertrophy was subsequently withdrawn from the market in June 1993 when the marketing licence was suspended.

This action was taken when a study undertaken in France indicated that the product was associated with reversible and dose-dependent hepatotoxiciy. In all, 23 cases of hepatitis were reported and elevated transaminase levels were detected in patients receiving the recommended dosage of 480 mg daily. Hepatotoxicity has not emerged as a problem associated with short-term use of moxisylyte. Only two additional cases of parenchymal

hepatitis have ever been notified to the WHO international adverse reaction data base.

Source: Communication to the WHO Collaborating Centre for International Drug Monitoring, Uppsala, Sweden from the Committee on Pharmacovigilance, France, June 1993.

Nicotine patches: cardiovascular reactions

Australia — Nicotine patches have recently become available in Australia as an aid to giving up smoking. Over 70 reports of suspected adverse reactions associated with these devices have subsequently been reported to the national ADR centre. Some of these are likely to result from withdrawal of nicotine rather than from transdermal administration of the drug. Neurological disturbances feature in about half of the reports. Most common are vivid or unusual dreams, while headache, dizziness or vertigo, paraesthesiae, anxiety, depression and amnesia account for most of the remainder.

Of greater importance are 13 reports of cardiovascular events, including palpitations, chest pain, hypertension, tachycardia and atrial fibrillation. Typical of several events which were reversible on withdrawal of the patch are symptoms suggestive of a cerebrovascular event which slowly resolved over a period of 10 days; an attack of anginal pain which was immediately relieved by removing the patch and taking glyceryl trinitrate; and severe chest pain radiating to the left arm which lasted several days.

These events, together with 11 cases of gastrointestinal symptoms in which nausea predominated, are tentatively attributed to nicotine overdosage. It is noted, in two instances, that adverse effects attributed to patches delivering 21 mg did not recur when patches delivering 14 mg were substituted. It is emphasized that patients using nicotine patches must stop smoking completely to avoid peak nicotine concentrations higher than those resulting from smoking alone. Prescribers, it is suggested, should advise their patients of the dangers of concomitant smoking for as long as the patch is in place.

Source: Adverse Drug Reactions Advisory Committee, *Australian Adverse Drug Reactions Bulletin*, **13:** No. 2, May 1994.

High-lipase pancreatins: reports of colonic strictures

United Kingdom — The Committee on Safety of Medicines has informed doctors that it has received 7 reports of fibrotic strictures of the large bowel developing in children with cystic fibrosis who had been taking capsules of pancreatin containing high levels of lipase and other enzymes for several months. The lesions were localized to the ileocaecal region and ascending colon, and 6 of the children — who were all aged between 3 and 13 years — required surgical resection. The histological appearance of the lesions was dissimilar from those associated with cystic fibrosis and Crohn's disease.

Each of the four high-lipase preparations currently marketed in Britain was associated with at least one of these 9 cases, 5 of which were reported from one specialized centre. In all, it is estimated that some 4000 British children with cystic fibrosis were using preparations containing high levels of lipase and other enzymes as replacement therapy at the time of the Committee's alert.

Whereas the Committee acknowledges that high-lipase products hold advantage for patients who need large quantities of pancreatin, doctors have been advised to urge their patients to use other types of pancreatin at least until the factors responsible for these cases are better understood. Doctors have also been advised to keep a close watch on patients who have recently discontinued high-lipase products for signs suggestive of intestinal obstruction.

Source: Notification from the Committee on Safety of Medicines dated 21 December 1993.

Pneumococcal vaccination: policy guidelines

Australia — The Thoracic Society of Australia and New Zealand has issued guidelines to doctors on the use of pneumococcal vaccines (1). The advice derives from a conclusion that the available evidence does not support a public health strategy aimed to vaccinate all individuals in specific risk groups, but clinicians are urged to consider discretionary vaccination of patients in the following categories:

1. Patients with functional or anatomical asplenia. Preferably, the vaccine should be administered before splenectomy, but not if it is likely that the patient will start chemotherapy within 14 days.

2. Adult patients with chronic alcoholism or chronic systemic disease involving the lungs, heart, liver or kidneys, particularly when the condition has resulted in admission to hospital within the past 5 years.

3. Patients with HIV infection which is asymptomatic or associated only with generalized lymphadenopathy.

4. Patients aged over two years of age who have nephrotic syndrome.

5. Patients with chronic and surgically inoperable leakage of cerebrospinal fluid.

The vaccine, which is most conveniently administered at the same time as influenza vaccine, is seldom associated with systemic adverse effects. Anaphylactoid reactions are estimated to occur in about 5 doses per million, while myalgia and severe local reactions occur in about 1% of cases. Animal studies have provided no evidence of embryotoxicity or teratogenicity, but it is recommended that vaccination is best deferred during pregnancy unless the risk of reinfection is increased substantially.

Antibody levels decline variably according to the serotype examined. The decline is faster in children, and in all patients with asplenia, nephrotic syndrome or immunosuppression. In children over 10 years of age with nephrotic syndrome, asplenia or sickle cell anaemia revaccination is recommended every 3–5 years. In other circumstances an interval of 6 years is recommended between vaccinations. Revaccination at intervals greater than 4 years has not been associated with an increased incidence of adverse reactions.

Reference

1. Torzillo, P. Pneumococcal vaccine: current status. *Australia and New Zealand Journal of Medicine*, **23:** 285-290 (1993).

Remoxipride: aplastic anaemia

United Kingdom — In December 1993, doctors were advised by the Committee on Safety of Medicines that use of remoxipride (Roxicam®, Astra), an antipsychotic drug used primarily in the treatment of schizophrenia, had been associated with cases of aplastic anaemia (1). Five such cases were reported from the UK among the 10 000 patients who were estimated to have received the product, and the Committee was aware of 3 other cases notified to other national regulatory authorities.

Four of the British patients were women aged from 35 to 44 years, who had received 150 to 600 mg daily for periods of 3 to 6 months. The fifth was a man aged 63 who had received 600 mg daily for 8 months. Since only one of these reactions was fatal, the prognosis was evidently ameliorated by early diagnosis. Doctors were warned to withdraw remoxipride immediately from any patient who develops signs of bruising, bleeding, fever or sore throat; never to administer the drug to a patient with a history of blood dyscrasia; always to confirm that the blood count is normal before treatment is started; and subsequently to monitor the blood count at weekly intervals for 6 months and at monthly intervals thereafter for as long as treatment is continued.

The Committee emphasized that remoxipride should be reserved for patients intolerant of other neuroleptic drugs, and that the decision to prescribe the product should always be taken by a specialist psychiatrist.

Subsequent to this expression of concern the manufacturer of the product decided to withdraw the product wordwide having regard to doubts on the value of blood monitoring in the prevention of the risk involved (2). Supplies remain available on a "named patient" basis.

Sources

1. Communication from Astra Arcus to WHO dated 14 March 1994.

2. Committee on Safety of Medicines. *Current Problems in Pharmacovigilance*, Vol. 19, November 1993.

Tamoxifen: stronger warning on uterine cancer

United States of America — The Food and Drug Administration has announced that updated information on the risk of uterine cancer in patients receiving tamoxifen as adjuvant therapy for breast cancer will be incorporated in product labelling.

Women who are receiving, or who have previously received tamoxifen are advised to undergo regular gynaecological examinations, and to consult their doctor promptly should they experience menstrual irregularities, abnormal vaginal bleeding, change in vaginal discharge, or pelvic pain or pressure.

The warning reflects interim findings in a Swedish study. During a follow-up period extending over 9 years, 23 of 1372 patients randomized to take tamoxifen have developed endometrial uterine cancer, compared with 4 of 1357 in the control group. An ongoing trial in North America (the National Surgical Adjuvant Breast and Bowel Project) has produced similar results after 6.8 years of follow-up. Although some deaths have been reported, most of these cancers were diagnosed and treated at an early stage.

Unpublished data from another trial that is still being evaluated suggest that an association may also exist between tamoxifen and cancers of the gastrointestinal tract. As yet, no such association has been detected in any other study. Concerns that tamoxifen may cause a DES (diethylstilbestrol)-like syndrome when administered during pregnancy have also been supported by the results of recent animal studies.

The National Cancer Institute maintains its view that the benefits of tamoxifen as a treatment for breast cancer far outweigh the potential risks of other cancers (see *WHO Drug Information,* **8**: 12, 1994). It emphasizes, none the less, that tamoxifen should not be used in the primary prevention of breast cancer except within the context of a planned clinical trial.

Source: From the Food and Drug Administration. Tamoxifen labelling includes stronger warning. *Journal of the American Medical Association*, **271:** 1472 (1994).

Thymoxamine and hepatotoxicity

United Kingdom — The Committee on Safety of Medicines has recently reviewed reports of hepatic reactions associated with use of the alfa adrenergic blocking agent, thymoxamine, which was first approved over 20 years ago for short-term symptomatic treatment of primary Raynaud's phenomenon at a recommended daily dose of 160 to 320 mg.

In 1993, the same product was voluntarily withdrawn by the manufacturer in France, where it was used at higher dosage (480 mg daily) to treat symptoms of benign prostatic hypertrophy, following 65 reports of acute hepatitis. Most of these cases, which were predominantly hepatocellular in nature, appeared to be dose dependent and reversible on withdrawal of treatment.

Only 13 cases of hepatic reactions to thymoxamine have been reported in the UK — although these account for 17% of all notified reactions to the product. The clinical presentations, which were varied, comprised impaired hepatic function, cholestatic jaundice and hepatitis. The reaction was often associated with a daily dose of 160 mg or less, and in most cases it occurred within 5 weeks of starting treatment and was reversible on withdrawal.

The Committee considers that the higher incidence of hepatitis associated with use of the product in France may reflect greater susceptibility in an older population of patients receiving higher doses. It advises doctors, none the less, to withdraw thymoxamine promptly and to request liver function tests when any patient under treatment either becomes generally unwell or develops symptoms or signs suggestive of hepatitis.

Source: Committee on Safety of Medicines. *Current Problems in Pharmacovigilance*, Vol. 19, November 1993.

Consultative Document

Interchangeable multi-source pharmaceutical products: WHO draft guideline on marketing authorization requirements

I. Introduction

The competitive pricing that results from the marketing of generic versions of off-patent pharmaceutical products significantly reduces drug costs. Before issuing a marketing authorization for a multi-source (generic) pharmaceutical product the national regulatory authority has to assess if it is therapeutically equivalent and interchangeable with the brand product marketed by the innovator company. Drug regulators attending the Sixth International Conference of Drug Regulatory Authorities (ICDRA) in Ottawa, Canada, in 1991, recommended that WHO should develop global standards and requirements for regulatory assessment and marketing authorization of interchangeable multi-source pharmaceutical products. Proposals for such guidelines are offered in this consultative document.

The term "generic pharmaceutical product" has somewhat different meanings in different jurisdictions, and in this document use of the term is avoided as much as possible, and the term "multi-source pharmaceutical product" has been applied. However, where the term "generic product" had to be used in this document it means a pharmaceutical product, usually intended to be interchangeable with the innovator product, which is usually manufactured without a licence from the innovator company, and marketed after expiry of patent or other exclusivity rights. Generic products may be marketed either under the nonproprietary approved name or under a new brand (proprietary) name. They may sometimes be marketed in dosage forms and/or strengths different from those of the innovator products.

The WHO Guidelines are based on provisions already elaborated by a number of drug regulatory authorities such as Australia, Canada, the European Union countries, Hungary, Japan, the Nordic countries, and the United States. Every care has been taken in developing the WHO Guidelines as a practicable administrative and regulatory tool for the broader constituency of WHO's Member States.

It is the expectation of WHO that all pharmaceutical products, whether purchased on tender or supplied through the public or private sector, are subjected to the same requirements for marketing authorization by the national drug regulatory authority. This is to assure that all available pharmaceutical products are safe, efficacious and of good quality and, when applicable, therapeutically equivalent and interchangeable. Bilateral or multilateral collaboration in regulatory affairs between the drug regulatory authorities assists countries with limited resources. Exchange of evaluation reports on the same product from the same manufacturer can accelerate the adoption of sound decisions at the national level. At the moment, confidentiality requirements

These proposed guidelines remain subject to consultation. Comments, which are invited from all interested parties, should be received by 31 August 1994 in:
The Division of Drug Management & Policies,
World Health Organization, 1211 Geneva 27, Switzerland

can, in some cases, restrict the exchange of assessment reports and the sharing of information on specific pharmaceutical products among drug regulatory authorities. Pharmaceutical companies and their representative bodies should be encouraged to adopt a policy of allowing such exchanges among national drug regulatory authorities providing confidentiality can be assured.

These Guidelines confirm that equivalence between interchangeable multi-source pharmaceutical products is one of the most important items which should be considered in every case as part of the marketing authorization procedure for products which contain established ingredients. In many cases data from bioequivalence studies involving human subjects are necessary to demonstrate equivalence, as part of the assessment of the safety and efficacy of the pharmaceutical product. The implementation of the Guideline, therefore, has both ethical and resource implications which need to be considered in those cases where evidence of equivalence is deemed necessary. Under the Guideline, the equivalence data need to be provided for each of the countries in which a multi-source product is to be marketed, and this could mean that studies on the same product have to be repeated for each country, in order to demonstrate equivalence (and hence interchangeability) with existing products for that particular market. Replication of such studies is not only wasteful of resources, but can also result in unnecessary exposure of volunteers and patients to risk, or potential risk, without specific benefit. Notwithstanding the potential problems which have been identified, it seems necessary to investigate further the feasibility of establishing a system of international reference products for determining equivalence.

A system of international reference products with documented quality, clinical efficacy and safety, including bioavailability should provide information particularly for developing countries as a basis for making decisions about the marketing authorization of multi-source, interchangeable pharmaceutical products. Furthermore, it could help to avoid unnecessary human studies through agreements that products intended for supply to different countries need only be tested once against the international reference product. Finally, an international reference product system could encourage the adoption of uniform bioavailability and quality standards for products in international commerce.

It is hoped, on the basis of further consultation, to seek formal acceptance of the WHO Guidelines by Member States as a contribution to harmonization of standards internationally, and to facilitate regulatory assessment and international movement of safe and efficacious pharmaceutical products of good quality.

II. Definition of terms

Definitions given below apply specifically to the terms used in this guide. They may have different meanings in other contexts.

Bioavailability
The rate and extent of absorption of an active drug ingredient from a dosage form as determined by its concentration/time curve in the systemic circulation or by its excretion in urine.

Bioequivalence
Two medicinal products are bioequivalent if they are pharmaceutically equivalent and their bioavailabilities (rate and extent of absorption) after administration in the same molar dose are similar to such a degree that their effects, with respect to both efficacy and safety, will be essentially the same.

Dosage form
The form of the completed pharmaceutical product, e.g., tablet, capsule, elixir, injection, suppository.

Equivalence
Two pharmaceutical products are equivalent if they are pharmaceutically equivalent and after administration in the same molar dose their effects, with respect to both efficacy and safety, will be essentially the same.

Generic product
The term "generic product" has somewhat different meanings in different jurisdictions and in this document use of the term is avoided as much as possible, and the term "multi-source pharmaceutical product" has been applied. However, where the term "generic product" had to be used in this document it means a pharmaceutical product, usually intended to be interchangeable with the innovator product, which is usually manufactured without a licence from the innovator company and marketed after expiry of patent or other exclusivity rights.

Generic products may be marketed either under the nonproprietary approved name (INN) or under a new brand (proprietary) name. They may some-

times be marketed in dosage forms and/or strengths different from those of the innovator products.

Innovator pharmaceutical product
Generally, the innovator product is that which was first authorized for marketing, as a patented drug, on the basis of documentation of safety, quality and efficacy (according to contemporary requirements).

In the case of drugs which have been available for many years, it may not be possible to identify an innovator pharmaceutical product.

Interchangeable pharmaceutical product
An interchangeable pharmaceutical product is one which is equivalent to a reference product.

Multi-source pharmaceutical products
Multi-source pharmaceutical products are pharmaceutically equivalent drug products that may or may not be equivalent. Multi-source pharmaceutical products that are equivalent are interchangeable.

Pharmaceutical equivalence
Products are pharmaceutical equivalents if they contain the same amount of the same active substance(s) in the same dosage form that meet the same or comparable standards and are intended to be administered by the same route. Pharmaceutical equivalence does not necessarily imply bioequivalence as differences in the excipients and/or the manufacturing process can lead to differences in product performance (in dissolution rate and/or bioavailability).

Reference listed pharmaceutical product
A pharmaceutical product already marketed, with which the new product is intended to be interchanged in clinical practice. The reference listed product may be the innovator product, or, where multiple interchangeable pharmaceutical products are already marketed, the product which is the market leader may be used.

III. Regulatory assessment of interchangeable multi-source pharmaceutical products

III.1. General considerations

The appropriate governmental authority should ensure that all pharmaceutical products subject to its control conform to acceptable standards of quality, safety and efficacy; and that all premises and practices employed to manufacture, store and distribute these products comply with requirements to ensure the continued conformity of the products to these standards until such time as they are delivered to the end user.

These objectives can ideally be accomplished effectively only if a mandatory system of marketing authorization for pharmaceutical products and licensing their manufacturers, importing agents and distributors is in place and adequate resources are available for implementation of these regulations. Health authorities in countries with limited resources have less capacity to undertake these tasks. To assure the quality of imported pharmaceutical products and drug substances, they are dependent on authoritative, reliable, and independent information from the drug regulatory authority of the exporting country. This information, including information on the regulatory status of a pharmaceutical product, and the manufacturer's compliance with GMP (Good Manufacturing Practices) in the exporting country, is most effectively obtained through the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce which provides a channel of communication between regulatory authorities in the importing and exporting countries (Resolutions WHA41.16 and WHA45.26).

The essential functions and responsibilities of a drug regulatory authority are further elaborated by WHO in the Guiding Principles for Small National Drug Regulatory Authorities (*WHO Technical Report Series*, No. 790: 64–79, 1990 and No. 825: 62-74, 1992).

III.2. Multi-source products and interchangeability

There are often economic pressures favouring the use of generic products. In some cases this can result in the purchase on contract of generic products by procurement agencies without prior licensing by the drug regulatory authority. However, all pharmaceutical products, including generic products, should be used in a country only after approval by the appropriate drug regulatory authority. Equally, pharmaceutical products intended exclusively for export should be subject to the same controls and marketing authorization requirements in regard to quality, safety and efficacy as pharmaceutical products intended for the domestic market in the exporting country.

Nominally equivalent interchangeable (generic) pharmaceutical products should contain the same

amount of the same therapeutically active ingredients in the same dosage form and they should meet required pharmacopoeial standards. However, they are usually not identical and in some instances their clinical interchangeability may be in question. Although differences in colour, shape and flavour are obvious and sometimes disconcerting to the patient, they are often inconsequential to the performance of the pharmaceutical product. However differences in sensitizing potential due to the use of different excipients and differences in stability and bioavailability could have obvious clinical implications. Regulatory authorities consequently need to consider not only the quality, efficacy and safety of such pharmaceutical products, but also their interchangeability one with another and with the original innovative pharmaceutical product. This concept of interchangeability applies not only to the dosage form but also to the instructions for use and even to the packaging specifications, when these are critical to stability and shelf-life.

Regulatory authorities should require that documentation of a generic pharmaceutical product addresses three sets of criteria. These relate to:

- manufacturing (GMP) and quality control;
- product characteristics and labelling; and
- equivalence with an interchangeable marketed pharmaceutical product.

Assessment of equivalence will normally require an *in vivo* study, or a justification that such a study should not be required in a particular case. *In vivo* study approaches include bioequivalence studies, pharmacodynamic studies, and comparative clinical trials. In selected cases *in vitro* studies may be sufficient to provide some indication of equivalence (see Section V.2, 4). The regulatory authority should be in a position to help local manufacturers by advising them on drugs that pose potential bioavailability problems and therefore need *in vivo* studies.

III.3. Technical data for regulatory assessment

For pharmaceutical products indicated for standard, well-established uses and that contain established ingredients, the following elements of information usually suffice as the basis both for marketing authorization and for a computerized data retrieval system:

- name of the product;
- active ingredient(s) (by international nonproprietary name(s)); their source; description of manufacturing methods and in-process controls;
- type of dosage form;
- route of administration;
- main therapeutic category;
- complete quantitative formula with justification and method of manufacture of the dosage form;
- quality control specifications for starting materials, intermediates and the final dosage form product; batch results, including, where appropriate, the batch(es) used in bioequivalence studies;
- batch number, manufacturing date;
- indications, dosage, method of use;
- contraindications, warnings, precautions, drug interactions;
- use in pregnancy and other special groups of patients;
- adverse effects;
- overdosage;
- equivalence data (comparative bioavailability, pharmacodynamic or clinical studies and comparative *in vitro* dissolution tests);
- stability data, shelf-life, recommended storage conditions;
- container, packaging, labelling;
- intended method of distribution:

  controlled drug; prescription item; pharmacy sale; general sale;

- manufacturer; licensing status (date of most recent inspection, date of licence and who issued the licence);
- importer/distributor;
- regulatory status in the exporting country and, where available, summary documents of

regulatory assessment from the exporting country;
regulatory status in other countries.

If the dosage form is a novel one intended to modify the drug delivery, such as a delayed-release tablet, or if a different route of administration is proposed, supporting data, including clinical studies, will normally be required.

III.4. Product information and promotion
The product information intended for prescribers and end-users should be available for all generic products authorized for marketing. The content of this information should be approved as a part of the product authorization. This information should be updated based on current information. The wording and illustrations used in subsequent promotion of the product should be fully consistent with this approved product information. All promotional activities should respect the WHO Ethical Criteria for Medicinal Drug Promotion (Resolution WHA41.17, May 1988).

III.5. Mutual acceptance of assessment data
Bilateral or multilateral collaboration between the drug regulatory authorities assists countries with limited resources. Sharing responsibilities in assessment and enhancing mutual cooperation provides a wider spectrum of expertise for evaluation. Harmonization of registration requirements between the drug regulatory authorities for registration of generics can accelerate the approval process. Furthermore, an agreed mechanism of quality assurance in relation to the assessment work of collaborating agencies is vital.

Exchange of evaluation reports on the same pharmaceutical product from the same manufacturer can accelerate the adoption of sound decisions at the national level. In some instances when the collaboration between authorities has been well established, even mutual recognition of approvals could take place.

At the moment, confidentiality requirements can restrict the exchange of evaluation reports and the sharing of information between drug regulatory agencies. Pharmaceutical companies and their representative bodies should be encouraged to adopt a policy of allowing such exchanges between national drug regulatory authorities providing confidentiality can be assured.

IV. Equivalence studies needed for marketing authoritzation

IV.1. Documentation of equivalence for marketing authorization

Pharmaceutically equivalent multi-source pharmaceutical products should be shown to be equivalent to one another in order to be considered interchangeable. Several test methods are available to assess equivalence, including:

(a) Comparative bioavailability (bioequivalence) studies, in which the active drug substance or one or more metabolites is measured in an accessible biologic fluid such as plasma, blood or urine.

(b) Comparative pharmacodynamic studies in humans.

(c) Comparative clinical trials.

(d) *In vitro* tests such as *in vitro* dissolution.

Each of these four modalities is discussed in subsequent sections of this guideline and special guidance is provided to conduct an assessment of bioequivalence studies. Other modalities have been used to assess bioequivalence, such as bioequivalence studies in animals, but are not discussed in this guideline because this approach is not accepted worldwide.

The application of any test procedure in the documentation of equivalence between two pharmaceutical products by a registration authority depends on many factors. These factors include characteristics of the active drug substance and the drug product and availability of resources for the conduct of a specific type of study. Where a drug produces meaningful concentrations in an accessible biologic fluid, such as plasma, bioequivalence studies are preferred. Where a drug does not produce measurable concentrations in an accessible biologic fluid, comparative clinical trials or pharmacodynamic studies may be necessary to document equivalence. If resources are limited, *in vitro* testing, preferably based on a documented *in vitro/in vivo* correlation, may sometimes provide some indication of equivalence between two pharmaceutical products.

Additional criteria that indicate when equivalence studies are necessary are discussed in the following two sections of the guideline (IV.2 and IV.3).

IV.2. When equivalence studies are not necessary

For certain formulations and circumstances, equivalence between two pharmaceutical products may be considered self-evident with no further requirement for documentation. Examples include:

(a) When multi-source pharmaceutical products are to be administered parenterally (e.g., intravenous, intramuscular, subcutaneous, intrathecal administration) as aqueous solutions and contain the same active substance(s) in the same concentration and the same excipients in comparable concentrations;

(b) When multi-source pharmaceutical products are solutions for oral use, contain the active substance in the same concentration, and do not contain an excipient that affects gastrointestinal transit or absorption of the active substance;

(c) When multi-source pharmaceutical products are a gas;

(d) When the multi-source pharmaceutical products are powders for reconstitution as a solution and the solution meets either criterion (a) or criterion (b) above;

(e) When multi-source pharmaceutical products are otic or ophthalmic products prepared as aqueous solutions and contain the same active substance(s) in the same concentration and essentially the same excipients in comparable concentrations;

(f) When multi-source pharmaceutical products are topical products prepared as aqueous solutions and contain the same active substance(s) in the same concentration and essentially the same excipients in comparable concentrations;

(g) When multi-source pharmaceutical products are inhalation products or nasal sprays, tested to be administered with or without essentially the same device, prepared as aqueous solutions, and contain the same active substance(s) in the same concentration and the same excipients in essentially the same concentrations. Special *in vitro* testing may be required to document comparable device performance of the multi-source inhalation product.

IV.3. When equivalence studies are necessary and types of studies required

Except for the dosage forms listed in Section IV.2, this guideline recommends that documentation of equivalence be requested by registration authorities for a multi-source pharmaceutical product in which the product is compared to the corresponding approved pharmaceutical product. Studies must be carried out using the formulation intended for marketing (see also Section IX, "Choice of reference products"). For certain drugs and dosage forms, subsequently termed "problem pharmaceutical products", *in vivo* documentation of equivalence, through either a bioequivalence study, a comparative clinical pharmacodynamic study, or a comparative clinical trial, is regarded as especially important. Examples of these drugs and dosage forms are listed below.

(a) Oral immediate release pharmaceutical products with systemic action:

(i) indicated for serious conditions requiring assured therapeutic response;

(ii) narrow therapeutic window/safety margin; steep dose-response curve;

(iii) pharmacokinetics complicated by variable or incomplete absorption (<70%) or absorption window, nonlinear pharmacokinetics, presystemic elimination/high first-pass metabolism >70%;

(iv) unfavourable physicochemical properties, e.g., low solubility, instability, metastable modifications, poor permeability, etc.;

(v) documented evidence for bioavailability problems related to the drug or drugs of similar chemical structure or formulations;

(vi) where a high ratio of excipients to active ingredients exists.

(b) Non-oral and non-parenteral immediate release pharmaceutical products designed to act by systemic absorption.

(c) Sustained or otherwise modified release pharmaceutical products designed to act by systemic absorption.

(d) Rational fixed combination products (see WHO Technical Report Series No. 825, 1992).

(e) Non-solution pharmaceutical products which are for non-systemic use (oral, nasal, ocular, dermal, rectal, vaginal, etc. application) and are intended to act without systemic absorption. In these cases, the bioequivalence concept is not suitable and comparative clinical or pharmacodynamic studies are required to prove therapeutic equivalence. This does not, however, exclude the potential need for drug concen-

tration measurements in order to assess unintended partial absorption.

In certain circumstances, equivalence may be assessed by the use of *in vitro* dissolution testing. Examples where dissolution testing may be considered acceptable include:

(a) Drugs not defined as problem pharmaceutical products;

(b) Different strengths of a multi-source formulation, when the pharmaceutical products are manufactured by the same manufacturer at the same manufacturing site, where:

- the qualitative composition between the strengths is essentially the same;
- the ratio of active ingredients and excipients between the strengths is essentially the same, or, in the case of small strengths, the ratio between the excipients is the same;
- an appropriate equivalence study has been performed on at least one of the strengths of the formulation (usually the highest strength unless a lower strength is chosen for reasons of safety); and
- pharmacokinetics have been shown to be linear over the therapeutic dose range.

Although this Guideline comments primarily on registration requirements for multi-source pharmaceutical products, it is to be noted that *in vitro* dissolution testing may also be suitable to confirm unchanged product quality and performance characteristics with minor formulation or manufacturing changes after approval (see Section VIII, page 83).

V. Tests for equivalence

V.1. Design and conduct of bioequivalence studies in man

The bioequivalence studies should be carried out in accordance with the provisions and prerequisites for a clinical trial, as outlined in the WHO Guidelines for Good Clinical Practice (GCP) for Trials on Pharmaceutical Products, Good Manufacturing Practice (GMP) and Good Laboratory Practice (GLP).

V.1.1. Subjects

(a) Selection of subjects

The subject population for bioequivalence studies should be as homogenous as possible and therefore studies should generally be performed with healthy volunteers in order to reduce variability other than in the pharmaceutical products. Clear criteria for inclusion/exclusion should be stated. If feasible, they should include males and females (however, the risk to women will need to be considered on an individual basis and, if necessary, a warning issued to them about any possible dangers to the fetus if they should become pregnant). They should normally be in the age range of 18 to 55 years with a weight within the normal range according to accepted life tables. The subjects should preferably be non-smokers. If smokers are included they should be identified as such. The suitability of the volunteers should be screened using standard laboratory tests, a medical history, and a physical examination. If necessary, special medical investigations may be carried out before and during studies depending on the pharmacology of the individual drug being investigated.

(b) Patients versus healthy volunteers

If unacceptable pharmacological effects or risk may ensue because of known adverse effects of the active substance for healthy volunteers, it may be necessary to use patients under treatment rather than healthy volunteers. This alternative should be explained by the sponsor.

(c) Monitoring the health of subjects during the study

During the study, the health of volunteers should be monitored so that onset of side-effects, toxicity, or any intercurrent disease may be recorded, and appropriate measures taken.

Health monitoring before, during and after the study must be carried out under the supervision of a qualified medical practitioner licensed in the jurisdiction in which the study takes place.

(d) Genetic phenotyping

Phenotyping and/or genotyping of subjects may be considered for safety reasons and to explore large inter-subject variations.

V.1.2. Design

(a) General study design

The study should be designed so as to set test conditions which reduce intra-subject and inter-subject variability and avoid biased results.

Standardization (exercise, diet, fluid intake, posture, restriction of the intake of alcohol, caffeine, certain fruit juices, and concomitant drugs in the time period before and during the study) is important to minimize the magnitude of variability other than in the pharmaceutical products.

A cross-over design with randomized allocation of volunteers to each leg is the first choice for bioequivalence studies. In these studies a wash-out period between administration of the drug product and the reference product of more than five times the dominant drug half-life is usual, but special consideration will need to be given to extending this period if active metabolites with longer half-lives are produced.

The administration of the product should be standardized with a defined time of day for ingestion, volume of fluid (150 ml is usual) and usually in the fasting state.

(b) Parameters to be assessed

In bioavailability studies the shape of, and the area under, the plasma concentration curve, or the profile of cumulative renal excretion and excretion rate are mostly used to assess extent and rate of absorption. Sampling points or periods should be chosen such that the time versus concentration profile is adequately defined to allow calculation of relevant parameters. From the primary results the bioavailability parameters desired are calculated, such as AUC_∞, AUC_t, C_{max}, t_{max}, Ae_∞, Ae_t, dAe/dt, or any other justifiable parameters (cf. Appendix 1). The method of calculating AUC-values should be specified. For additional information $t_{1/2}$ and MRT can be calculated. For steady-state studies AUC_t, and % peak trough fluctuation can be calculated. The exclusive use of modelled parameters is not recommended unless the pharmacokinetic model has been validated for the active substance and the products.

(c) Additional considerations for complicated drugs

Drugs which would show unacceptable pharmacological effects in volunteers (e.g., serious adverse events, or where the drug is toxic or particularly potent or the trial necessitates a high dose) may require crossover studies in patients or sometimes parallel group design studies in patients.

Drugs with long half-lives may require a parallel design or the use of truncated Area Under Curve (AUCt) data or a multi-dose study. Truncated AUC has been defined as AUC up to 72 hours.

Drugs for which the rate of input into the systemic circulation is important may require the collection of more samples around the time of the t_{max}.

Multi-dose studies may be needed for:

- drugs with non-linear kinetics (including those with saturable plasma protein binding);
- cases where the assay sensitivity is too low to cover a large enough portion of the AU_∞;
- drug substance combinations, if the ratio of plasma concentrations of the individual drug substances is important;
- controlled-release dosage forms.

(d) Number of subjects

The number of subjects required for a sound bioequivalence study is determined by the error variance associated with the primary parameters to be studied (as estimated from a pilot experiment, from previous studies or from published data), by the significance level desired, and by the deviation from the reference product compatible with bioequivalence and with safety and efficacy. It should be calculated by appropriate methods (see Section V.1.7) and should not be smaller than 12. In most of the cases 18–24 subjects may be needed.* The number of recruited subjects should always be justified.

(e) Chemical analysis

Knowledge of the stability of the active substance and/or its biotransformation product in the sample material is a prerequisite for obtaining reliable results.

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* **See**: Diletti, E., Hauschke, D., Steinijans, V.W. Sample size determination for bioequivalence assessment by means of confidence intervals. *International Journal of Clinical Pharmacology, Therapeutics and Toxicology*, 1991, **29**:1-8; Hauschke, D., Steinijans, V.W., Diletti, E., Burke, M. Sample size determination for bioequivalence assessment using a multiplicative model. *Journal of Pharmacokinetics & Biopharmacy*, 1992, **20**:559-563; and Phillips, K.E. Power of the two one-sided tests procedure in bioequivalence. *Journal of Pharmacokinetics & Biopharmacy*, 1990, **18**:137-144).

V.1.3. Studies of metabolites
Use of metabolite data in bioequivalence studies requires careful consideration. Generally, evaluation of bioequivalence will be based upon the measured concentrations of the pharmacologically active drug substance and its active metabolite(s) if present. If it is impossible to measure the active drug substance, a major biotransformation product may be used. However, both parent and metabolite must exhibit linear pharmacokinetics. The measurement of concentrations of biotransformation product is essential if the substance studied is a prodrug. If urinary excretion (rate) is measured, the product determined should represent a major fraction of the dose (>40%). Although measurement of a major active metabolite is usually acceptable, measurement of an inactive metabolite can only rarely be justified.

V.1.4. Measurement of individual isomers for chiral drug substance products
A non-stereoselective assay is currently acceptable for bioequivalence studies of immediate release formulations.

V.1.5. Validation of analytical test methods
All analytical test methods must be well-characterized, fully validated and documented. They should meet requirements of specificity, accuracy, sensitivity and precision. For this item reference is made to the Conference Report on Analytical Validation: Bioavailability, Bio-equivalence and Pharmacokinetic Studies, *Pharmaceutical Research*, Vol. 9, No. 4, 1992. Results of validation should be reported. Some important points are:

- validation comprises before-study and within-study phases;
- validation must cover the intended use of the assay;
- the calibration range must be appropriate to the study samples;
- if an assay is to be used at different sites, it must be validated at each site and cross-site comparability must be established;
- an assay which is not in regular use requires sufficient revalidation to show that it is performed according to the original validated specifications (the revalidation study must be documented, usually as an appendix to the study report);
- within a study, the use of two or more methods to assay samples in the same matrix over a similar calibration range is strongly discouraged;
- if different studies are to be compared and the samples from the different studies have been assayed by different methods and the methods cover a similar concentration range and the same matrix, then the methods should be cross-validated.

Results of validation should be reported.

V.1.6. Sample retention
Sufficient samples of each batch of the pharmaceutical products used in the studies, and a record of their analyses and characteristics, must be kept for reference under appropriate storage conditions as guided by national regulations. When specifically requested these reserve samples may be required by the authorities to recheck the products.

V.1.7. Statistical analysis and acceptance criteria

(a) General aspects
The primary concern in bioequivalence assessment is to limit the risk of accepting equivalence if it does not hold true. Thus the risk (α) is that which the regulatory agencies are willing to accept for erroneously concluding equivalence.

The statistical method of choice at present is to derive a parametric or non-parametric 100 $(1-2\alpha)$% confidence interval, and to decide for equivalence if the confidence interval is fully contained within a clinically relevant and justified acceptance range. Alpha is set at 5% leading, in the parametric case, to the shortest (conventional) 90% confidence interval based on an analysis of variance or, in the non-parametric case, to the 90% confidence intervals.*

The statistical procedures should be specified before the data collection starts (see Appendix 2, page 84). The procedures should lead to a decision scheme which is symmetrical with respect to the two formulations (i.e., leading to the same decision whether the new formulation is compared to reference product or reference product to the new formulation).

* **See:** Hauschke, D. et al. *International Journal of Clinical Pharmacology, Therapy and Toxicology*, 1990; **28**: 72–78. Hollander M., Wolfe, D.A. *Nonparametric Statistical Methods*. New York: John Wiley & Sons, 1973, Chapter 4.3.

Concentration and concentration-related quantities like AUC, rate constants and half-lives should preferably be analyzed after logarithmic transformation; t_{max} will usually be analysed without such transformation.

If t_{max} is to be subjected to a statistical analysis this should be based on non-parametric methods. Other parameters may also be evaluated by non-parametric methods, in which case descriptive statistics should be given that do not require specific distributional assumptions, e.g., medians instead of means.

Assumptions of the design or analysis should be addressed, and the possibility of differing variations in the formulations should be investigated. This covers investigation of period effects, sequence or carry-over effects, and homogeneity of variance (homoscedascity).

Outlying observations should be reviewed for their impact on the conclusions. Medical or pharmacokinetic explanations for such observations should be sought.

(b) Acceptance ranges

Regarding AUC, the 90% confidence interval should generally be within the acceptance range 80 to 125%. For drugs with a particularly narrow therapeutic range, the AUC acceptance range may need to be smaller, and this should be justified clinically.

C_{max} does not characterize the rate of absorption particularly well and there is no consensus on any other parameter which might be more suitable. The acceptance range for C_{max} may be wider than for the AUC (see Appendix 2, page 84).

V.1.8. Reporting of results

The report of a bioequivalence study should give the complete documentation of its protocol, conduct and evaluation complying with Good Clinical Practice rules (see WHO Guideline for GCP for Trials on Pharmaceutical Products). The responsible investigators should sign for their respec-tive sections of the report. Names and affiliations of the responsible investigators, site of the study and period of its execution should be stated. The names and batch numbers of the pharmaceutical products used in the study as well as the composition(s) of the tests product(s) should be given. The analytical validation report should be attached. Results of *in vitro* dissolution tests should be provided. In addition, the applicant should submit a signed statement confirming the identity of the test product with the pharmaceutical product which is submitted for registration.

All results should be presented in a clear way. The procedure for calculating the parameters used (e.g., AUC) from the raw data should be specified. Deletion of data should be justified. If results are calculated using pharmacokinetic models, the model and the computing procedure used should be justified. Individual plasma concentration/time curves should be drawn on a linear/linear, and facultatively also on a lin/log scale. All individual data and results should be given, also of eventually dropped-out subjects. Drop-out and withdrawal of subjects should be reported and accounted for. Test results of representative samples should be included.

The statistical report should be sufficiently detailed, so as to enable the statistical analyses to be repeated if necessary. If the statistical methods applied deviate from those specified in the trial protocol, the reasons for the deviations should be stated.

V.2. Pharmacodynamic studies

Studies in healthy volunteers or patients using pharmacodynamic measurements may be used for establishing equivalence between two pharmaceutical products if quantitative analysis of the drug and/or metabolite(s) in plasma or urine cannot be made with sufficient accuracy and sensitivity. Furthermore, pharmacodynamic studies in humans are required if measurements of drug concentrations cannot be used as surrogate endpoints for the demonstration of efficacy and safety of the particular pharmaceutical product, e.g., for topical products without an intended absorption of the drug into the systemic circulation.

If pharmacodynamic studies are to be used they must be performed as rigorously as bioequivalence studies, and the principles of GCP (see WHO Guideline for GCP for Trials on Pharmaceutical Products) must be followed.

The following requirements must be recognized when planning, conducting and assessing the results of a study intended to demonstrate equivalence by means of measuring pharmacodynamic drug responses.

1. The response which is measured should be a pharmacological or therapeutic effect which is relevant to the claims of efficacy and/or safety.

2. The methodology must be validated for precision, accuracy, reproducibility and specificity.

3. Neither the test nor the reference product should produce a maximal response in the course of the study, since it may be impossible to distinguish differences between formulations given in doses which give maximum or near-maximum effects. Investigation of dose-response relationships may be a necessary part of the design.

4. The response should be measured quantitatively under double-blind conditions and be recordable in a machine-produced or machine-recorded fashion on a repetitive basis to provide a record of the pharmacodynamic events which are substitutes for plasma concentrations. In those instances where such measurements are not possible, recordings on visual analog scales may be used. In other instances where the data are limited to qualitative (categorized) measurements, appropriate special statistical analysis will be required.

5. Non-responders should be excluded from the study by prior screening. The criteria by which responders versus non-responders are identified must be stated in the protocol.

6. In instances where an important placebo effect can occur, comparison between pharmaceutical products can only be made by *a priori* consideration of the placebo effect in the study design. This may be achieved by adding a third phase with placebo treatment in the design of the study.

7. The underlying pathology and natural history of the condition must be considered in the study design. There should be knowledge of the reproducibility of base-line conditions.

8. A cross-over design can be used. Where this is not appropriate a parallel group study design should be chosen.

In studies in which continuous variables could be recorded, the time course of the intensity of the drug action can be described in the same way as in a study in which plasma concentrations were measured, and parameters can be derived which describe the area under the effect–time curve, the maximum response and the time when maximum response occurred.

The statistical considerations for the assessment of the outcome of the study are in principle, the same as outlined for the bioequivalence studies. However, a correction for the potential non-linearity of the relationship between the dose and the area under the effect-time curve should be performed on the basis of the outcome of the dose-ranging study as mentioned above. However, it should be noted that the conventional acceptance range as applied for bioequivalence assessment is not appropriate in most of the cases but should be defined on a case-by-case basis and described in the protocol.

V.3. Clinical trials

The methodology issues for establishing equivalence between pharmaceutical products by means of a clinical trial in patients with a therapeutic endpoint have not yet been discussed as extensively as for bioequivalence trials. However, important items can be identified which need to be defined in the protocol:

(a) the target parameters from which the intensity and the onset, if applicable and relevant, of the response are to be derived;

(b) the acceptance range must be defined on the basis of clinical knowledge and judgement on a case-by-case basis and described in the protocol (the conventional acceptance range as applied for bioequivalence assessment is not appropriate);

(c) the statistical procedures must take into consideration that the conventional testing approach is not suitable for confirming equivalence;

(d) where appropriate, a placebo leg should be included in the design;

(e) in some cases, it is relevant to include safety endpoints in the final comparative assessments.

V.4. *In vitro* dissolution

Comparative *in vitro* dissolution studies may be useful in the documentation of equivalence between two multi-source pharmaceutical products. The application of *in vitro* dissolution testing as the sole documentation of equivalence is recommended only for drugs that are not problem pharmaceutical products (see Section IV.3, page 76). Because of many limitations associated with the use of *in vitro* dissolution in the documentation of equivalence, this Guideline recommends that its application for this purpose be kept to a minimum. The Guideline recognizes that where *in vivo* equivalence studies cannot be performed, appropriate dissolution data may identify inadequate release of an active drug substance from a formulation.

Approval of multi-source formulations using comparative *in vitro* dissolution studies should be based on generation of comparative dissolution profiles rather than single point dissolution tests, such as are described in various compendia. Development and application of specifications and statistical methods to define nonequivalence are appropriate. These specifications and methods are most reasonable with suitable product development studies that generate formulations with different performance characteristics. In the absence of this formulation development, specifications for *in vitro* dissolution should be drawn from the pilot (bio-batch) or production batch(es) used in the documentation of equivalence.

VI. *"In vitro"* dissolution tests

The value of an *in vitro* dissolution test to assess equivalence is increased if suitable development and validation studies on the dissolution procedure are performed. These studies may involve the manufacture of different pharmaceutical formulations in the drug development process to identify formulation, or manufacture process variables that affect *in vivo* performance, as assessed, for example, through a bioequivalence study. With the availability of different formulations with variable performance characteristics, the possibility for developing discriminatory *in vitro* dissolution tests exists.

VI.1. Dissolution testing for product development and registration purposes

In product development, dissolution tests should attempt to discriminate differences in formulation and/or process variables. In this respect generation of drug release profiles (3 or 4 time-points) is preferred rather than single points.

For registration/licensing purposes a minimum of two batches of the test product should be sampled and a minimum of 6 dosage units should be taken from each batch. These batches should be on industrial scale (normally not less than 100 000 units). If pilot batches are used, the applicant should provide a justification. Dissolution testing should also be completed on the same batches that had been used for bioequivalence studies.

The following data should be recorded and included in the registration dossiers:

(a) Comparative results for test and reference products after intervals appropriate for products and conditions under investigation (normally minimum three sampling times).

(b) For each sampling time, the observed data, individual values, the range and the coefficient of variation (relative standard deviation) should be reported.

(c) The analytical method should be described together with information on validation relative to the dosage form under investigation (see WHO recommendations on analytical validation: WHO Technical Report Series No.823, 1992, pp.117-121 and No.790, 1990, pp.10-13).

(d) Information on batches tested:

- for test products: batch no., date of manufacture, scale, (pilot plant, full production);
- for reference products: batch no., expiry date, date of manufacture when available.

VI.2. Dissolution test as a quality control method

The dissolution test selected in the analytical development phase should as a minimum, allow the impact of the formulation and process variables on the release rate to be determined. In other words, the test ought to have a discriminating power regarding differences in formulation and process parameters. Attempts should also be made to correlate the dissolution characteristics with *in vivo* performance (in those cases where bioavailability studies are deemed to be necessary).

The test may be considered as a useful check for several characteristics of the dosage form:

- particle size distribution, crystal form and other solid state properties of the active ingredients;
- mechanical properties of the form itself (resistance to crushing force for tablets, integrity of the shell for capsules and coated tablets, etc.).

The test is used by the manufacturer on marketed products for verification of the batch-to-batch consistency. It is also used to test release characteristics of a dosage form in storage, i.e., to measure stability of the release rate.

The dissolution test in the individual monograph of *The International Pharmacopoeia* may be useful even for dosage forms including immediate release forms containing freely soluble active ingredients, as a safeguard against occasional grossly

inadequate formulation. Many substances may be considered as potential candidates for the introduction of a dissolution test in *The International Pharmacopoeia.*

VII. Suprabioavailability

A new formulation with increased bioavailability compared to an existing pharmaceutical product is defined as being "suprabioavailable". Options in this situation are:

(i) The dosage form, if reformulated to be bioequivalent with the existing pharmaceutical product could be accepted as interchangeable with the existing pharmaceutical product. This may not be ideal as dosage forms with low bioavailability tend to be variable in performance.

(ii) A dosage form with the content of active substance reduced to allow for the increased bioavailability could be accepted as a new (improved) dosage form. This would normally need to be supported by clinical trial data. Such a pharmaceutical product must not be accepted as interchangeable with the existing pharmaceutical product, and would normally become the reference product for future interchangeable pharmaceutical products. The name of the new pharmaceutical product should preclude confusion with the older approved pharmaceutical product(s).

VIII. Studies need to support new post-marketing manufacturing conditions

With all pharmaceutical products, extensive *in vitro* and/or *in vivo* testing may be required, if significant post-marketing changes are made. Significant changes include changes in: (i) formulation; (ii) site of manufacture; (iii) process of manufacture; and (iv) manufacturing equipment. The types and extent of further testing required depend on the magnitude of the changes made. If a major change is made, the product might become a new pharmaceutical product. Reference should be made to national regulatory authorities in this regard.

IX. Choice of reference product

The innovator pharmaceutical product is usually the most logical reference product for related generics because, in general, its quality will have been well assessed and its efficacy and safety will have been securely established in clinical trials and post-marketing monitoring schemes. There is, however, currently no global agreement on the selection of a reference product. The selection is made variably at national level by the drug regulatory authority having regard either to the most widely used "leading" product within the market or the pharmaceutical product that was first to be approved within that market. The possibility exists for significant differences to emerge between reference products adopted in different countries.

This being so, consideration needs to be given to the feasibility of developing reference materials on a global basis. The pharmaceutical industry and its representative bodies should be invited to collaborate in the preparation, maintenance and international acceptance of a system of international reference standards for pharmaceutical products with defined quality and bioavailability characteristics.

Appendix 1: Explanation of the symbols in paragraph V.1.2 and other commonly used pharmacokinetic abbreviations

C_{max}	The observed maximum or peak concentration of drug (or metabolite) in plasma, serum or whole blood.	Ae	Cumulative urinary recovery of parent drug (or metabolite). The Ae symbol may be qualified by a specific time (e.g., from zero to 12 hours, Ae_{12}).
C_{min}	Minimum plasma concentration.		
C_{max}-ratio	The ratio of geometric means of the test and reference C_{max} values.	Ae_t	Ae from zero to last quantifiable concentration.
C_{av}	Average plasma concentration.	Ae_∞	Ae from zero to infinite time, obtained by extrapolation.
AUC	The area under the drug (or metabolite) concentration in plasma (or serum or whole blood) *versus* time curve. The AUC symbol may be qualified by a specific time (e.g., from zero to 12 hours, AUC_{12}).	Ae_t	Ae over one dosing interval at steady-state.
		dAe/dt	Urinary excretion rate of parent drug (or metabolite).
AUC_t	AUC from zero to the last quantifiable concentration.	t_{max}	The time after administration of the drug at which C_{max} is observed.
AUC_∞	AUC from zero to infinity, obtained by extrapolation.	t_{max}-diff	The difference of arithmetic means of the test and reference t_{max} values.
AUC_t	AUC over one dosing interval (t) at steady-state.	$t_{1/2}$	Plasma (serum, whole blood) half-life.
AUC-ratio	The ratio of geometric means of the test and reference AUC values.	MRT	Mean residence time.

Appendix 2: Technical aspects of bioequivalence statistics

Introduction: The pharmacokinetic characteristics to be tested, the procedure for testing and the norms to be maintained should be stated beforehand in the protocol. A *post hoc* change of the methods described for the statistical evaluation is only acceptable if protocol adherence would preclude a meaningful evaluation and if such change of procedure has been fully justified.

In testing for equivalence of the main characteristics AUC and C_{max}, the multiplicative model is used which has as consequence that data should be logarithmically transformed before statistical analysis.

Acceptance ranges for main characteristics

AUC-ratio	The 90% confidence interval for this measure of relative bioavailability should lie within a bioequivalence range of 0.80 to 1.25. In case of an especially narrow therapeutic range the acceptance range may need to be tightened. A larger acceptance range may be acceptable if clinically appropriate.
C_{max}-ratio	This measure of relative bioavailability is inherently more variable than e.g., the AUC-ratio, and a wider acceptance range may be appropriate. The range used should be justified taking into account safety and efficacy considerations.
t_{max}-diff	Statistical evaluation of t_{max} only makes sense if there is a clinically relevant claim for rapid release or action or signs for a relation to adverse effects. The non-parametric 90% confidence interval for this measure of relative bioavailability should lie within a clinically relevant range.

International Nonproprietary Names for Pharmaceutical Substances (INN)

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

Lists of Proposed (1–65) and Recommended (1–31) International Nonproprietary Names can be found in *Cumulative List No. 8, 1992.* The statements indicating action and use are based largely on information supplied by the manufacturer. This information is merely meant to provide an indication of the potential use of new substances at the time they are accorded Proposed International Nonproprietary Names. WHO is not in a position either to uphold these statements or to comment on the efficacy of the action claimed. Because of their provisional nature, these descriptors will neither be revised nor included in the Cumulative Lists of INNs.

Dénominations communes internationales des Substances pharmaceutiques (DCI)

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

On trouvera d'autres listes de Dénominations communes internationales proposées (1–65) et recommandées (1–31) dans la *Liste récapitulative No. 8, 1992.* Les mentions indiquant les propriétés et les indications des substances sont fondées sur les renseignements communiqués par le fabricant. Elles ne visent qu'à donner une idée de l'utilisation potentielle des nouvelles substances au moment où elles sont l'objet de propositions de DCI. L'OMS n'est pas en mesure de confirmer ces déclarations ni de faire de commentaires sur l'efficacité du mode d'action ainsi décrit. En raison de leur caractère provisoire, ces informations ne figureront pas dans les listes récapitulatives de DCI.

Denominaciones Comunes Internacionales para las Sustancias Farmacéuticas (DCI)

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

Las listas de Denominaciones Comunes Internacionales Propuestas (1–65) y Recomendadas (1–31) se encuentran reunidas en *Cumulative List No. 8, 1992.* Las indicaciones sobre acción y uso que aparecen se basan principalmente en la información facilitada por los fabricantes. Esta información tiene por objeto dar una idea únicamente de las posibilidades de aplicación de las nuevas sustancias a las que se asigna una DCI Propuesta. La OMS no está facultada para respaldar esas indicaciones ni para formular comentarios sobre la eficacia de la acción que se atribuye al producto. Debido a su carácter provisional, esos datos descriptivos no deben incluirse en las listas recapitulativas de DCI.

Proposed International Nonproprietary Names: List 71

Comments on, or formal objections to, the proposed names may be forwarded by any person to the INN Programme of the World Health Organization within four months of the date of their publication in *WHO Drug Information*, i.e., for **List 71 Proposed INN not later than 30 November 1994.**

Dénominations communes internationales proposées: Liste 71

Des observations ou des objections formelles à l'égard des dénominations proposées peuvent être adressées par toute personne au Programme des Dénominations communes internationales de l'Organisation mondiale de la Santé dans un délai de quatre mois à compter de la date de leur publication en anglais dans *WHO Drug Information*, c'est à dire pour la **Liste 71 de DCI Proposées le 30 novembre 1994 au plus tard.**

Denominaciones Comunes Internacionales Propuestas: Lista 71

Cualquier persona puede dirigir observaciones u objeciones respecto de las denominaciones propuestas, al Programa de Denominaciones Comunes Internacionales de la Organización Mundial de la Salud, en un plazo de cuatro meses, contados desde la fecha de su publicación en la versión inglesa de *WHO Drug Information*, es decir, para **la Lista 71 de DCI Propuestas el 30 de noviembre de 1994** a más tardar.

Proposed INN (Latin, English, French, Spanish)	*Chemical name or description: Action and use: Molecular formula Chemical Abstracts Service (CAS) registry number: Graphic formula*
DCI Proposée	*Nom chimique ou description : Propriétés et indications: Formule brute Numéro dans le regisitre du CAS: Formule développée*
DCI Propuesta	*Nombre químico o descripción: Acción y uso: Fórmula empírica Número de registro del CAS: Fórmula desarrollada*

acidum gadoxeticum

gadoxetic acid

dihydrogen [*N*-[(2*S*)-2-[bis(carboxymethyl)amino]-3-(*p*-ethoxyphenyl)propyl]-*N*-[2-[bis(carboxymethyl)amino]ethyl]glycinato(5-)]gadolinate(2-)
paramagnetic contrast medium

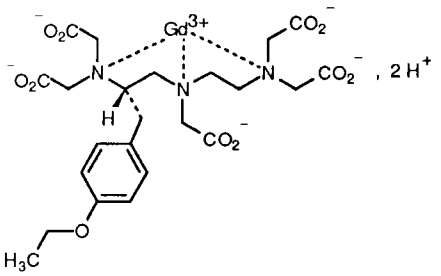
acide gadoxétique

dihydrogéno[*N*-[(2*S*)-2-[bis(carboxyméthyl)amino]-3-(4-éthoxyphényl)propyl]-*N*-[2-[bis(carboxyméthyl)amino]éthyl]glycinato(5-)]gadolinate(2-)
produit de contraste paramagnétique

ácido gadoxetico

dihidrógeno [*N*-[(2*S*)-2-[bis(carboximetil)amino]-3-(*p*-etoxifenil)propil]-*N*-[2-[bis(carboximetil)amino]etil]glicinato(5-)]gadolinato(2-)
medio paramagnético de contraste

$C_{23}H_{30}GdN_3O_{11}$ 135326-11-3



acidum ibandronicum
ibandronic acid

[1-hydroxy-3-(methylpentylamino)propylidene]diphosphonic acid
calcium regulator

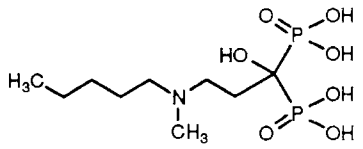
acide ibandronique

acide [1-hydroxy-3-[méthyl(pentyl)amino]propylidène]bisphosphonique
régulateur du calcium

ácido ibandrónico

ácido [1-hidroxi-3-(metilpentilamino)propilideno]difosfónico
regulador del calcio

$C_9H_{23}NO_7P_2$ 114084-78-5



acidum olpadronicum
olpadronic acid

[3-(dimethylamino)-1-hydroxypropylidene]diphosphonic acid
calcium regulator

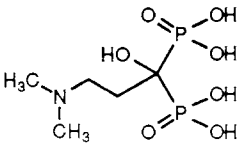
acide olpadronique

acide [3-(diméthylamino)-1-hydroxypropylidène]bisphosphonique
régulateur du calcium

ácido olpadrónico

ácido [3-(dimetilamino) -1-hidroxipropilideno]difosfónico
regulador del calcio

$C_5H_{15}NO_7P_2$ 63132-39-8



acidum zoledronicum
zoledronic acid

(1-hydroxy-2-imidazol-1-ylethylidene)diphosphonic acid
calcium regulator

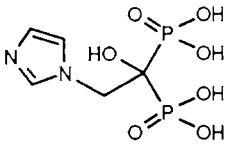
acide zolédronique

acide [1-hydroxy-2-(1*H*-imidazol-1-yl)éthylidène]bisphosphonique
régulateur du calcium

ácido zoledrónico

ácido (1-hidroxi-2-imidazol-1-iletiliden)difosfónico
regulador del calcio

$C_5H_{10}N_2O_7P_2$ 118072-93-8



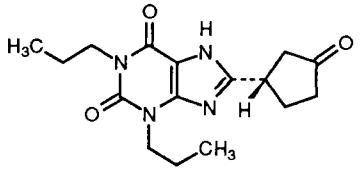
apaxifyllinum

apaxifylline (-)-(*S*)-8-(3-oxocyclopentyl)-1,3-dipropylxanthine
nootropic agent

apaxifylline (-)-(*S*)-8-(-3-oxocyclopentyl)-1,3-dipropyl-3,7-dihydro-1*H*-purine-2,6-dione
nootrope

apaxifilina (-)-(*S*)-8-(3-oxociclopentil)-1,3-dipropilxantina
nootropo

$C_{16}H_{22}N_4O_3$ 151581-23-6



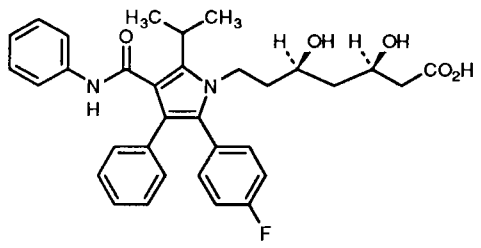
atorvastatinum

atorvastatin (β*R*,δ*R*)-2-(*p*-fluorophenyl)-β,δ-dihydroxy-5-isopropyl-3-phenyl-4-(phenylcarbamoyl)pyrrole-1-heptanoic acid
antihyperlipidaemic

atorvastatine acide (3*R*,5*R*)-7-[2-(4-fluorophényl)-5-(1-méthyléthyl)-3-phényl-4-[(phénylamino)carbonyl]-1*H*-pyrrol-1-yl]-3,5-dihydroxyheptanoïque
hypolipémiant

atorvastatina ácido (β*R*,δ*R*)-2-(*p*-fluorofenil)-β,δ-dihidroxi-5-isopropil-3-fenil-4-(fenilcarbamoil)-pirrol-1-heptanoico
antihiperlipémico

$C_{33}H_{35}FN_2O_5$ 134523-00-5



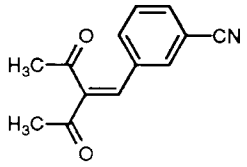
balaziponum

balazipone *m*-(2-acetyl-3-oxo-1-butenyl)benzonitrile
cytoprotective

balazipone 3-(2-acétyl-3-oxobut-1-ényl)benzonitrile
cytoprotecteur

balazipona *m*-(2-acetil-3-oxo-1-butenil)benzonitrilo
citoprotector

$C_{13}H_{11}NO_2$ 137109-71-8



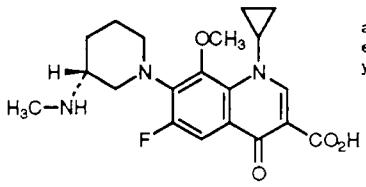
balofloxacinum

balofloxacin (±)-1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-[3-(methylamino)piperidino]-4-oxo-3-quinolinecarboxylic acid
antibacterial

balofloxacine acide (*RS*)-1-cyclopropyl-6-fluoro-8-méthoxy-7-[3-(méthylamino)pipéridin-1-yl]-4-oxo-1,4-dihydroquinoléine-3-carboxylique
antibactérien

balofloxacino ácido (±)-1-ciclopropil-6-fluoro-1,4-dihidro-8-metoxi-7-[3-(metilamino)-piperidino]-4-oxo-3-quinolincarboxílico
antibacteriano

$C_{20}H_{24}FN_3O_4$ 127294-70-6



and enantiomer
et énantiomère
y enantiomero

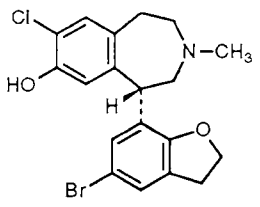
berupipamum

berupipam (+)-(5*S*)-5-(5-bromo-2,3-dihydro-7-benzofuranyl)-8-chloro- 2,3,4,5-tetrahydro-3-methyl-1*H*-3-benzazepin-7-ol
antipsychotic

bérupipam (+)-(*S*)-5-(5-bromo-2,3-dihydrobenzofuran-7-yl)-8-chloro-3-méthyl-2,3,4,5-tétrahydro-1*H*-3-benzazépin-7-ol
psychotrope

berupipam (+)-(5*S*)-5-(5-bromo-2,3-dihidro-7-benzofuranil)-8-cloro- 2,3,4,5-tetrahidro-3-metil-1*H*-3-benzazepin-7-ol
antipsicótico

$C_{19}H_{19}BrClNO_2$ 150490-85-0



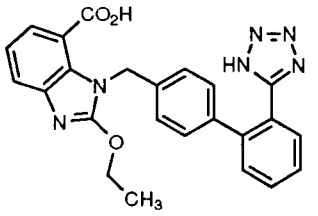
candesartanum

candesartan — 2-ethoxy-1-[*p*-(*o*-1*H*-tetrazol-5-ylphenyl)benzyl]-7-benzimidazolecarboxylic acid
angiotensin II receptor antagonist

candésartan — acide 2-éthoxy-1-[4-[2-(1*H*-tétrazol-5-yl)phényl]benzyl]-1*H*-benzimidazole-7-carboxylique
antagoniste du récepteur de l'angiotensine II

candesartan — ácido 2-etoxi-1-[*p*-(*o*-1*H*-tetrazol-5-ilfenil)bencil]-7-bencimidazolcarboxílico
antagonista del receptor de angiotensina II

$C_{24}H_{20}N_4O_3$ 145040-37-5



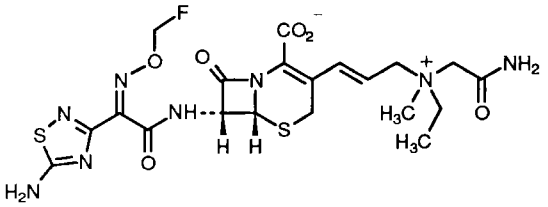
cefluprenamum

cefluprenam — (-)-[(*E*)-3-[(6*R*,7*R*)-7-[2-(5-amino-1,2,4-thiadiazol-3-yl)glyoxylamido]-2-carboxy-8-oxo-5-thia-1-azabicyclo [4.2.0]oct-2-en-3-yl]allyl](carbamoylmethyl)ethyl= methylammonium hydroxide, inner salt, 7^2-(*Z*)-[*O*- (fluoromethyl)oxime]
antibiotic

céfluprénam — (-)-(2-amino-2-oxoéthyl)[(*E*)-3-[(6*R*,7*R*)-7-[[(*Z*)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-[(fluorométhoxy)imino]acétyl]amino]-2-carboxylato-8-oxo-5-thia-1-azabicyclo= [4.2.0]oct-2-én-3-yl]prop-2-ényl]éthylméthylammonium
antibiotique

cefluprenam — hidróxido de (-)-[(*E*)-3-[(6*R*,7*R*)-7-[2-(5-amino-1,2,4-tiadiazol-3-il)glioxilamido]-2-carboxi-8-oxo-5-tia-1-azabiciclo [4.2.0]oct-2-en-3-il]alil](carbamoilmetil) etilmetilamonio ,sal interna , 7^2-(*Z*)-[*O*-(fluorometil)oxima
antibiótico

$C_{20}H_{25}FN_8O_6S_2$ 116853-25-9



cefoselisum

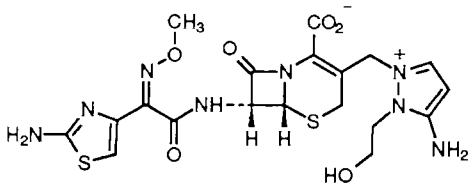
cefoselis — (-)-5-amino-2-[[(6*R*,7*R*)-7-[2-(2-amino-4-thiazolyl)glyoxylamido]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]-1-(2-hydroxyethyl)= pyrazolium hydroxide, inner salt, 7^2-(*Z*)-(*O*-methyloxime)
antibiotic

céfosélis

(-)-5-amino-2-[[(6*R*,7*R*)-7-[[(*Z*)-2-(2-aminothiazol-4-yl)-2-(méthoxyimino)= acétyl]amino]-2-carboxylato-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-én-3-yl]= méthyl]-1-(2-hydroxyéthyl)-1*H*-pyrazolium
antibiotique

cefoselis

(-)-5-amino-2-[[(6*R*,7*R*)-7-[[(*Z*)-2-(2-aminotiazol-4-il)-2-(metoxiimino)acetil]amino]-2-carboxilato-8-oxo-5-tia-1- azabiciclo[4.2.0]oct-2-en-3-il]metil]-1-(2 hidroxietil)-1*H*-pirazolio
antibiótico
$C_{19}H_{22}N_8O_6S_2$ 122841-10-5



cilmostimum

cilmostim

1-223-colony-stimulating factor 1 (human clone p3ACSF-69 protein moiety reduced) dimer, cyclic (7→90), (7'→ 90'), (31→31'), (48→139), (48'→ 139'), (102→146), (102'→ 146')-heptakis(disulfide)
immunomodulator

cilmostime

(7→90), (7'→ 90'), (31→31'), (48→139), (48'→ 139'), (102→146), (102'→ 146')-heptakis(disulfure cyclique) du dimère de 1-223-facteur 1 de stimulation des colonies (partie protéique réduite du clone humain p3ACSF-69)
immunomodulateur

cilmostim

(7→90), (7'→ 90'), (31→31'), (48→139), (48'→ 139'), (102→146), (102'→ 146')-heptakis(disulfuro cíclico) del dímero de 1- 223-factor 1 de estimulación de colonias (fracción proteica reducida del clon humano p3ACSF-69)
inmunomodulador

$C_{2198}H_{3430}N_{588}O_{704}S_{28}$ 148637-05-2

cipamfylline

cipamfylline

8-amino-1,3-bis(cyclopropylmethyl)xanthine
polymorphonuclear neutrophil modulator

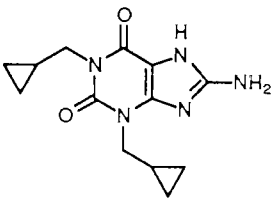
cipamfylline

8-amino-1,3-bis(cyclopropylméthyl)-3,7-dihydro-1*H*-purine-2,6-dione
modulateur des polymorphonucléaires neutrophiles

cipamfilina

8-amino-1,3-bis(ciclopropilmetil)xantina
modulador de los neutrofilos polimorfonucleares

$C_{13}H_{17}N_5O_2$ 132210-43-6

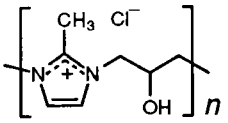


colestimidum
colestimide — 2-methylimidazole polymer with 1-chloro-2,3-epoxypropane
antihyperlipidaemic

colestimide — copolymère de 2-méthylimidazole et de 1-chloro-2,3-époxypropane
hypolipémiant

colestimida — polímero de 2-metilimidazol con 1-cloro-2,3-epoxipropano
antihiperlipémico

$(C_4H_6N_2.C_3H_5ClO)n$ 95522-45-5



dacliximabum
dacliximab — immunoglobulin G 1 (human-mouse monoclonal clone 1H4 γ-chain anti-human interleukin 2 receptor), disulfide with human-mouse monoclonal clone 1H4 light chain, dimer
immunosuppressant

dacliximab — immunoglobuline G 1 (chaîne γ de l'anticorps monoclonal du clone homme-souris 1H4 dirigé contre le récepteur de l'interleukine 2 humain), dimère du disulfure avec la chaîne légère de l'anticorps monoclonal du clone homme-souris 1H4
immunosuppresseur

dacliximab — inmunoglobulina G 1(cadena γ del anticuerpo monoclonal del clon humano-murino 1H4 anti-receptor de la interleukina 2 humano), dimero del disulfuro con la cadena ligera del anticuerpo monoclonal del clon humano-murino
inmunosupresor

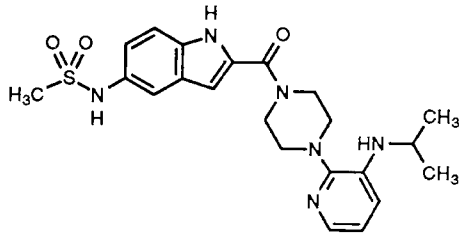
$C_{6394}H_{9888}N_{1696}O_{2012}S_{44}$ 152923-56-3

delavirdinum
delavirdine — 1-[3-(isopropylamino)-2-pyridyl]-4-[(5-methanesulfonamidoindol-2-yl)carbonyl]-piperazine
antiviral

délavirdine — 1-[3-[(1-méthyléthyl)amino]pyridin-2-yl]-4-[[5-[(méthylsulfonyl)amino]-1*H*-indol-2-yl]carbonyl]pipérazine
antiviral

delavirdina — 1-[3-(isopropilamino)-2-piridil]-4-[(5-metanosulfonamidoindol-2-il)carbonil]-piperazina
antiviral

$C_{22}H_{28}N_6O_3S$ 136817-59-9



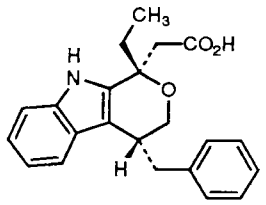
dexpemedolacum

dexpemedolac (1*S*,4*R*)-4-benzyl-1-ethyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indole-1-acetic acid
analgesic

dexpémédolac acide 2-[(1*S*,4*R*)-4-benzyl-1-éthyl-1,3,4,9-tétrahydropyrano[3,4-*b*]indol-1-yl]-acétique
analgésique

dexpemedolaco ácido (1*S*,4*R*)-4-bencil-1-etil-1,3,4,9-tetrahidropirano[3,4-*b*]indol-1-acético
analgésico

$C_{22}H_{23}NO_3$ 114030-44-3



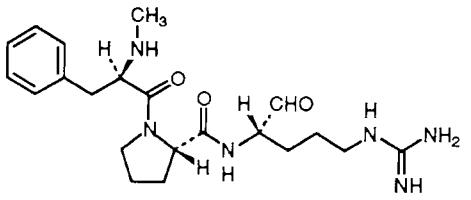
efegatranum

efegatran *N*-methyl-D-phenylalanyl-*N*-[(1*S*)-1-formyl-4-guanidinobutyl]-L-prolinamide
thrombin inhibitor

égégatran (2*S*)-*N*-[(1*S*)-1-formyl-4-guanidinobutyl]-1-[(2*R*)-2-(méthylamino)-3-phénylpropanoyl]pyrrolidine-2-carboxamide
inhibiteur de la thrombine

efegatran *N*-metil-D-fenilalanil-*N*-[(1*S*)-1-formil-4-guanidinobutil]-L-prolinamida
inhibidor de la trombina

$C_{21}H_{32}N_6O_3$ 105806-65-3



efletirizinum
efletirizine

[2-[4-[bis(*p*-fluorophenyl)methyl]-1-piperazinyl]ethoxy]acetic acid
histamine-H_1 receptor antagonist

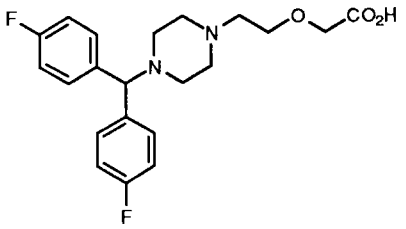
éflétirizine

acide 2-[2-[4-[bis(4-fluorophényl)méthyl]pipérazin-1-yl]éthoxy]acétique
antagoniste des récepteurs H_1 de l'histamine

efletirizina

ácido [2-[4-[bis(*p*-fluorofenil)metil]-1-piperazinil]etoxi]acético
antagonista de los receptores H_1 de la histamina

$C_{21}H_{24}F_2N_2O_3$ 150756-35-7



eprosartanum
eprosartan

(*E*)-2-butyl-1-(*p*-carboxybenzyl)-α-2-thienylimidazole-5-acrylic acid
angiotensin II receptor antagonist

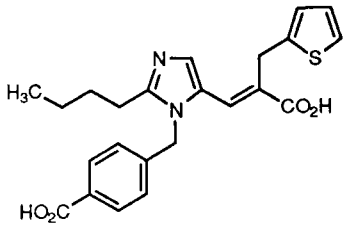
éprosartan

acide (*E*)-3-[2-butyl-1-(4-carboxybenzyl)-1*H*-imidazol-5-yl]-2-[(2-thiényl)méthyl]=prop-2-énoïque
antagoniste du récepteur de l'angiotensine II

eprosartan

ácido (*E*)-2-butil-1-(*p*-carboxibencil)-α-2-tienilimidazol-5-acrílico
antagonista del receptor de angiotensina II

$C_{23}H_{24}N_2O_4S$ 133040-01-4



follitropinum alfa
follitropin alfa

follicle-stimulating hormone, glycoform α
α-subunit:
chorionic gonadotropin (human α-subunit protein moiety reduced)
β-subunit:
follicle-stimulating hormone (human clone λ 15B β-subunit protein moiety reduced)
hormone

follitropine alfa

hormone folliculo-stimulante, forme glycosylée α
Sous-unité α :
gonadotropine chorionique (partie protéique réduite de la sous-unité α humaine)
Sous-unité β :
hormone folliculo-stimulante (partie protéique réduite de la sous-unité β du clone humain λ 15B)
hormone

follitropina alfa

hormona estimulante del folículo, glicoforma α
subunidad α :
gonadotropina coriónica (fracción proteica reducida de la subunidad α humana)
subunidad β :
hormona estimulante del folículo (fracción proteica reducida de la subunidad β del clon humano humane λ 15B)
hormona

α : $C_{437}H_{682}N_{122}O_{134}S_{13}$ 56832-30-5

β : $C_{538}H_{833}N_{145}O_{171}S_{13}$ 110909-60-9

9002-68-0

fuladectinum

fuladectin

a mixture of components A_4 and A_3 (80:20) :
component A_4:
4'-[2-[[(2a*E*,4*E*,5'*S*,6*S*,6'*R*,7*R*,8*E*,11*R*,13*R*,15*S*,17a*R*,20*R*,20a*R*,20b*S*)-6'-ethyl-3',4',5',6,6',7,10,11,14,15,17a,20,20a,20b-tetradecahydro-20,20b-dihydroxy-5',6,8,19-tetramethyl-17-oxospiro[11,15-methano-2*H*,13*H*,17*H*-furo[4,3,2-*pq*][2,6]benzodioxacyclooctadecin-13,2'-[2*H*]pyran]-7-yl]oxy]ethyl]-*N*-methylmethanesulfonanilide
component A_3:
4'-[2-[[(2a*E*,4*E*,5'*S*,6*S*,6'*R*,7*R*,8*E*,11*R*,13*R*,15*S*,17a*R*,20*R*,20a*R*,20b*S*)-3',4',5',6,6',7,10,11,14,15,17a,20,20a,20b-tetradecahydro-20,20b-dihydroxy-5',6,6',8,19-pentamethyl-17-oxospiro[11,15-methano-2*H*,13*H*,17*H*-furo[4,3,2-*pq*][2,6]benzodioxacyclooctadecin-13,2'-[2*H*]pyran]-7-yl]oxy]ethyl]-*N*-methylmethanesulfonanilide

fuladectine

mélange des constituants A_4 et A_3 (80:20) :
constituant A_4 :
N-[4-[2-[[(2a*E*,4*E*,8*E*)-(2'*R*,5'*S*,6*S*,6'*R*,7*R*,11*R*,15*S*,17a*R*,20*R*,20a*R*,20b*S*)-6'-éthyl-20,20b-dihydroxy-5',6,8,19-tétraméthyl-7-oxo-3',4',5',6,6',7,10,11,14,15,17a,20,20a,20b-tétradécahydrospiro[11,15-méthano-2*H*,13*H*,17*H*-furo[4,3,2-*pq*][2,6]benzodioxacyclooctadécène-13,2'-[2*H*]pyran]-7-yl]oxy]éthyl]phényl]-*N*-méthylméthanesulfonamide
constituant A_3 :
N-[4-[2-[[(2a*E*,4*E*,8*E*)-(2'*R*,5'*S*,6*S*,6'*R*,7*R*,11*R*,15*S*,17a*R*,20*R*,20a*R*,20b*S*)-20,20b-dihydroxy-5',6,6',8,19-pentaméthyl-7-oxo-3',4',5',6,6',7,10,11,14,15,17a,20,20a,20b-tétradécahydrospiro[11,15-méthano-2*H*,13*H*,17*H*-furo[4,3,2-*pq*][2,6]benzodioxacyclooctadécène-13,2'-[2*H*]pyran]-7-yl]oxy]éthyl]phényl]-*N*-méthylméthanesulfonamide
antihelmintique (vét.)

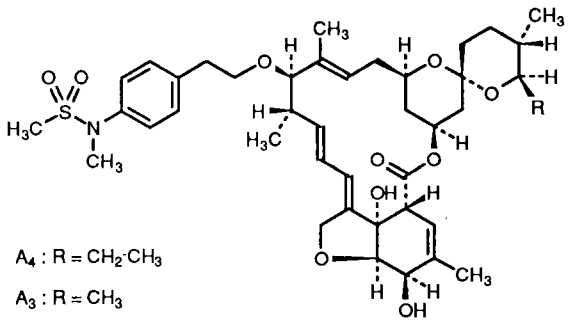
fuladectina

mezcla de los componentes A_4 y A_3 (80:20) :
componente A_4 :
4'-[2-[[(2a*E*,4*E*,5'*S*,6*S*,6'*R*,7*R*,8*E*,11*R*,13*R*,15*S*,17a*R*,20*R*,20a*R*,20b*S*)-6'-etil-3',4',5',6,6',7,10,11,14,15,17a,20,20a,20b-tetradecahidro-20,20b-dihidroxi-5',6,8,19-tetrametil-17-oxospiro[11,15-metano-2*H*,13*H*,17*H*-furo[4,3,2-*pq*][2,6]benzodioxaciclooctadecin-13,2'-[2*H*]piran]-7-il]oxi]etil]-*N*-metilmetanesulfonanilida

componente A_3:
4'-[2-[[(2a*E*,4*E*,5'*S*,6*S*,6'*R*,7*R*,8*E*,11*R*,13*R*,15*S*,17a*R*,20*R*,20a*R*,20b*S*)-3',4',5',6,6',7,10,11,14,15,17a,20,20a,20b-tetradecahidro-20,20b-dihidroxi-5',6,6',8,19-pentametil-17-oxospiro[11,15-metano-2*H*,13*H*,17*H*-furo[4,3,2-*pq*][2,6]benzodioxaciclooctadecin-13,2'-[2*H*]piran]-7-il]oxi]etil]-*N*-metilmetanesulfonanilida
anthelmíntico (vet.)

A_4, 80%: $C_{42}H_{59}NO_{10}S$ 150702-32-2

A_3, 20%: $C_{41}H_{57}NO_{10}S$ 150702-33-3



A_4 : R = CH_2-CH_3

A_3 : R = CH_3

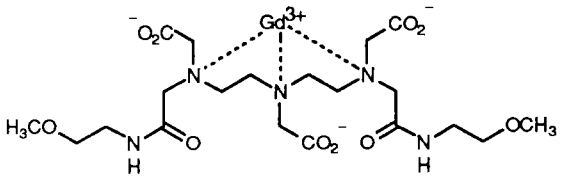
gadoversetamidum

gadoversetamide
[*N*,*N*-bis[2-[[(carboxymethyl)[(2-methoxyethyl)carbamoyl]methyl]amino]ethyl]=glycinato(3-)]gadolinium
diagnostic agent

gadoversétamide
[*N*,*N*-bis[2-[(carboxyméthyl)[2-[(2-méthoxyéthyl)amino]-2-oxoéthyl]amino]=éthyl]glycinato(3-)]gadolinium
produit à usage diagnostique

gadoversetamida
[*N*,*N*-bis[2-[[(carboximetil)[(2-metoxietil)carbamoil]metil]amino]etil]glicinato(3-)]=gadolinio
agente de diagnóstico

$C_{20}H_{34}GdN_5O_{10}$ 131069-91-5



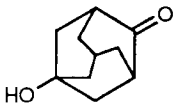
idramantonum

idramantone
5-hydroxy-2-adamantanone
immunostimulant

idramantone
5-hydroxytricyclo[3.3.1.1^{3,7}]décan-2-one
immunostimulant

idramantona
5-hidroxi-2-adamantanona
inmunoestimulante

$C_{10}H_{14}O_2$ 20098-14-0



ifetrobanum

ifetroban

o-[[(1*S*,2*R*,3*S*,4*R*)-3-[4-(pentylcarbamoyl)-2- oxazolyl]-7-oxabicyclo[2.2.1]hept-2-yl]methyl]hydrocinnamic acid
thromboxane A_2 receptor antagonist

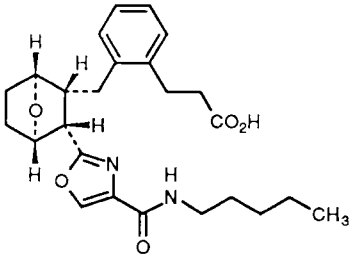
ifétroban

acide 3-[2-[[(1*S*,2*R*,3*S*,4*R*)-3-[4-[(pentylamino)carbonyl]oxazol-2-yl]-7-oxa= bicyclo[2.2.1]hept-2-yl]méthyl]phényl]propanoïque
antagoniste du récepteur du thromboxane A_2

ifetroban

ácido *o*-[[(1*S*,2*R*,3*S*,4*R*)-3-[4-(pentilcarbamoil)-2-oxazolil]-7-oxabiciclo= [2.2.1]hept-2-il]metil]hidrocinámico
antagonista del receptor de tromboxano A_2

$C_{25}H_{32}N_2O_5$ 143443-90-7



imidaprilatum

imidaprilat

(4*S*)-3-[(2*S*)-*N*-[(1*S*)-1-carboxy-3-phenylpropyl]alanyl]-1-methyl-2-oxo-4-imidazolidinecarboxylic acid
angiotensin-converting enzyme inhibitor

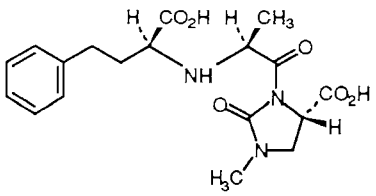
imidaprilate

acide (*S*)-3-[(*S*)-2-[[(*S*)-1-carboxy-3-phénylpropyl]amino]propanoyl]-1-méthyl-2-oxo-imidazolidine-4-carboxylique
inhibiteur de l'enzyme de conversion de l'angiotensine

imidaprilat

ácido (4*S*)-3-[(2*S*)-*N*-[(1*S*)-1-carboxi-3-fenilpropil]alanil]-1-metil-2-oxo-4-imidazolidincarboxílico
inhibidor de la enzima conversora de la angiotensina

$C_{18}H_{23}N_3O_6$ 89371-44-8



inolimomabum

inolimomab — immunoglobulin G 1 (mouse monoclonal B-B10 γ-chain anti-human interleukin-2 receptor α-chain), disulfide with mouse monoclonal B-B10 κ-chain, dimer
immunosuppressant

inolimomab — immunoglobuline G 1 (chaîne γ de l'anticorps monoclonal de souris B-B10 dirigé contre la chaîne α du récepteur de l'interleukine-2 humain), dimère du disulfure avec la chaîne κ de l'anticorps monoclonal de souris B-B10
immunosuppresseur

inolimomab — inmunoglobulina G 1 (cadena γ del anticuerpo monoclonal de ratón B-B10 anti-cadena α del receptor de interleukina-2 humana), dímero del disulfuro con la cadena κ del anticuerpo monoclonal de ratón B-B10
inmunosupresor

152981-31-2

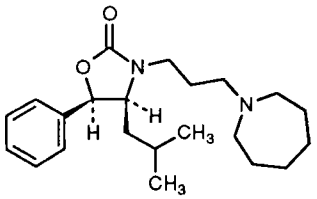
ipenoxazonum

ipenoxazone — (+)-(4*S*,5*R*)-3-[3-(hexahydro-1*H*-azepin-1-yl)propyl]-4-isobutyl-5-phenyl-2-oxazolidinone
NMDA receptor antagonist

ipénoxazone — (+)-(4*S*,5*R*)-3-[3-(hexahydro-1*H*-azépin-1-yl)propyl]-4-(2-méthylpropyl)-5-phényloxazolidin-2-one
antagoniste des récepteurs du NMDA

ipenoxazona — (+)-(4*S*,5*R*)-3-[3-(hexahidro-1*H*-azepin-1-il)propil]-4-isobutil-5-fenil-2-oxazolidinona
antagonista del receptor de NMDA

$C_{22}H_{34}N_2O_2$ 104454-71-9



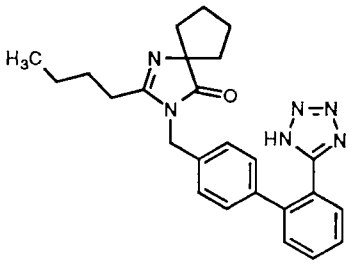
irbesartanum

irbesartan — 2-butyl-3-[*p*-(*o*-1*H*-tetrazol-5-ylphenyl)benzyl]-1,3- diazaspiro[4.4]non-1-en-4-one
angiotensin II receptor antagonist

irbésartan — 2-butyl-3-[4-[2-(1*H*-tétrazol-5-yl)phényl]benzyl]-1,3-diazaspiro[4.4]non-1-én-4-one
antagoniste du récepteur de l'angiotensine II

irbesartan — 2-butil-3-[*p*-(*o*-1*H*-tetrazol-5-ilfenil)bencil]-1,3-diazaspiro[4.4]non-1-en-4-ona
antagonista del receptor de angiotensina II

$C_{25}H_{28}N_6O$ 138402-11-6



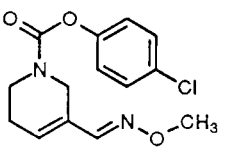
itamelinum

itameline — *p*-chlorophenyl 3-formyl-5,6-dihydro-1(2*H*)-pyridinecarboxylate, *O*-methyloxime
cholinergic

itaméline — (*E*)-3-[(méthoxyimino)méthyl]-5,6-dihydropyridine-1(2*H*)-carboxylate de 4-chlorophényle
cholinergique

itamelina — *p*-clorofenil 3-formil-5,6-dihidro-1(2*H*)-piridinacarboxilato, *O*-metiloxima
colinérgico

$C_{14}H_{15}ClN_2O_3$ 121750-57-0



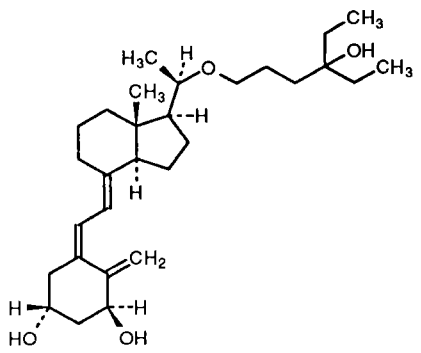
lexacalcitolum

lexacalcitol — (5*Z*,7*E*,20*R*)-20-[(4-ethyl-4-hydroxyhexyl)oxy]-9,10-secopregna-5,7,10(19)-triene-1α,3β-diol
vitamin D analogue

lexacalcitol — (5*Z*,7*E*)-(20*R*)-20-[(4-éthyl-4-hydroxyhexyl)oxy]-9,10-sécoprégna-5,7,10(19)-triène-1α,3β-diol
analogue de la vitamine D

lexacalcitol — (5*Z*,7*E*,20*R*)-20-[(4-etil-4-hidroxihexil)oxi]-9,10-secopregna-5,7,10(19)-trieno-1α,3β-diol
análogo de la vitamina D

$C_{29}H_{48}O_4$ 131875-08-6



lutropinum alfa

lutropin alfa

luteinizing hormone (human α-subunit reduced complex human β-subunit reduced), glycoform α
α-subunit:
chorionic gonadotropin (human α-subunit protein moiety reduced)
β-subunit:
luteinizing homone (human β-subunit protein moiety reduced)
hormone

lutropine alfa

hormone lutéinisante (complexe de sous-unités α humaine réduite et de sous-unité β humaine réduite), forme glycosylée α
Sous-unité α :
gonadotropine chorionique (partie protéique réduite de la sous-unité α humaine)
Sous-unité β :
hormone lutéinisante (partie protéique réduite de la sous-unité β humaine)
hormone

lutropina alfa

hormona luteinizante (complejo de los subunidadas α humana reducida y β humana reducida), glicoforma α
subunidad α :
gonadotropina coriónica (fracción proteica reducida de la subunidad α humana)
subunidad β :
hormona luteinizante (fracción proteica reducida de la subunidad β humana)
hormona

α : $C_{437}H_{682}N_{122}O_{134}S_{13}$ 56832-30-5

β : $C_{577}H_{929}N_{165}O_{161}S_{14}$ 152923-57-4

monteplasum

monteplase

84-L-serineplasminogen activator (human tissue-type 2-chain form), cyclic (6→36), (32'→48'), (34→43), (40'→109'), (51→73), (56→62), (75→83), (92→173), (113→155), (120'→ 264), (134'→209'), (144→168), (166'→182'), (180→261), (199'→227'), (201→243), (232→256)-heptadecakis(disulfide)
thrombolytic

montéplase

(6→36), (32'→48'), (34→43), (40'→109'), (51→73), (56→62), (75→83), (92→173), (113→155), (120'→ 264), (134'→209'), (144→168), (166'→182'), (180→261), (199'→227'), (201→243), (232→256)-heptadécakis(disulfure cyclique) du 84-L-sérine(activateur du plasminogène, humain, de type tissulaire, constitué de deux châines)
thrombolytique

monteplasa

84-L-serina activador del plasminógeno (tipo tisular humano forma bicatenaria), (6→36), (32'→48'), (34→43), (40'→109'), (51→73), (56→62), (75→83), (92→173), (113→155), (120'→ 264), (134'→209'), (144→168), (166'→182'), (180→261), (199'→227'), (201→243), (232→256)-heptadecakis(disulfuro cíclico)
trombolítico

$C_{2569}H_{3896}N_{746}O_{783}S_{39}$

nacolomabum tafenatoxum

nacolomab tafenatox

20-244-immunoglobulin G 1 (mouse monoclonal r-C242Fab-SEA clone pKP941 Fab fragment γ-chain anti-human colorectal tumor antigen C242) (244→ 1')-protein with enterotoxin A (*Staphyloccoccus aureus*), disulfide with mouse monoclonal r-C242Fab-SEA clone pKP941 κ-chain
immunomodulator

nacolomab tafénatox

20-244-immunoglobuline G1 (chaîne γ du fragment Fab de l'anticorps monoclonal de souris r-C242Fab-SEA, clone pKP941, anti-antigène C242 de tumeur colorectale humaine) (244→ 1')-protéine avec l'entérotoxine A (*Staphylococcus aureus*), disulfure avec la chaîne κ de l'anticorps monoclonal de souris r-C242Fab-SEA, clone pKP941
immunomodulateur

nacolomab tafenatox

20-244-inmunoglobulina G 1 (cadena γ del fragmento Fab del anticuerpo monoclonal de ratón r-C242Fab-SEA, clon pKP941, antiantígeno C 242 de tumor colorrectal humano) (244→1)-proteina con la enterotoxina A (*Staphyloccoccus aureus*), disulfuro con la cadena κ del anticuerpo monoclonal de ratón r-C242Fab-SEA, clon pKP941
inmunomodulador

150631-27-9

nemorubicinum

nemorubicin

(1*S*,3*S*)-3-glycoloyl-1,2,3,4,6,11-hexahydro-3,5,12-trihydroxy-10-methoxy-6,11-dioxo-1-naphthacenyl 2,3,6-trideoxy-3-[(*S*)-2-methoxymorpholino]-α-L-*lyxo*-hexopyranoside
antineoplastic

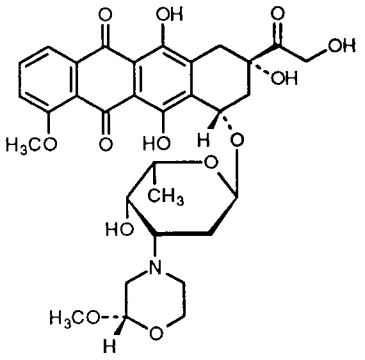
némorubicine

(8*S*,10*S*)-6,8,11-trihydroxy-8-(2-hydroxyacétyl)-1-méthoxy-10-[[3-[(2*S*)-2-méthoxymorpholin-4-yl]-2,3,6-tridésoxy-α-L-*lyxo*-hexopyranosyl]oxy]-7,8,9,10-tétrahydronaphtacène-5,12-dione
antinéoplasique

nemorubicina

(1*S*,3*S*)-3-glicoloil-1,2,3,4,6,11-hexahidro-3,5,12-trihidroxi-10-metoxi-6,11-dioxo-1-naftacenil 2,3,6-tridesoxi-3-[(*S*)-2-metoximorfolino]-α-L-*lixo*-hexo-piranósido
antineoplásico

$C_{32}H_{37}NO_{13}$ 108852-90-0



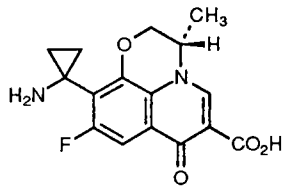
pazufloxacinum

pazufloxacin (-)-(3*S*)-10-(1-aminocyclopropyl)-9-fluoro-2,3-dihydro-3-methyl-7-oxo-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylic acid
antibacterial

pazufloxacine acide (-)-(3*S*)-10-(1-aminocyclopropyl)-9-fluoro-3-méthyl-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylique
antibactérien

pazufloxacino ácido (-)-(3*S*)-10-(1-aminociclopropil)-9-fluoro-2,3-dihidro-3-metil-7-oxo-7*H*-pirido[1,2,3-*de*]-1,4-benzoxazina-6-carboxílico
antibacteriano

$C_{16}H_{15}FN_2O_4$ 127045-41-4



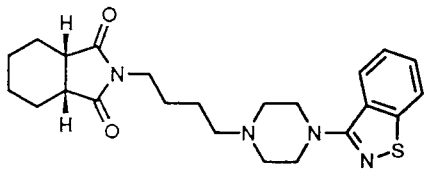
perospironum

perospirone *cis-N*-[4-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]butyl]-1,2-cyclohexane-dicarboximide
antipsychotic

pérospirone *cis*-2-[4-[4-(1,2-benzisothiazol-3-yl)pipérazin-1-yl]butyl]hexahydro-2*H*-isoindole-1,3-dione
psychotrope

perospirona *cis-N*-[4-[4-(1,2-bencisotiazol-3-il)-1-piperazinil]butil]-1,2-ciclohexanodicarboximida
antipsicótico

$C_{23}H_{30}N_4O_2S$ 150915-41-6



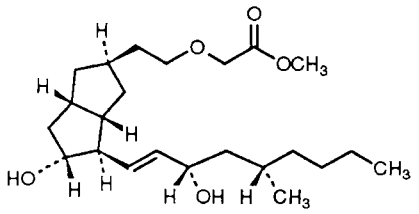
pimilprostum

pimilprost (+)-methyl [2-[(2*R*,3a*S*,4*R*,5*R*,6a*S*)-octahydro-5-hydroxy-4-[(1*E*,3*S*,5*S*)-3-hydroxy-5-methyl-1-nonenyl]-2-pentalenyl]ethoxy]acetate
platelet aggregation inhibitor

pimilprost (+)-2-[2-[(2*R*,3a*S*,4*R*,5*R*,6a*S*)-5-hydroxy-4-[(*E*)-(3*S*,5*S*)-3-hydroxy-5-méthylnon-1-ényl]octahydropentalén-2-yl]éthoxy]acétate de méthyle
antiagrégant plaquettaire

pimilprost (+)-2-[2-[(2*R*,3a*S*,4*R*,5*R*,6a*S*)-5-hidroxi-4-[(*E*)-(3*S*,5*S*)-3-hidroxi-5-metilnon-1-enil]octahidropentalen-2-il]etoxi]acetato de metilo
inhibidor de la agregación plaquetaria

$C_{23}H_{40}O_5$ 139403-31-9



regavirumabum

regavirumab immunoglobulin G 1 (human monoclonal γ-chain anti-human cytomegalovirus glycoprotein B), disulfide with human monoclonal κ-chain, dimer
immunomodulator

régavirumab immunoglobuline G1 (chaîne γ de l'anticorps monoclonal humain anti-glycoprotéine B de cytomégalovirus humain), dimère du disulfure avec la chaîne κ de l'anticorps monoclonal humain

immunomodulateur

regavirumab inmunoglobulina G 1 (cadena γ del anticuerpo monoclonal humano antiglicoproteina B de Citomegalovirus humano), dímero del disulfuro con la cadena κ del anticuerpo monoclonal humano
inmunomodulador

153101-26-9

rocepafantum

rocepafant

6-(*o*-chlorophenyl)-7,10-dihydro-1-methylthio-4*H*-pyrido[4',3':4,5]thieno[3,2-*f*]-*s*-triazolo[4,3-*a*] [1,4]diazepine-9(8*H*)-carboxy-*p*-anisidide
platelet-activating factor antagonist

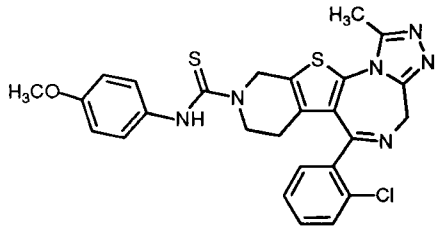
rocépafant

6-(2-chlorophényl)-*N*-(4-méthoxyphényl)-1-méthyl-7,10-dihydro-4*H*-pyrido=[4',3':4,5]thiéno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazépine-9(8*H*)-carbothioamide
antagoniste du facteur activant les plaquettes

rocepafant

6-(*o*-clorofenil)-7,10-dihidro-1-metiltio-4*H*-pirido[4',3' :4,5]tieno[3,2-*f*]-*s*-triazolo[4,3-*a*][1,4]diazepina-9(8*H*)-carboxi-*p*-anisidida
antagonista del factor de activación de plaquetas

$C_{26}H_{23}ClN_6OS_2$ 132418-36-1



ruzadolanum

ruzadolane

3-[[2-[4-(2,4-difluorophenyl)-1-piperazinyl]ethyl] thio]-*s*-triazolo[4,3-*a*]pyridine
analgesic

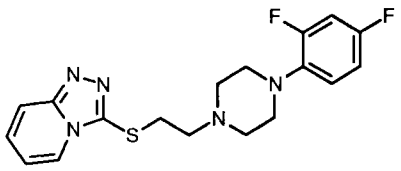
ruzadolane

3-[[2-[4-(2,4-difluorophényl)pipérazin-1-yl]éthyl]thio]-1,2,4-triazolo[4,3-*a*]pyridine
analgésique

ruzadolano

3-[[2-[4-(2,4-difluorofenil)-1-piperazinil]etil]tio]-*s*-triazolo[4,3-*a*]piridina
analgésico

$C_{18}H_{19}F_2N_5S$ 115762-17-9



teverelixum

teverelix

N-acetyl-3-(2-naphthyl)-D-alanyl-*p*-chloro-L-phenylalanyl-3-(3-pyridyl)-D-alanyl-L-seryl-L-tyrosyl-N^6-carbamoyl-D-lysyl-L-leucyl-N^6-isopropyl-L-lysyl-L-prolyl-D-alaninamide
luteinizing-hormone-releasing-hormone inhibitor

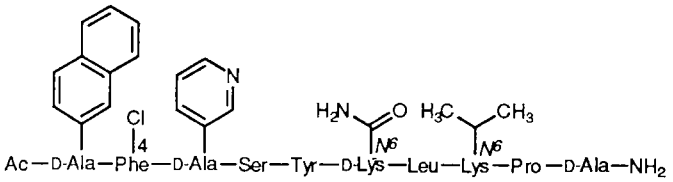
tévérélix

[*N*-acétyl-3-(naphtalén-2-yl)-D-alanyl]-(4-chloro-L-phénylalanyl)-[3-(pyridin-3-yl)-D-alanyl]-L-séryl-L-tyrosyl-[N^6-(aminocarbonyl)-D-lysyl]-L-leucyl-[N^6-(1-méthyl=éthyl)-L-lysyl]-L-prolyl-D-alaninamide
inhibiteur de l'hormone de libération de la lutéostimuline

teverelix

[*N*-acetil-3-(naftalen-2-il)-D-alanil]-(4-cloro-L-fenilalanil)-[3-(piridin-3-il)-D-alanil]-L-seril-L-tirosil-[N^6-(aminocarbonil)-D-lisil]-L-leucil-[N^6-(1-metiletil)-L-lisil]-L-prolil-D-alaninamida
inhibidor de la hormona de liberación de hormona luteinizante

$C_{74}H_{100}ClN_{15}O_{14}$ 144743-92-0



versetamidum

versetamide

N,N-bis[2-[[(carboxymethyl)[(2-methoxyethyl)carbamoyl]methyl]amino]ethyl]=glycine
diagnostic agent

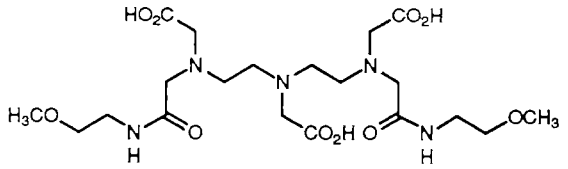
versétamide

N,N-bis[2-[(carboxyméthyl)[2-[(2-méthoxyéthyl)amino]-2-oxoéthyl]amino]éthyl]=glycine
produit à usage diagnostique

versetamida

N,N-bis[2-[[(carboximetil)[(2-metoxietil)carbamoil]metil]amino]etil]glicina
agente de diagnóstico

$C_{20}H_{37}N_5O_{10}$ 129009-83-2



verteporfinum

verteporfin

a mixture (50:50) of : (±)-*trans*-3,4-dicarboxy-4,4a-dihydro-4a,8,14,19-tetramethyl-18-vinyl-23*H*,25*H*-benzo[*b*]porphine-9,13-dipropionic acid, 3,4,9-trimethyl ester and (±)-*trans*-3,4-dicarboxy-4,4a-dihydro-4a,8,14,19-tetramethyl-18-vinyl-23*H*,25*H*-benzo[*b*]porphine-9,13-dipropionic acid, 3,4,13-trimethyl ester
photosensitizing agent

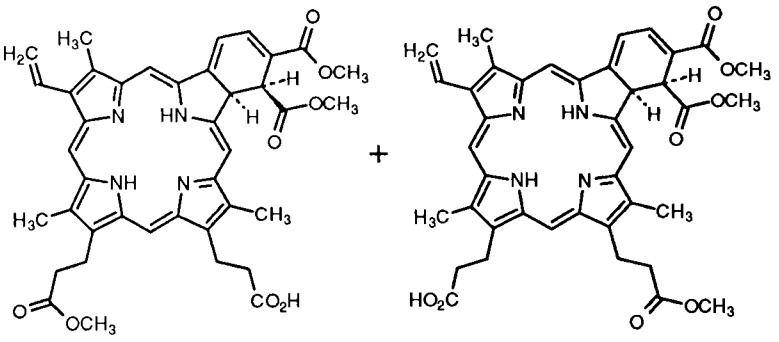
vertéporfine

mélange sensiblement équimoléculaire : d'acide 3-[(±)-*trans*-18-éthényl-3,4-bis(méthoxycarbonyl)-13-[2-(méthoxycarbonyl)éthyl]-4a,8,14,19-tétraméthyl-4,4a-dihydro-23*H*,25*H*-benzo[*b*]porphyrin-9-yl]propanoïque et d'acide 3-[(±)-*trans*-18-éthényl-3,4-bis(méthoxycarbonyl)-9-[2-(méthoxycarbonyl)éthyl]-4a,8,14,19-tétraméthyl-4,4a-dihydro-23*H*,25*H*-benzo[*b*]porphyrin-13-yl]propanoïque
photosensibilisant

verteporfina

mezcla (50:50) del : 3,4,9-trimetil ester del ácido (±)-*trans*-3,4-dicarboxi-4,4a-dihidro-4a,8,14,19-tetrametil-18-vinil-23*H*,25*H*-benzo[*b*]porfina-9,13-dipropiónico, con el 3,4,13-trimetil ester del ácido (±)-*trans*-3,4-dicarboxi-4,4a-dihidro-4a,8,14,19-tetrametil-18-vinil-23*H*,25*H*-benzo[*b*]porfina-9,13-dipropiónico
agente fotosensibilizante

$C_{41}H_{42}N_4O_8$ 129497-78-5



zafirlukastum

zafirlukast

cyclopentyl 3-[2-methoxy-4-[(*o*-tolylsulfonyl) carbamoyl]benzyl]-1-methylindole-5-carbamate
leuktriene receptor antagonist

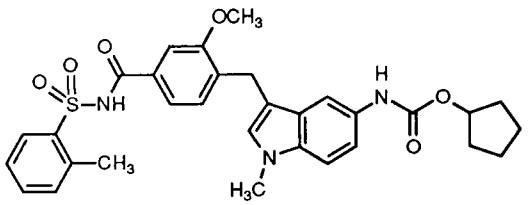
zafirlukast

[3-[2-méthoxy-4-[[[(2-méthylphényl)sulfonyl]amino]carbonyl]benzyl]-1-méthyl-1*H*-indol-5-yl]carbamate de cyclopentyle
antagoniste du récepteur des leukotriènes

zafirlukast

ciclopentil 3-[2-metoxi-4-[(*o*-tolilsulfonil)carbamoil]bencil]-1-metilindol-5-carbamato
antagonista del receptor de leucotrieno

$C_{31}H_{33}N_3O_6S$ 107753-78-6



zifrosilonum

zifrosilone

2,2,2-trifluoro-3'-(trimethylsilyl)acetophenone
acetylcholinesterase inhibitor

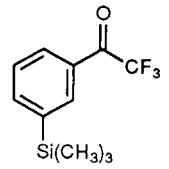
zifrosilone

2,2,2-trifluoro-1-[3-(triméthylsilyl)phényl]éthanone
inhibiteur de l'acétylcholinestérase

zifrosilona

2,2,2-trifluoro-3'-(trimetilsilil)acetofenona
inhibidor de la acetilcolinesterasa

$C_{11}H_{13}F_3OSi$ 132236-18-1



zucapsaicinum
zucapsaicin

(*Z*)-8-methyl-*N*-vanillyl-6-nonenamide
analgesic

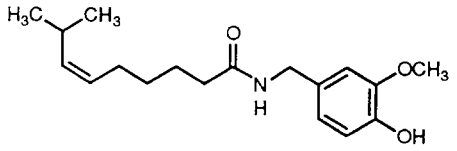
zucapsaïcine

(*Z*)-*N*-(4-hydroxy-3-méthoxybenzyl)-8-méthylnon-6-énamide
analgésique

zucapsaicina

(*Z*)-8-metil-*N*-vanilil-6-nonenamida
analgésico

$C_{18}H_{27}NO_3$ 25775-90-0



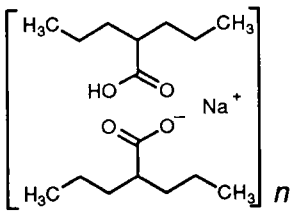
AMENDMENTS TO PREVIOUS LISTS

Supplement to WHO Chronicle Vol. 37, No. 5, 1983

Proposed International Nonproprietary Names (Prop. INN): List 50

p. 26 valproatum seminatricum
valproate semisodium

replace the chemical name and the molecular formula by the following:
sodium hydrogen bis(2-propylvalerate), oligomer
$(C_{16}H_{31}NaO_4)_n$



WHO Drug Information, Vol. 4, No. 4, 1990

Proposed International Nonproprietary Names (Prop. INN): List 64

p. 3 aprikalimum
aprikalim

replace the chemical name by the following:
(-)-(1*R*, 2*R*)-tetrahydro-*N*-methyl-2-(3-pyridyl)thio-2*H*-thiopyran-2-carboxamide 1-oxide

WHO Drug Information, Vol. 7, No. 4, 1993

Proposed International Nonproprietary Names (Prop. INN): List 70

p. 2 afovirsenum
afovirsen

add the following CAS registry number:
151356-08-0

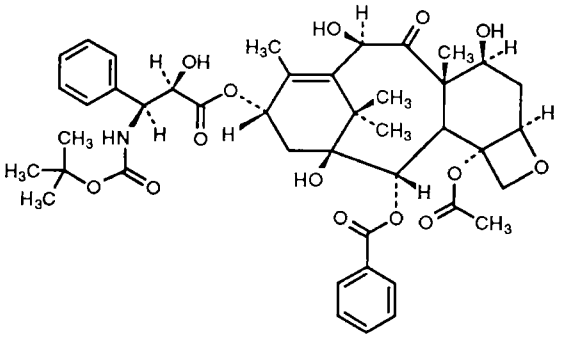
p. 4 desirudinum
desirudin

replace the description by the following:
63-desulfohirudin (*Hirudo medicinalis* isoform HV1)

p. 16 docetaxelum
docetaxel

replace the chemical name, the molecular formula, CAS registry number and the graphic formula by the following:
(2*R*,3*S*)-*N*-carboxy-3-phenylisoserine, *N*-*tert*-butyl ester, 13-ester with 5β-20-epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4-acetate 2-benzoate

$C_{43}H_{53}NO_{14}$ 114977-28-5



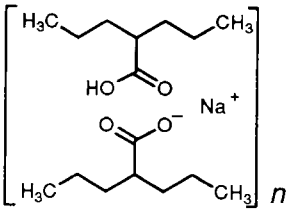
MODIFICATIONS APPORTÉES AUX LISTES ANTÉRIEURES

Supplément à la Chronique OMS, Vol. 37, No. 5, 1983

Dénominations communes internationales proposées (DCI Prop.): Liste 50

p. 26 valproatum seminatricum
valproate semisodique

remplacer le nom chimique, la formule brute et la formule developée par:
oligomère du complexe d'acide 2-propylpetanoïque et de 2-propylpentanoate de sodium
$(C_{16}H_{31}NaO_4)_n$



Informations pharmaceutiques OMS, Vol. 4, No. 4, 1990

Dénominations communes internationales proposées (DCI Prop.): Liste 64

p. 4 aprikalimum
aprikalim

remplacer le nom chimique par:
(-)-(1*R*, 2 *R*)-*N*-méthyl-2-(pyridin-3-yl)tétrahydro-2*H*-thiopyrane-2-carbothioamide 1-oxyde

Informations pharmaceutiques OMS, Vol. 7, No. 4, 1993

Dénominations communes internationales proposées (DCI Prop.): Liste 70

p. 2 afovirsenum
afovirsen

insérer le numéro dans le registre du CAS:
151356-08-0

p. 4 desirudinum
désirudine

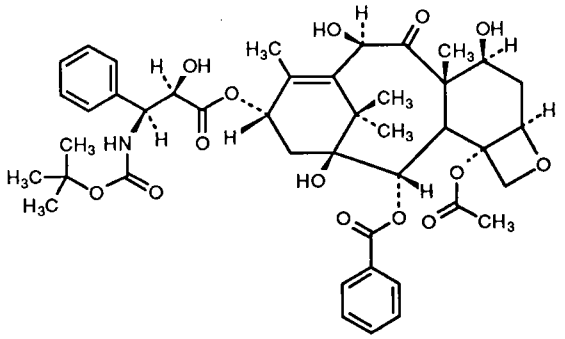
remplacer la description par:
63-désulfohirudine (*Hirudo medicinalis*, isoforme HV1)

p. 12 *supprimer*
technetium (^{99m}Tc) furifosminum
furifosmine technétium (^{99m}Tc)

insérer
technetium (^{99m}Tc) furifosminum
technétium (^{99m}Tc) furifosmine

p. 16 docetaxelum
docétaxel

remplacer le nom chimique, la formule brute et la formule developée et le numéro dans le registre de CAS par:
(2*R*,3*S*)-3-[[(1,1-diméthyléthoxy)carbonyl]amino]-2-hydroxy-3-phénylpropanoate de 4-(acétyloxy)-2α-(benzoyloxy)-5β,20-époxy-1,7β,10β-trihydroxy-9-oxotax-11-én-13α-yle
$C_{43}H_{53}NO_{14}$ 114977-28-5



MODIFICACIONES A LAS LISTAS ANTERIORES

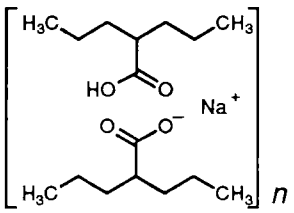
Suplemento de Crónica de la OMS, Vol. 37, No. 5, 1983

Denominaciones Comunes Internacionales Propuestas (DCI Prop.): Lista 50

p. 26 valproatum seminatricum
valproato semisódico

sustituyase el nombre químico y la fórmula empírica por los siguientes:
bis(2-propilvalerato) de hidrogeno y sodio, oligómero

$(C_{16}H_{31}NaO_4)_n$



Información Farmacéutica, OMS, Vol. 4, No. 4, 1990

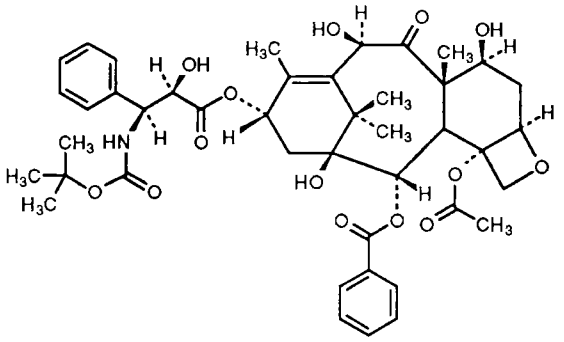
Denominaciones Comunes Internacionales Propuestas (DCI Prop.): Liste 64

p. 3	aprikalimum	*sustituyase el nombre químico por lo siguiente:*
	aprikalim	(-)-(1*R*, 2*R*)-tetrahidro-*N*-metil-2-(3-piridil)tio-2*H*-tiopiran-2-carboxamida 1-óxido

Información Farmacéutica, OMS, Vol. 7, No. 4, 1993

Denominaciones Comunes Internacionales Propuestas (DCI Prop.): Liste 70

p. 2	afovirsenum	*insertar el siguiente número de registro del CAS :*
	afovirseno	151356-08-0
p. 3	desirudinum	*sustituyase la fórmula empírica por la siguiente:*
	desirudina	63-desulfohirudina (isoforma HV1 de *Hirudo medicinalis*)
p. 16	docetaxelum	*sustituyanse el nombre químico, la fórmula empírica, el número de registro del CAS y la fórmula desarrollada por los siguientes:*
	docetaxel	(2*R*,3*S*)-*N*-carboxi-3-fenilisoserina, *N*-*terc*-butil éster, 13-éster con 5β-20-epoxi-1,2α,4,7β,10β,13α-hexahidroxitax-11-en-9-ona 4-acetato 2-benzoato
		$C_{43}H_{53}NO_{14}$ 114977-28-5



Annex 1

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

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

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

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

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

A. Such notice shall be given by publication in the *Chronicle of the World Health Organization*[1] 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.*[1]

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.*[1]

A. Such objection shall:

(i) identify the person objecting;

* Text adopted by the Executive Board of WHO in resolution EB15.R7 (*Off. Rec. Wld Health Org.*, 1955, **60**, 3) and amended by the Board in resolution EB43.R9 (*Off. Rec. Wld Hlth Org.*, 1969, **173**, 10).

[1] The title of this publication was changed to *WHO Chronicle* in January 1959. From 1987 onwards lists of INNs are published in *WHO Drug Information.*

(ii) state his interest in the name;

(iii) set forth the reasons for his objection to the name proposed.

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

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

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

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

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

Annex 2

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

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

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

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

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

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

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

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

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

* In its twentieth report (WHO Technical Report Series, No. 581, 1975), the WHO Expert Committee on Nonproprietary Names for Pharmaceutical Substances reviewed the general principles for devising, and the procedures for selecting, international nonproprietary names (INN) in the light of developments in pharmaceutical compounds in recent years. The most significant change has been the extension to the naming of synthetic chemical substances of the practice previously used for substances originating in or derived from natural products. This practice involves employing a characteristic "stem" indicative of a common property of the members of a group. The reasons for, and the implications of, the change are fully discussed.

7. To facilitate the translation and pronunciation of INN, "f" should be used instead of "ph", "t" instead of "th", "e" instead of "ae" or "oe", and "i" instead of "y"; the use of the letters "h" and "k" should be avoided.

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

9. Group relationship in INN (see Guiding Principle 2) should if possible be shown by using a common stem. The following list contains examples of stems for groups of substances, particularly for new groups. There are many other stems in active use.[1] Where a stem is shown without any hyphens it may be used anywhere in the name.

Latin	*English*	
-acum	-ac	anti-inflammatory agents of the ibufenac group
-actidum	-actide	synthetic polypeptides with a corticotropin-like action
-adolum	-adol)	analgesics
-adol-	-adol-)	
-astum	-ast	antiasthmatic, antiallergic substances not acting primarily as antihistaminics
-astinum	-astine	antihistaminics
-azepamum	-azepam	diazepam derivatives
-bactamum	-bactam	β-lactamase inhibitors
bol	bol	steroids, anabolic
-buzonum	-buzone	anti-inflammatory analgesics, phenylbutazone derivatives
-cain-	-cain-	antifibrillant substances with local anaesthetic activity
-cainum	-caine	local anaesthetics
cef-	cef-	antibiotics, cefalosporanic acid derivatives
-cillinum	-cillin	antibiotics, derivatives of 6-aminopenicillanic acid
-conazolum	-conazole	systemic antifungal agents, miconazole derivatives
cort	cort	corticosteroids, except prednisolone derivatives
-dipinum	-dipine	calcium channel blockers, nifedipine derivatives
-fibratum	-fibrate	clofibrate derivatives
gest	gest	steroids, progestogens
gli-	gli-	sulfonamide hypoglycaemics
io-	io-	iodine-containing contrast media
-ium	-ium	quaternary ammonium compounds
-metacinum	-metacin	anti-inflammatory substances, indometacin derivatives
-mycinum	-mycin	antibiotics, produced by *Streptomyces* strains
-nidazolum	-nidazole	antiprotozoal substances, metronidazole derivatives
-ololum	-olol	β-adrenoreceptor antagonists
-oxacinum	-oxacin	antibacterial agents, nalidixic acid derivatives
-pridum	-pride	sulpiride derivatives
-pril(at)um	pril(at)	angiotensin-converting enzyme inhibitors
-profenum	-profen	anti-inflammatory substances, ibuprofen derivatives
prost	prost	prostaglandins
-relinum	-relin	hypophyseal hormone release-stimulating peptides
-terolum	-terol	bronchodilators, phenethylamine derivatives
-tidinum-tidine		histamine H_2-receptor antagonists
-trexatum	-trexate	folic acid antagonists
-verinum	-verine	spasmolytics with a papaverine-like action
vin-	vin-)	vinca alkaloids
-vin-	-vin-)	

[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.

Annexe 1

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

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

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

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

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

A. Cette notification est faite par une insertion dans la *Chronique de l'Organisation mondiale de la Santé*[1] et par l'envoi d'une lettre aux Etats Membres et aux commissions nationales de pharmacopée ou autres organismes désignés par les Etats Membres.

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

B. Cette notification contient les indications suivantes:

(i) dénomination mise à l'étude;

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

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

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

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

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

4. Des observations sur la dénomination proposée peuvent être adressées à l'Organisation mondiale de la Santé par toute personne, dans les quatre mois qui suivent la date de publication de la dénomination dans la *Chronique de l'Organisation mondiale de la Santé*[1] (voir l'article 3).

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* Le texte reproduit ici a été adopté par le Conseil exécutif dans la résolution EB15.R7 *(Actes off. Org. mond. Santé*, 1955, **60**, 3) qui l'a ultérieurement amendé par la résolution EB43.R9 *(Actes off. Org. mond. Santé*, 1969, **173**, 10).

[1] Depuis janvier 1959, cette publication porte le titre de *Chronique OMS*. A partir de 1987, les listes des DCIs sont publiées dans les *Informations pharmaceutiques OMS*.

5. Toute personne intéressée peut formuler une objection formelle contre la dénomination proposée dans les quatre mois qui suivent la date de publication de la dénomination dans la *Chronique de l'Organisation mondiale de la Santé*[1] (voir l'article 3).

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

i) nom de l'auteur de l'objection;

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

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

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

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

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

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

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

Annexe 2

DIRECTIVES GENERALES POUR LA FORMATION DE DENOMINATIONS COMMUNES INTERNATIONALES APPLICABLES AUX SUBSTANCES PHARMACEUTIQUES*

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

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

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

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

3. Lorsqu'on formera la DCI de la première substance d'un nouveau groupe pharmacologique, on tiendra compte de la possibilité de former ultérieurement d'autres DCI appropriées pour les substances apparentées du même groupe.

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

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

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

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

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

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

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

Latin	*Français*	
-acum	-ac	substances anti-inflammatoires du groupe de l'ibufénac
-actidum	-actide	polypeptides synthétiques agissant comme la corticotropine
-adolum	-adol)	analgésiques
-adol-	-adol-)	
-astum	-ast	antiasthmatiques, antiallergiques n'agissant pas principalement en tant qu'antihistaminiques
-astinum	-astine	antihistaminiques
-azepamum	-azépam	substances du groupe du diazépam
-bactamum	-bactame	inhibiteurs de β - lactamases
bol	bol	stéroïdes anabolisants
-buzonum	-buzone	analgésiques anti-inflammatoires du groupe de la phénylbutazone
-cain-	-caïn-	substances antifibrillantes à action anesthésique locale
-cainum	-caïne	anesthésiques locaux
cef-	céf-	antibiotiques, dérivés de l'acide céphalosporanique
-cillinum	-cilline	antibiotiques, dérivés de l'acide 6-aminopénicillanique
-conazolum	-conazole	agents antifongiques systémiques du groupe du miconazole
cort	cort	corticostéroïdes, autres que les dérivés de la prednisolone
-dipinum	-dipine	inhibiteurs du calcium du groupe de la nifédipine
-fibratum	-fibrate	substances du groupe du clofibrate
gest	gest	stéroïdes progestogènes
gli-	gli-	sulfamides hypoglycémiants
io-	io-	produits de contraste iodés
-ium	-ium	ammoniums quaternaires
-metacinum	-métacine	substances anti-inflammatoires du groupe de l'indométacine
-mycinum	-mycine	antibiotiques produits par des souches de *Streptomyces*
-nidazolum	-nidazole	substances antiprotozoaires du groupe du métronidazole

[1] Une liste plus complète de segments clés est contenue dans le document de travail Pharm S/Nom.15 qui est régulièrement mis à jour et qui peut être demandé auprès de l'Unité pharmaceutique, OMS, Genève.

Latin	*Français*	
ololum	-olol	antagonistes des récepteurs β -adrénergiques
-oxacinum	-oxacine	substances antibactériennes du groupe de l'acide nalidixique
-pridum	-pride	substances du groupe du sulpiride
-profenum	-profène	substances anti-inflammatoires du groupe de l'ibuprofène
-pril(at)um	-pril(ate)	inhibiteurs de l'enzyme de conversion de l'angiotensine
prost	prost	prostaglandines
-relinum	-réline	peptides stimulant la libération d'hormones hypophysaires
-terolum	-térol	bronchodilatateurs, dérivés de la phénéthylamine
-tidinum	-tidine	antagonistes des récepteurs H_2 de l'histamine
-trexatum	-trexate	antagonistes de l'acide folique
-verinum	-vérine	spasmolytiques agissant comme la papavérine
vin-	vin-)	alcaloïdes du type vinca
-vin-	-vin-)	

Anexo 1

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

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

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

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

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

A. Esta notificación se hará mediante una publicación en la *Crónica de la Organización Mundial de la Salud*[1] y el envío de una carta a los Estados Miembros y a las comisiones nacionales de las farmacopeas u otros organismos designados por los Estados Miembros.

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

* El texto corregido que aquí se reproduce fue adoptado por el Consejo Ejecutivo en la resolución EB15.R7 (*Act. of. Org. mund. Salud*, 1955, **60**, 3) y enmendado por el Consejo en la resolución EB43.R9 (*Act. of. Org. mund. Salud*, 1969, **173**, 10).

[1] Denominada *Crónica de la OMS* desde enero de 1959. A partir de 1987, las listas de DCI se publican en *Información Farmacéutica OMS*.

B. En estas notificaciones se incluyen los siguientes datos:

(i) denominación sometida a estudio;

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

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

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

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

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

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

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

A. Esta objeción deberá acompañarse de los siguientes datos:

i) nombre de la persona que formula la objeción;

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

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

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

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

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

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

B. solicitará de los Estados Miembros la adopción de todas las medidas necesarias para impedir la adquisición de derechos de propiedad sobre la denominación, incluso la prohibición de registrarla como marca de fábrica o como nombre comercial.

Anexo 2

PRINCIPIOS GENERALES DE ORIENTACION PARA FORMAR DENOMINACIONES COMUNES INTERNACIONALES PARA SUSTANCIAS FARMACEUTICAS*

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

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

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

3. Al idear la DCI de la primera sustancia de un nuevo grupo farmacológico, deberá tenerse en cuenta la posibilidad de formar DCI convenientes para las sustancias emparentadas que vengan a incrementar el nuevo grupo.
4. Al idear DCI para ácidos, se preferirán las de una sola palabra; sus sales deberán denominarse sin modificar el nombre de ácido; p. ej., "oxacilina" y "oxacilina sódica", "ibufenaco" e "ibufenaco sódico".

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

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

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

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

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

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

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

[1] El documento de trabajo Pharm S/Norm 15, que se pone al día regularmente, contiene una lista más extensa de partículas comunes. Las personas que deseen recibirlo deberán solicitar su envío al Servicio de Preparaciones Farmacéuticas, OMS, Ginebra (Suiza).

Latin	*Español*	
-acum	-aco	antiinflamatorios del grupo del ibufenaco
-actidum	-actida	polipéptidos sintéticos de acción semejante a la corticotropina
-adolum	-adol }	analgésicos
-adol-	-adol- }	
-astum	-ast	antiasmáticos y antialérgicos que no actúan principalmente como antihistamínicos
-astinum	-astina	antihistamínicos
-azepamum	-azepam	sustancias del grupo del diazepam
-bactamum	-bactam	inhibidores de β - lactamasas
bol	bol	esteroides anabólizantes
-buzonum	-buzona	analgésicos antiinflamatorios del grupo de la fenilbutazona
-cain-	-cain-	antifibrilantes con actividad anestésica local
-cainum	-caina	anestésicos locales
cef-	cef-	antibióticos derivados del ácido cefalosporánico
-cillinum	-cilina	antibióticos derivados del ácido 6-aminopenicilánico
-conazolum	-conazol	antifúngicos sistémicos del grupo del miconazol
cort	cort	corticosteroides, excepto los del grupo de la prednisolona
-dipinum	-dipino	antagonistas del calcio del grupo del nifedipino
-fibratum	-fibrato	sustancias del grupo del clofibrato
gest	gest	esteroides progestágenos
gli-	gli-	sulfonamidas hipoglucemiantes
io-	io-	medios de contraste que contienen yodo
-ium	-io	compuestos de amonio cuaternario
-metacinum	-metacina	antiinflamatorios del grupo de la indometacina
-mycinum	-micina	antibióticos, producidos por cepas de *Streptomyces*
-nidazolum	-nidazol	antiprotozoarios del grupo del metronidazol
-ololum	-olol	bloqueadores β-adrenérgicos
-oxacinum	-oxacino	antibacterianos del grupo del ácido nalidíxico
-pridum	-prida	sustancias del grupo de la sulpirida
-pril(at)um	-pril(at)	inhibidores de la enzima transformadora de la angiotensina
-profenum	-profeno	antiinflamatorios del grupo del ibuprofeno
prost	prost	prostaglandinas
-relinum	-relina	péptidos estimulantes de la liberación de hormonas hipofisarias
-terolum	-terol	broncodilatadores derivados de la fenetilamina
-tidinum	-tidina	antagonistas del receptor H_2 de la histamina
-trexatum	-trexato	antagonistas del ácido fólico
-verinum	-verina	espasmolíticos de acción semejante a la de la papaverina
vin-	vin- }	alcaloides de la vinca
-vin-	-vin- }	