PROPOSED INN LIST 68
INTERNATIONAL NONPROPRIETARY NAMES FOR PHARMACEUTICAL SUBSTANCES
WORLD HEALTH ORGANIZATION · GENEVA
WHO Drug Information provides an overview of topics relating to drug development and regulation that are of current relevance and importance, and includes the lists of proposed and recommended International Nonproprietary Names for Pharmaceutical Substances (INN). Its contents reflect, but do not present, WHO policies and activities and they embrace socioeconomic as well as technical matters.

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

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General Policy Topics

Meta-analysis

Practising doctors need to know how accumulated knowledge on a given set of therapeutic options is best translated into appropriate clinical management. Meta-analysis provides them with an answer in quantitative terms. It offers an "ultimate" estimate of the comparative risks and benefits associated with alternative courses of action. In doing so, it provides a norm for the practising doctor to follow. Its potential influence on the routine practice of medicine is profound. Yet the term has slipped into the medical lexicon before being securely defined. Accredited by use, meta-analysis none the less remains problematic through lack of ground rules.

The basic assumption — and it can never be more than an assumption — is that independent studies designed to test the same hypothesis often approximate so closely in the criteria by which the subjects are selected and managed that the data obtained may legitimately be combined or integrated for analytical purposes (1). This inevitably offends statistical purists who regard controlled comparison through rigorous elimination of known sources of bias as an inviolate tenet of biological investigation. In clinical experimentation — both prospective and retrospective — screening criteria are used positively and precisely to admit comparable subjects to investigation. In meta-analysis comparability is sought — but with less assurance that it will be achieved — by excluding specific studies from a pre-existing pool of independent but similar experiments. The appeal of meta-analysis — the use of all relevant available information to obtain a unified quantitative answer to a complex clinical problem — is understandably compelling. But, because there is less assurance that like has been compared with like, it can sometimes be unrealistically naive.

When the technique was first applied, it was reasonable to assume that its conceptual and analytical basis would become refined with time and that its limitations would become better defined (2). However, now that it is more widely used, it is applied with less, rather than more discrimination. It has become commonplace, for instance, to resort to meta-analysis — in default of planned multi-centre studies — to present conclusions on the performance of a new drug to national regulatory authorities when the individual studies lack the statistical power to demonstrate a clinically important therapeutic effect with reasonable certainty (3). Even more questionably, it is used as a means of arbitration when the results of the individual trials are discordant.

Proponents of meta-analysis readily concede that it is far from a precise statistical tool. Sceptics question its very legitimacy as a quantitative technique (4). The complexity of biological responses and their multifactorial determinants demand that searching tests of comparability must always be applied to data obtained from different trials as a precondition of aggregating them for quasi-statistical purposes (5).

These concerns are far from hypothetical. They have been vindicated by hard experience. A persuasive example is provided by three markedly different interpretations of the risks associated with passive smoking provided by three independent meta-analyses (6-8). Plausible explanations for these differences and some salutary advice about indiscriminate aggregation of data have been offered in a recent issue of Pharmaceutical Medicine (9). Disconcertingly, the article simply spells out principles long-established as fundamental to the analysis of biological phenomena: univariate analysis cannot be appropriately applied to the exploration of clearly multivariate problems; only data obtained from well-designed and carefully-executed studies that satisfy explicit a priori inclusion and exclusion criteria should be admitted for meta-analysis; and data from trials that have produced mutually incompatible results can never be safely aggregated for any analytical purpose.

Meta-analysis has not attenuated or changed the basic tenets of biological investigation. Nor can it ever generate from a series of inconclusive and inconsistent studies a result that is more reliable than the sum of the parts. Inconsistencies in biological phenomena need to be examined and, whenever possible, explained. Understanding will never be advanced if tiresome unexplained differences in results are simply obscured. Meta-analysis must never supplant either scientific enquiry or the classical academic approach to review writing in medicine.
References


Essential drugs: for patients or for populations?

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By preparing guidelines and models for lists of essential drugs which should be readily available to those who need them, WHO has performed a valuable service to the developing world. The purpose of such lists is clear: “To extend the accessibility of the most necessary drugs to those populations whose basic health needs cannot be met by the existing supply system”(1). The onus is on each individual country to evaluate and adopt a list of essential drugs according to its own policy in the field of health.

Some countries, concerned with abuse of existing regulations by commercial interests, have drawn up stringent proposals which will undoubtedly benefit the majority of the population and protect them from exploitation. Under new legislation in Nigeria, for example, “any drug which is not on the essential drugs list cannot be imported, manufactured, sold, exposed for sale or distributed” (2). However, while the concept and principle of an essential drugs list is excellent, its rigid and exclusive implementation may highlight the conflict which sometimes arises between the needs of society and those of the individual. The very success and radical nature of such policies, while being for the general good, may be harmful or dangerous to the health of some patients, whose diseases are sufficiently rare for their needs to be overlooked in the compilation of drug lists. For such individuals, specific remedies or physiological replacement excluded from the list may be lifesaving, and may be essential for long-term therapy.

Nobody would question the inclusion of thyroxine in a list of essential drugs, even though severe hypothyroidism may be rare in a given community, because the value of replacement treatment for the affected individuals is common knowledge. Equally, sufferers from cystic fibrosis require pancreatic enzymes with their meals because, even before they were born, their pancreas was destroyed. But, because cystic fibrosis is less well known — and virtually absent from large parts of the world — pancreatic enzymes are not included in national lists of essential drugs even in countries with populations of predominantly European descent, such as some in Latin America.

In these countries the calculated numbers of patients with cystic fibrosis must run into tens of thousands according to the known gene frequency, even though the proportion of these patients that are actually diagnosed may be as low as 10% (3). Partly because they are not recognized, and partly because adequate treatment is not available, affected children die at an early age. The disease consequently has a low prevalence despite a high incidence. As a result, it continues to be regarded as a very rare disease by the health authorities and the medical profession, and this perception means that, when it does occur, it is frequently unrecognized. Whereas mean life expectancy for cystic fibrosis is now approximately 30 years in the industrialized countries of Europe and North America, it only reaches 6 years even for the minority who are diagnosed and treated in Latin America (4).

Families unfortunate enough to have children with cystic fibrosis usually avail themselves of all the information they can obtain. They are well aware of the treatment available in Europe and North America, and the corresponding enhancement of life expectancy. Similar treatment is not available in their own countries because the essential drugs lists are being applied restrictively. Thus, an instrument intended to make necessary drugs available to the majority of patients has the effect of denying drugs that are essential to the unfortunate few.

Heading the essential drugs required by children with cystic fibrosis are capsules containing pancreatic enzymes. They may have to take many of these with each meal if they are to digest their food properly. In addition, because they often become infected with organisms such as Pseudomonas aeruginosa, they frequently require antibiotics not
widely used for other types of infection. I have encountered many affected families who are placed in severe financial hardship because they love their children and can only obtain the “forbidden” but essential enzyme treatment by bribing airline staff to smuggle these preparations in, at vastly inflated cost and at the risk of criminal prosecution. But even this strategy is only available to the more prosperous families.

Cystic fibrosis is only one example of many potentially treatable conditions that are excluded from effective care by the restrictive interpretation of essential drugs lists. The number of such conditions will grow with better diagnostic awareness. As this happens, there will be a need for greater diversity of drugs, and the need to accommodate exceptions to the general rule must be widely appreciated by those who legislate for the health of populations. There must be ways to reconcile the needs of society with those of the individual. Cooperation must be established between the health services and nongovernmental agencies representing responsible professional opinion and with patient groups acting to defend minority interests.

National cystic fibrosis associations, for example, are able to provide lists of named patients, and to distribute imported drugs to those in need. They can also provide to the public health services a list of drugs which they believe to be essential for their patients, as exemplified in the table below, together with any necessary supporting information. Such a list will need to be kept under frequent review and varied according to local needs, not least because antibiotic usage must be controlled in the light of changing drug resistance patterns. It is also inevitable, following the identification of the responsible gene in 1989, that new forms of treatment for the disease will be developed within the next few years.

Where such associations do not exist, the responsible clinician must be able to apply to the appropriate service for necessary exemptions to be authorized on behalf of his patients, and not be balked by junior officials with no authority to vary the regulations. The essential drugs concept must be interpreted in a way that operates to the benefit — never to the detriment — of individual patients.

References


3. Raskin, S. DNA data suggests the incidence of cystic fibrosis in Brazil may be tenfold more than observed. American Journal of Human Genetics, 51 (Suppl):1437 (1992).


Drugs Used in Cystic Fibrosis

**Nutritional**

- Pancreatic extracts (replacement therapy).
- Multivitamin preparations.
- Vitamin E.

**Antimicrobial therapy**

- Broad spectrum antibiotics, e.g., ampicillin, amoxicillin, amoxicillin/clavulanic acid compounds.
- Antistaphylococcal agents, e.g. cloxacillin, flucloxacillin.
- Antipseudomonal agents, e.g. carbenicillin, ticarcillin, aminoglycosides such as gentamicin or tobramycin, selected cefalosporins such as ceftazidime.
Acetylsalicylic acid in peripheral arterial disease

Acetylsalicylic acid, even at low dosage, exerts an antithrombotic effect, apparently because it inhibits clot formation by irreversibly reducing the capacity of platelets to aggregate (1). This process of aggregation is believed to be a crucial and perhaps ultimate step in coronary and peripheral artery occlusion (2). Indeed, acetylsalicylic acid has already been shown, when administered promptly, to reduce the mortality associated with acute cardiac infarction (3). Five years ago it was also shown in a large prospective study that 325 mg, taken indefinitely on alternate days, significantly protects against the risk of a first myocardial infarction (4, 5). This study, which involved middle-aged doctors in the USA, has now been extended in order to assess whether the same dose of acetylsalicylic acid affords protection against peripheral atherosclerotic disease (6). It is estimated that, by middle age, almost 1% of men in North America have signs of peripheral arterial occlusive disease (7). Each year some 30 000 of these undergo femoral artery bypass procedures and almost 40 000 limbs are amputated (8).

Within 5 years, 56 of some 22 000 doctors taking part in the latter study had needed peripheral arterial surgery. Twenty of these had been randomly allocated to take acetylsalicylic acid and 37 had been taking placebo. The relative risk of undergoing peripheral surgery among those taking acetylsalicylic acid was 0.54 (95% confidence intervals 0.30–0.95; p=0.03).

Antiplatelet therapy has previously been shown to reduce the risk of arterial occlusion in comparable degree among patients convalescing after peripheral arterial surgery or angioplasty (9,10). It has been suggested that intra-arterial thrombolytic drugs should be used, in the absence of contraindications, in virtually all patients with acutely ischaemic lower limbs (11). In many countries, however, expense precludes their use. There is obvious need, where this constraint exists, to assess the antithrombotic effect of oral acetylsalicylic acid in these patients. There is also a need, as the authors of the recent study suggest, to confirm or refute the possibility that low-dose acetylsalicylic acid reduces the need for peripheral artery surgery in individuals with and without a history of claudication (8).

References


Acute pulmonary embolism: a place for thrombolytic therapy?

Acute pulmonary embolism remains a serious medical emergency. It is a matter of concern that many cases still remain unrecognized during life and that clear, internationally-recognized criteria for diagnosis and assessment are lacking (3). Women have been assumed to be at greater risk as a consequence of estrogen use, childbearing and a higher frequency of thrombophlebitis, but even this is now contested (2). Each year, over 30,000 deaths are attributed to the condition in North America alone (1). Prompt anticoagulation with heparin and warfarin undoubtedly saves lives, but even with the best of management, about 10% of treated patients die whilst in hospital (4, 5).

In the mid-1970s there was expectation that treatment with urokinase or streptokinase, the first parenterally-administered antithrombotic agents, might hold advantage over heparin in the crucial initial phase of treatment. The results of comparative trials were largely disappointing (6–8), but interest was rekindled a few years ago with the introduction of tissue plasminogen activator (tPA) and other fibrin-specific thrombolytic agents (9–12).

A recent review of published trials in which the response to treatment was monitored using either radiographic or haemodynamic techniques concludes that there is still insufficient evidence to determine whether thrombolytic therapy is of clinical benefit either in terms of morbidity or mortality (13). One encouraging finding, based on a sample of only 40 patients, is that, seven years after treatment, patients receiving thrombolytic therapy had significantly lower pulmonary vascular resistance than patients receiving heparin (14). However, it is not yet certain that this apparent advantage is of clinical consequence, and it has to be weighed against one report of a 10-fold excess of minor bleeding events during treatment among patients receiving tPA (12).

The patients who might be expected to benefit most from thrombolytic treatment are those in shock as a consequence of massive pulmonary obstruction. Too little information is provided in the published literature to offer an insight into the relative value of different approaches to treatment in these circumstances (13). None the less, since more than one in three of these patients may be expected to die in the short term (5, 14), thrombolytic therapy for critically ill patients has come to be regarded as routine in many hospital centres (13).

Only a multicentre prospective study of international dimensions is likely to provide the basis for formulating definitive therapeutic guidelines. Given the high cost of thrombolytic agents, the investment could be readily justified. Meanwhile, pending the results of such a study, the case for employing thrombolytic therapy in acute pulmonary embolism simply rests unproven.

References


Venous thromboembolism: heparins — fractionated and unfractionated — in prophylaxis and treatment....

Approaches to prevention and treatment of acute deep vein thrombosis have changed little since heparin and oral anticoagulants were introduced over 40 years ago. Thrombolytic agents, which are discussed above, are of equivocal value and uncompetitively costly in this setting. Antiplatelet agents, including acetylsalicylic acid — which has gained importance in the management of thrombus in the coronary and cerebral arteries — have far less effect on thrombus in the low pressure venous and atrial systems where deposition of fibrin rather than platelet activation is the prime causative factor (1).

It has been estimated that some 25% of patients undergoing major surgery, and perhaps 50% of those requiring major orthopaedic procedures, develop venous thrombosis (2). Subcutaneous heparin — 5000 IU injected two or three times daily throughout the perioperative period — reduces this risk by as much as 70% (3–5). However, many surgeons remain reticent to resort to a prophylactic measure that is associated with a substantial risk of major haemorrhage (5).

When low-molecular-weight fractions of heparin were first developed it was hoped that this risk of bleeding might be reduced (6, 7). The various preparations that are now available commercially differ somewhat in their anticoagulant properties and even, perhaps, in their clinical effects. In general, they are comparable in their antithrombotic activity to unfractionated heparin (8). They differ from the latter, however, in that they are relatively weak inhibitors of platelet function (9), and they are virtually without effect on activated partial thromboplastin time and other widely used heparin-sensitive clotting assays (10, 11).

In the prophylactic setting, despite early indications that they might reduce the risk of haemorrhage (12, 13), there is no conclusive evidence to show that fractionated preparations hold advantage over less expensive unfractionated heparins (6, 14). None the less, it remains possible that they may hold advantage in the treatment of established, uncomplicated deep-vein thrombosis (13).

Because fractionated heparins are both more extensively bioavailable and more persistent in their effect than unfractionated heparin preparations (15–18), it is practicable to administer them subcutaneously in therapeutic dosage. This is an important advantage, since therapeutic doses of unfractionated heparin have to be infused intravenously at rates determined by repeated monitoring of the activated partial-thromboplastin time.

Early experience in many centres — based largely on venographic data rather than clinical outcome — has suggested that twice daily subcutaneous injection of fractionated preparations is as effective as continuous intravenous infusion of unfractionated preparations in dispersing venous thrombus (14, 19). Direct clinical confirmation of this equivalence has now been obtained in a randomized multicentre study involving 400 US patients (13). New episodes of venous thromboembolism occurred within 3 months in 6 of 213 patients who received a fractionated preparation, at an average dose of some 12 000 International Factor Xa Inhibitory Units subcutaneously once daily for 6 days, and in 15 of 219 patients who received unfractionated heparin intravenously for the same period at a daily dose of 30 000 to 40 000 units daily.

An unexpected but encouraging result was that major bleeding, which occurred in 11 patients receiving infusions of unfractionated heparin, was reported in only one patient taking the fractionated preparation. Whether or not this reflects a dosage effect rather than an intrinsic difference between fractionated and unfractionated heparins (20), the
clinical importance of the finding is uncontested. For reasons that remain unestablished, however, this initial advantage was ultimately lost because bleeding episodes during the subsequent extended period of warfarin therapy were more frequent among the patients who had received the fractionated preparation.

The possibility remains that, for patients with established deep vein thrombosis, subcutaneous administration of fractionated heparins may prove to be not only simpler but also safer than intravenous infusion of unfractionated heparin. If this is so, it may become feasible for the first time to treat some cases of uncomplicated deep vein thrombosis in an outpatient setting. Opportunities for reducing health care costs while at the same time enhancing patient safety arise infrequently. The therapeutic application of fractionated heparins clearly merits continued investigation.

References


....and for how long are anticoagulants really needed?

It was first shown over 30 years ago that use of anticoagulants can reduce mortality associated with thromboembolism (1). Ever since, controversy has persisted over the time for which it is necessary to inhibit coagulation in patients with deep vein thrombosis. Various estimates, ranging from 3 weeks to 6 months, have been proposed on the basis of small prospective, controlled studies (2-5). However, a recent meta-analysis of these results has suggested that rates of recurrence and haemorrhage are independent of the period of treatment (6).

Only large multicentre prospective studies could resolve this uncertainty (7). The challenge has now been broached in a British trial in which the effects of warfarin therapy continued for either 4 weeks or 12 weeks were compared in a sample of 756 patients with venous thromboembolism, after initial administration of heparin (8). Only some 15% of the patients had recently undergone surgery and, among these, the incidence of treatment failure and recurrence in both groups was about 2.5%. Among the remaining 85% of patients, however, the risk of an unsatisfactory outcome was some fivefold greater and the longer period of treatment held clear advantage.

The paucity of controlled, objective evidence on the benefits and risks of anticoagulant therapy is surprising. On the basis of this one study it seems that 4 weeks of anticoagulation is adequate for patients with acute postoperative venous thromboembolism. Other patients who develop deep vein thrombosis or pulmonary embolism, and particularly those in whom no underlying cause or risk factor is identified, should remain on warfarin for at least 3 months.

References


Beta-adrenoreceptor agonists and asthma deaths

For several years controversy has persisted over the use of beta-adrenoreceptor agonist agents in asthma. During the mid-1970s these drugs rather than corticosteroids were widely advocated for long-term maintenance therapy. However, a decade later, a retrospective analysis undertaken in New Zealand showed that increased use of beta-adrenoreceptor agonists had been accompanied by a rising trend in the number of deaths attributed to the disease (1). The first of several case-control studies inspired by this finding (1-5) showed that the relative risk of death or near death was greatest among patients using fenoterol (1). However, further analyses — and a review of the literature (6, 7) — revealed the existence of similar associations with use of oral and nebulized salbutamol, high doses of isoproterenol, theophylline, and oral corticosteroids (5).

One possible interpretation of these studies is that patients who are most severely incapacitated make the greatest use of drugs (8-12). Indeed, this is an inevitable corollary of orthodox asthma management protocols (13). The argument is still propounded, however, that fenoterol is intrinsically more hazardous than salbutamol and other beta-adrenoreceptor agonists and that it should no longer be used (14, 15).

Whereas basic differences have been described in the actions of fenoterol and salbutamol at beta-adrenergic receptors (16), the epidemiological data are most simply explained by assuming that dosage
differences alone account for the apparent difference in the strength of the association between these two beta-adrenoreceptor agonists and death from asthma (14, 17, 18). This has motivated the manufacturer of fenoterol to introduce a 100 mcg/dose formulation wherever it was not formerly available.

What conclusions can now be drawn from this debate? Advice recently set out in a letter to the New England Journal of Medicine translates the epidemiological knowledge into sound clinical practice (19). It advises doctors to reassure asthmatic patients that beta agonists are safe and even life-saving in the short term, and that they can be taken during acute attacks. Only when they are used continuously do they apparently pose a risk which is still being investigated. Any patient who needs to refill a prescription for a beta-adrenoreceptor agonist aerosol more frequently than every two months should also receive anti-inflammatory treatment with an inhaled corticosteroid or sodium cromoglicate.

Patients with newly diagnosed asthma should be carefully assessed before primary treatment is started. They may be provided with one canister of a beta-adrenoreceptor agonist for use only when symptoms occur or when the peak expiratory flow rate falls below a threshold value.

Patients already inhaling beta-adrenoreceptor agonists in large quantities should be advised that the habit may aggravate their condition. They should be encouraged to reduce their use by setting the threshold for inhalation at a lower peak expiratory flow rate (some 50% of the best value). Use of inhaled steroids should be adjusted to the lowest maintenance dose that induces an acceptable response. Only rarely is it necessary either to prescribe supplementary bronchodilators — such as ipratropium bromide or theophylline — for daily use, or to bring patients into hospital to reassure them that they can safely stop or reduce the use of beta-adrenoreceptor agonists.

References


Pertussis vaccines: cellular and acellular

Relatively recent concerns that whole-cell pertussis vaccines used for the past 50 years may have caused occasional cases of encephalopathy, sometimes resulting in permanent neurological damage and death (1, 2), have inspired the development of alternative "acellular" vaccines (3). These products contain various antigenic components of Bordetella pertussis including, most commonly, pertussis toxin, filamentous haemagglutinin (an outer membrane protein), and other agglutinins. They are less likely to cause the local reactions, fever and febrile convulsions associated with whole-cell vaccines (3-6). There is also some evidence that, when administered to older children, they are comparable in efficacy to whole-cell vaccines (9, 10). However, evidence of their protective efficacy in infants still rests largely on studies of immunogenicity and reactivity (6-8).

Studies of their protective efficacy in the primary immunization of younger children are still in progress. However, in Japan, acellular vaccines are already employed routinely to immunize children over two years of age, and one product has recently been approved in the USA for booster doses in children aged 15 months and over (11).

For several reasons this new generation of pertussis vaccines requires meticulous assessment. Firstly, the new products commonly cost at least twice as much as the whole-cell vaccines. Secondly, the evidence associating whole-cell pertussis vaccines with severe neurological damage is now widely contested (12-19). Indeed, if a risk exists at all, it is so small as to be virtually unmeasurable (8). Thirdly, although no direct comparisons of efficacy have yet been made, it is possible that the more reactogenic whole-cell vaccines may offer greater protection against severe illness than the newer products.

Estimates of the efficacy of these vaccines are highly dependent upon the case definition for pertussis (8). A protection rate against severe illness of some 95% was recently recorded in the USA among some 300 pre-school children fully immunized with whole-cell vaccines who were subsequently exposed to pertussis infection within their households (20). Re-analysis of some apparently disappointing data on the efficacy of two acellular vaccines (21) indicates that a similar degree of protection against severe illness may be conferred by the newer vaccines (22-24). Only prospective randomized studies can yield reliable comparative data, and it is doubtful that the results would justify the considerable effort and expense involved.

It might be more profitable to search for advantageous properties among the newer vaccines (8). There is need for a vaccine that induces longer lasting immunity, and for one that is sufficiently immunogenic to offer protection in the first few months of life (25). Since the adult population remains an important reservoir of infection, there is also a place for a less reactogenic vaccine that could be used safely to boost immunity in later life (26). Without tangible incentives, however, and without reasonable expectation of success, there is little likelihood that the necessary investment of time and effort will be dedicated to such ends.

References


**Thiazide therapy: who needs potassium supplements?**

After 30 years of use, thiazide diuretics still provide an appropriate point of departure for most patients in a stepped programme of antihypertensive therapy (1). In 1985, however, demonstration within a large multicentre study of an apparent association between use of thiazides and an increased incidence of sudden death, raised concerns about the propensity of these drugs to induce dangerous electrolyte disturbances (2).

It is usually assumed that thiazides predispose to ventricular arrhythmias by reducing serum potassium concentrations (3-6), but the evidence supporting this hypothesis is equivocal. Some studies have demonstrated a correlation (3, 7-9), while others have not (10-12). In these circumstances other risk factors, including decreased serum magnesium concentrations (3-5) and decreased intracellular concentrations of both potassium and magnesium (8) have been proposed.
Economic as well as therapeutic advantage is to be gained from characterizing which patients are at risk and the nature of their underlying electrolyte disturbance. Some doctors prescribe a potassium supplement or a potassium-sparing diuretic only for patients who become distinctly hypokalemic. Even though the cost of these supplementary medicines can exceed that of the primary therapy, many others prescribe them routinely for every hypertensive patient receiving a thiazide diuretic (11-14).

A prospective comparative trial has recently been completed which offers an objective basis for assessing the need for electrolyte supplements (15). Concentrations of potassium and magnesium were monitored both in plasma and cells of more than 200 hypertensive patients with abnormalities of the electrocardiogram. All were treated with hydrochlorothiazide 50 mg daily, and each was assigned at random to receive placebo or supplements of either potassium 40 mmol/day, potassium 40 mmol/day and magnesium 400 mg/day, or triamterene 100 mg/day.

After 2 months of hydrochlorothiazide therapy, there was no significant change in mean intracellular potassium and magnesium concentrations within mononuclear cells. Mean serum potassium concentrations had fallen, on average, in similar degree in all the treatment groups. However, serum potassium concentrations fell below 3.0 mmol/l only among 6 of 60 patients who received no potassium supplement and, of these, 5 had a high frequency of ventricular ectopic activity. Several previous studies have similarly suggested that ventricular arrhythmias are liable to occur below this threshold serum potassium concentration (3, 12, 16). More prolonged thiazide therapy or use of higher daily doses may, of course, induce hypokalemia in a higher proportion of patients. The authors of this study remain confident, however, that careful monitoring of serum potassium concentrations, particularly during the first few months of diuretic therapy, with a view to treating the minority of patients who become hypokalaemic, is a less expensive therapeutic option than routine prescribing of potassium supplements.

References


Magnesium and acute cardiac infarction

Several small prospective clinical studies have suggested that intravenous infusion of magnesium salts reduces mortality in acute myocardial infarction, but none has had sufficient statistical power to be conclusive (1-4). The effect appears to result from a pharmacological action of magnesium salts rather than correction of a deficit (5). Magnesium might simply act physiologically in these circumstances as a calcium channel blocking agent (5); it might dilate the coronary arteries (6, 7), or exert an antiarrhythmic (8-12) or antiplatelet action (13, 14), or it might directly protect the myocardium (15-17).

Pooled analysis of the results of these trials (1-4, 8-10) has suggested that infusion of magnesium sufficient to raise serum concentrations by 30-100% may halve the risk of death when administered early after onset of infarction (18). However, the confidence interval is wide, while timing and dosage varied widely (30-90 mmol of magnesium sulfate or chloride given over 24-48 hours).

Since these results were published a large, randomized, double-blind placebo-controlled study involving 2316 patients with suspected myocardial infarction who were admitted to the coronary care unit of a large regional hospital in the United Kingdom has been completed (19). On admission each patient received either intravenous magnesium sulfate (8 mmol over 5 minutes followed by 65 mmol over 24 hours) or physiological saline. At 28 days both expected mortality and left ventricular failure had been reduced by about 25% among the patients who had received magnesium (95% confidence intervals: 1-43%, and 7-39%, respectively). 7.8% of patients receiving magnesium and 10.3% of those receiving placebo had died. The two groups did not differ significantly in the incidence of heart block, or in the proportion of patients to receive antiarrhythmic drugs, direct current cardioversion, or temporary pacing. Nor was there any indication that either of the outcomes was influenced by administration of thrombolytic agents or acetylsalicylic acid, or by previous treatment with beta adrenergic blocking agents, calcium antagonists, or diuretics.

The authors conclude that magnesium is most likely to have a direct protective action on the myocardium, but they accept that several of the subgroup analyses are of low statistical power. Further information on the regimen used in this trial will shortly become available with the completion of another large prospective study (20) and data on the long-term outcome of patients admitted to the recently published study are still being collected.

It is highly unlikely, when these results become available, that they will fundamentally modify the advice that the authors of this paper now offer: "Magnesium infusion is a simple and safe treatment which can be generally used for suspected acute myocardial infarction. The point estimate of benefit is a reduction over the first 4 weeks of about 25 deaths per 1000 patients treated. No contraindications have been identified, though in the presence of moderate to severe renal failure, adjustment of the maintenance infusion will be necessary to avoid accumulation of magnesium".

References


General Information

More reports of multiresistant Salmonella typhi

Chloramphenicol still remains the most effective drug for treating typhoid fever in many parts of the world but reports from several countries indicate that multiresistant forms of Salmonella typhi are spreading from their apparent foci of origin in the Indian subcontinent. Plasmid-mediated resistance to a wide range of antibiotics including chloramphenicol, ampicillin, trimethoprim and sulfamethoxazole has now been recorded in North America (1-3), Europe (4), and the eastern Mediterranean region (5). Most of these accounts refer to the detection of carriers exclusively among travellers and expatriates, but the most recent — from Ontario, Canada — describes the isolation of multiresistant strains not only from travellers returning from India and Bangladesh but from their contacts within Canada (3).

Plasmids coding for resistance to the widely used antityphoid drugs, chloramphenicol, ampicillin, and trimethoprim/sulfamethoxazole pose a formidable therapeutic challenge. Each of the isolates obtained in Canada was susceptible to the fluoroquinolones — norfloxacin and ciprofloxacin — and to the third generation cephalosporins, cefalothin, cefmaneole, cefotaxime, and cefoxitin. The potential of fluoroquinolones to disturb growth of cartilage in experimental animals still excludes their use in children (6). In these circumstances third-generation cephalosporins offer the only secure option (7).

References


Anti-inflammatory drugs: new insights into adverse gastrointestinal effects

It is now beyond reasonable dispute that use of nonsteroidal anti-inflammatory drugs is associated with an increased risk of gastric ulceration. The evidence derives from both epidemiologic and endoscopic investigations (1), and from prospective as well as retrospective studies (2-8). Acute gastric erosions may occur within weeks of starting treatment (5) and there is evidence of a dose-related risk (7).

Less has been published about possible adverse effects of these drugs on the small intestinal mucosa. However, not only have ulceration and perforation been associated with several compounds (8-12), but reports of diffuse inflammatory changes (13, 14) and increased mucosal permeability among patients on long-term nonsteroidal anti-inflammatory drug therapy (15-17) have suggested that enteropathy resulting in weight loss and iron deficiency anaemia (18, 19) may well be a common complication of treatment. Indeed, inflammatory changes identified both by leukocytic infiltration of the ileum (13) and enteroscopic examination (20) have been estimated to occur in some two-thirds of all patients on long-term therapy.

A lower, but none the less highly significant incidence of intestinal ulceration has recently been recorded at autopsy among patients receiving these drugs (21). Three of the patients in this series had died of peritonitis from perforated "nonspecific small intestinal ulcers". The authors propose that non-
steroidal anti-inflammatory drugs may be responsible for a large proportion of hitherto unexplained ulcers of the small intestine.

References


Immunity, vitamins and trace elements

The importance of correcting vitamin A deficiency among children in developing countries as a defence against potentially lethal acute infections has been decisively confirmed in recent years. In a broader context, nutritional status has long been recognized as an important determinant of immune competence. Protein-energy malnutrition impairs several aspects of cell-mediated immunity (1), and various studies have been undertaken to show that restoration of specific vitamins and trace elements...
to physiological levels may ameliorate specific deficiencies in the immune response (2–6). Until recently, however, no formal comparative study had been conducted to explore whether correction of these nutritional deficits confers tangible clinical benefit.

The clinical correlates of improved micronutrient status have now been investigated within a group of some 100 independent, apparently healthy, elderly Canadian volunteers who received at random either placebo or a daily oral dietary supplement containing: vitamin A 400 retinol equivalents, beta-carotene 16 mg, thiamine 2.2 mg, riboflavin 1.5 mg, nicotinic acid 16 mg, pyridoxime hydrochloride 3.0 mg, folate 400 µg, cyanocobalamin 4.0 µg, ascorbic acid 80 mg, colecalciferol 4 mg, vitamin E 44 mg, iron 16 mg, zinc 14 mg, copper 1.4 mg, selenium 20 µg, iodine 0.2 mg, calcium 200 mg, and magnesium 100 mg (7).

On average, subjects receiving dietary supplements for 1 year had taken antibiotics for half the number of days as those receiving placebo. These differences were highly significant (mean [SD]: 23 [5] vs 48 [7] days per year). Subjects who had received supplements were also reported to have significantly higher numbers of certain T-cell subsets and natural killer cells, higher antibody responses, enhanced proliferation response to mitogen, and increased interleukin-2 production. The improvement in these immunological responses was most evident among subjects who were shown to be deficient initially in one or more micronutrients and who responded well to supplementation.

With the exception of vitamin E and betacarotene, which were included at somewhat higher doses, the supplements did not exceed recommended dietary allowances. In these amounts they could readily have been provided in a normal balanced diet. The study merits confirmation, not least because of the unexpectedly high incidence of intercurrent infections among the control subjects. Should this be done, the addition of a third group in whom micronutrient deficiencies are corrected by dietary adjustment alone would add an instructive additional dimension to the study.

References


Stereoisomerism and drug development

Many synthetically manufactured compounds exist in different stereometric forms (or enantiomers) — molecules that are identical in atomic constitution and bonding but that differ in the spatial arrangement of their atoms around one or more asymmetric (or chiral) centres.

Geometric (or cis/trans) isomers and diastereoisomers (isomers of compounds with more than one chiral centre that are not mirror images of one another) are both chemically and pharmacologically distinct. They are also, in general, readily separable and they are treated as different compounds in pharmaceutical development programmes.

Mirror image enantiomers, in contrast, differ physically only in their optical rotatory properties and, except in a biological system (or chiral environment) in which only one of the enantiomers is recognized, they are chemically identical. Until recently, it was impracticable to separate optical enantiomers on a commercial scale. Such compounds were consequently generally developed for therapeutic use as 1:1 racemates without studying or characterizing the properties of each enantiomer, even though it was recognized that the two components might have different pharmacokinetic properties and qualitatively or quantitatively different pharmacological or toxicological effects.

In those instances in which the two components of a racemate have been studied separately, differences in pharmacokinetic properties have frequently been found. In general, these are unlikely to have therapeutic implication, but they inevitably create uncertainty about the interpretation of blood level assays that fail to distinguish between the two components. Differences in therapeutic effects are unpredictable. Sometimes they are negligible; sometimes one of the enantiomers is biologically inactive (as is the case with propranolol); sometimes the two have different pharmacological properties (d-sotalol is antidysrhythmic, while l-sotalol is a beta-adrenergic blocking agent); and, most importantly in a clinical context, one enantiomer may be toxic within the therapeutic dosage range (as is the case with thalidomide, levamisole and carnitine).

The US Food and Drug Administration has concluded that few untoward consequences have resulted from the widespread use of racemates in pharmaceutical preparations. None the less, because many single enantiomers can now be produced on a commercial scale either by asymmetric syntheses or chiral separation procedures, the agency is inviting comments on a policy statement concerned with the development of new stereoisomeric drugs. This sets out the case for characterizing and studying the chemical and biological properties of the individual enantiomers of racemic mixtures early in the process of product development in order to provide a basis for selecting either the mixture or one of its components for further investigation. Implementation of such a policy would have potential impact on virtually every aspect of the drug development programme. New requirements would range from the need to devise techniques to identify and quantify all enantiomers early in the development process, to an obligation to assure and monitor the stereoisomeric composition of the finished product throughout its shelf-life.

The FDA does not address the budgetary implications of the policy. Its scientific rigour cannot be denied, but a searching cost-benefit analysis of its implementation, no matter how speculative, would lend realistic perspective to the plans.

Source: FDA’s Policy Statement for the Development of New Stereoisomeric Drugs. Available from: CDER Executive Secretariat Staff, Center for Drug Evaluation and Research (HFD-8), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, USA.

More on paediatric prescribing in new product labelling

United States of America — It has become almost a norm for the data sheet supplied with a newly-introduced drug containing a new molecular entity to state that safety and efficacy in children has not been established. One survey conducted by the American Academy of Pediatrics in 1990 estimated that 80% of such drugs introduced in the USA
between 1984 and 1989 were unaccompanied by any information on paediatric use.

Many of these new products are of potential value in paediatric practice. Too often, none the less, the manufacturer is deterred from investigating this potential by assuming that indications for paediatric use must be based on separate well-controlled randomized studies in children. Inevitably, according to the Food and Drug Administration, most doctors are reticent to prescribe newly released drugs for children, and those that do are likely to use them inappropriately.

The FDA, in clarifying related policy, has emphasized that it is prepared to waive the requirement for rigorously controlled clinical studies in children when other data can satisfy regulatory requirements. Data from pharmacokinetic studies in children will often be needed to determine appropriate paediatric dosage. But in some cases extrapolation based on soundly designed studies in adults may suffice provided there are no grounds — having regard to pharmacodynamic studies, safety reports and premarketing or postmarketing studies — for believing that the product may perform in a different manner in children.

The FDA routinely reviews novel new-drug applications with a view to determining whether studies in children need to be conducted before marketing approval, whether they can reasonably be deferred to the postmarketing period, or whether they need to be conducted at all. It now proposes to amend labelling regulations to require inclusion of statements about specific identified risks to children supplemented, when necessary, by specific warnings against use by children, advice regarding unsafe dosages, and unsafe methods of administration.


**Mumps vaccines and meningoencephalitis**

Meningoencephalitis complicates about one in 400 cases of natural mumps infections. It is sometimes severe, it occasionally results in permanent neurological sequelae, and it is associated with an estimated mortality of 1.6 per 10 000 cases. Vaccines containing attenuated strains of mumps virus have been available for many years. Immuno-

zation provides good protection against the disease, but it sometimes induces a transient meningoencephalitic reaction (1-3).

Within the United Kingdom, combined measles, mumps, rubella vaccines were introduced in 1988, and the most widely used have contained the Urabe AM9 strain of mumps virus — Pluserix-MMR® (SmithKline Beecham) and Immrrava® (Pasteur-Merieux). Less widely used was a product containing the Jeryl Lynn strain of virus — MMR II® (Merck, Sharpe and Dohme). Cases of meningoencephalitis associated with vaccination had generally been assumed to occur in Britain with an incidence of about 1: 4 million doses (4). However, much higher incidences had been reported from Japan (5, 6), and a detailed survey recently undertaken by one area health authority in the UK that involved laboratory confirmation of cases has recently indicated that the incidence of vaccine-induced meningitis is far higher with Urabe than with Jeryl Lynn strains, and may approach 1: 4000 doses (7).

The latter estimate is based on detection of mumps virus and lymphocytosis in samples of cerebrospinal fluid obtained from 8 children who developed signs of meningoencephalitis 17 to 21 days after immunization. Admission to hospital was considered to be warranted in each case, but none of the children was severely ill and, as yet, no long-term sequelae have been reported. Eighty per cent of 22 817 children immunized during the period under review received the Urabe strain, and viruses resembling this strain were demonstrated within each of 5 isolates that were typed. A retrospective survey of all cases of lymphocytic meningitis admitted to hospital within the region over the previous 3 years has since confirmed the existence of a strong association with immunization with the Urabe strain 17 to 34 days previously.

In the light of these findings, the UK Department of Health decided to withdraw from use combined vaccines containing the Urabe strain of virus with immediate effect. In an open letter to British doctors (8) it has explained that "the risk benefit ratio remains strongly in favour of immunization of all children with any MMR vaccine. However, MMR II is preferred where this is available because of the much lower risk of vaccine-associated meningitis". It is understood that no action has been taken to withdraw the licence of any vaccine containing attenuated mumps virus currently available within the UK.
The reaction of national authorities in Europe to the UK decision has been varied. Whereas some have withdrawn vaccines containing the Urabe strain, others continue to use these products in their immunization programmes. It is understood that SmithKline Beecham will maintain supplies of these vaccines in order to assure maintenance of vaccination programmes when no other supplies are available.

Already, shortages of products containing the Jeryl Lynn strains of virus have been reported from the UK, even though Merck Sharpe and Dohme has increased production of MMR II from 20,000 to 100,000 doses per week. MMR vaccine is also manufactured in Switzerland by the Swiss Serum and Vaccine Institute which uses the Rubini strain, and by manufacturers in Japan which use the Hoshino or Torii strains, both of which are claimed to be similar to the Urabe strain. It is unlikely, however, that these manufacturers will be able to meet increased demand for supplies.

It is important that the data generated within the UK should in no circumstances be interpreted as justifying the suspension of existing immunization programmes. The incidence and severity of meningitis following natural infection greatly exceeds that associated with any protective vaccine currently known to be available in international commerce.

References

Non-sedating antihistamines and cardiac arrhythmias

United States of America — The manufacturers of two non-sedating antihistamines, terfenadine (Seldane®, Marion Merrell Dow) and astemizole (Hismanal®, Janssen) have included new warnings in the labelling for these products to indicate that electrocardiographic changes, including prolongation of the QT interval, cardiac arrest, torsades de pointes and other ventricular arrhythmias may occur when the maximum recommended drug plasma concentrations are exceeded (1). A warning to this effect was first included in the labelling for terfenadine in August 1990. It has now been strengthened because further adverse reactions have been reported and because drug interaction studies have provided additional relevant information.

Doctors are advised to caution patients that they should not exceed the recommended dose for terfenadine of 60 mg twice daily, and to ensure that they do not prescribe this drug for patients who either have significant hepatic impairment or who are taking ketoconazole or the macrolide antibiotics, erythromycin and troleandomycin. Rising plasma concentrations resulting from retarded metabolism of terfenadine are presumed to have induced serious cardiac reactions in these patients.

The adverse events associated with astemizole have usually occurred after substantial overdosage, but arrhythmias have occasionally been reported in patients who have taken only 2–3 times the recommended maximum dose of 10 mg daily. Reports have recently been received of 2 patients who developed arrhythmias when they took astemizole with erythromycin and ketoconazole (2). Blood concentrations have been found to be greatly increased in patients taking ketoconazole and also, it has been presumed, its close congener, itraconazole. Since astemizole is extensively metabolized in the liver, doctors are advised not to prescribe the drug for patients with significant hepatic impairment and to caution all patients that they should in no circumstances exceed the stated dose.
In several instances, syncopal episodes have been reported to precede the development of severe arrhythmias. Doctors have consequently been advised to warn patients taking either of these drugs that they should immediately discontinue treatment and seek medical advice in the event that they experience such symptoms.

Sources

United Kingdom — Terfenadine and astemizole are exempted from prescription control within the UK. However, because of their apparent potential to induce ventricular arrhythmias, the Committee on Safety of Medicines has asked the manufacturers of preparations containing either of these ingredients to revise the labelling and to issue information leaflets warning patients to consult their doctor before using the product if they are receiving advice or treatment for other conditions.

By October 1992, the Committee had received 13 reports of possible arrhythmias induced by terfenadine and 7 reports implicating astemizole. Six of these patients died and several were known to have exceeded the recommended dose. In reviewing information generated in the USA and the UK the Committee has concluded that all these events are likely to have been associated with one of the following risk factors:

— exceeding the recommended maximum daily dose;
— concurrent administration of other drugs with a potential to induce arrhythmias, including antiarrhythmics, neuroleptics, tricyclic antidepressants, diuretics (and other drugs that can induce electrolyte imbalances);
— pre-existing prolongation of the QT interval;
— clinically-significant hepatic disease; and
— concurrent administration of drugs that are potent inhibitors of the metabolism of terfenadine and astemizole in the liver. These include erythromycin or ketoconazole, and possibly other macrolide antibiotics and imidazole anti-fungal agents.

Doctors have been requested to advise patients not to take terfenadine or astemizole if any of these risk factors apply.


Standardized instructions for oral contraceptives

United States of America — The Food and Drug Administration has prepared standard, simplified instructions to be included in package inserts for all brands of combined estrogen and progestogen oral contraceptives (1). The instructions currently provided, which differ from brand to brand, have frequently caused confusion and sometimes, through misunderstanding, risk of unwanted pregnancy. The new advice is based on published research findings (2-7) and particular attention has been accorded to directions for first use of such products and for re-establishing contraceptive protection after a lapse of one or more days.

The standardized instructions provide only two starting options: either to start on day 1 of the next menstrual cycle or on the following Sunday. Users are advised that the "Day 1" start is more effective since no back-up contraceptive methods are required during the first week of treatment.

Any user who is uncertain how to proceed after missing one or more pills, is advised to resume taking pills as originally scheduled, to employ a back-up method of contraception, and if necessary to seek professional advice.

References


Injectable contraceptive approved by FDA

United States of America — The Food and Drug Administration has recently approved depot medroxyprogesterone acetate, 150 mg in single dose vials (Depo Provera®, Upjohn), as an injectable contraceptive. The product, which was developed during the late 1960s, has long been available for this purpose in many other countries, and for almost 10 years it has been included in WHO’s Model List of Essential Drugs. It was at the centre of controversy for several years while the results of carcinogenicity studies in beagle bitches, which are no longer considered relevant to contraceptive use in women, remained in dispute. Multi-national studies conducted in both developed and developing countries have since indicated that the risk of cancer, including breast cancer, associated with use of the product is minimal or absent.

To sustain the contraceptive effect, injections need to be given regularly at three-month intervals. Efficacy approaches 99% and the most common adverse effects are menstrual irregularities and weight gain. Pregnancy should be positively excluded before the first injection is administered because low birth weight has been associated with intrauterine exposure to the drug. Other contraindications include acute hepatic disease, unexplained vaginal bleeding, breast cancer, and venous thromboembolism. Less frequent adverse reactions include headache, nervousness, abdominal pain, dizziness, weakness and fatigue. Investigations are ongoing into the possibility that long-term use contributes to osteoporosis.


Haemodialysis and chronic aluminium poisoning

United States of America — Following investigation of a case of chronic aluminium poisoning in a patient on haemodialysis (1) the Centers for Disease Control discovered that a large proportion of patients treated in the same centre had raised serum aluminium levels, and that the recent deaths of 3 of the patients were attributable to aluminium toxicity which results in anaemia, impaired bone metabolism, transient or permanent neurological symptoms and death (2).

The danger results from the corrosive action of the acidified portion of bicarbonate-based dialysis solutions — which are now used in the majority of dialysis facilities in the United States — on aluminium contained in components of the delivery system.

Centers have been advised on the precautions needed to ensure that leaching of trace elements into the dialysate does not occur (3, 4).

References


Flucloxacillin: cholestatic jaundice

United Kingdom — Since flucloxacillin was first marketed in the United Kingdom more than 20 years ago, doctors have reported a total of 31 cases of hepatic dysfunction associated with its use. However, a recent post-marketing study undertaken within the UK indicates that flucloxacillin may induce cholestatic jaundice with a frequency of 1:13 000 - 22 000 patients treated. A similar study undertaken in Australia suggests that patients over the age of 55 years, and those treated for more than 2 weeks are particularly susceptible.

Two of the cases reported in the UK terminated in the death of the patient, but in each case other hepatotoxic drugs had been prescribed. Cholestatic hepatitis was confirmed histologically in 5 cases and inadvertent rechallenge was positive in 3
instances. The Committee on Safety of Medicines has advised doctors that the condition is serious, extensively under-reported and probably underdiagnosed.


### Herbal products: more potential carcinogens

**Germany** — The Federal Health Office has announced an intention to withdraw from the market all herbal products containing derivatives of *Rubiae tinctorum radix*, including lucidine and other derivatives of anthraquinone.

Lucidine is partially converted in vivo to 1-hydroxy-anthaquinone which has been shown in animal experiments to induce tumour formation in the intestinal and gastric mucosa and in the liver.

**Source:** Communication from the Federal Health Office, Berlin, 29 April 1992.

### Human interleukin-2 for renal cancer

**United States of America** — The Food and Drug Administration has approved aldesleukin, (Proleukin®, Chiron), a form of human interleukin-2 produced by recombinant DNA techniques, to treat metastatic renal cell carcinoma in adult patients (1-3). Of 225 patients treated, regression of the tumour occurred in 15% and no evidence of cancer remained in 4%. The median period of response was 23 months.

It is estimated that 4% of the patients died during clinical trials as a result of a wide spectrum of drug-associated adverse events. Notable among these reactions was a state of hypotension and reduced organ perfusion resulting from “capillary leak syndrome”. Other frequent and serious reactions included cardiac dysrhythmias, angina pectoris, myocardial infarction, respiratory failure, anaemia, thrombocytopenia, gastrointestinal bleeding, renal failure requiring dialysis, neurological and mental changes, and infections.

The FDA emphasizes that treatment should be administered only to hospitalized patients under the supervision of a specialist oncologist and in an institution in which specialized intensive care facilities are also available.

### Atovaquone for treatment of Pneumocystis carinii pneumonia

**Canada/United States of America** — The US Food and Drug Administration and the Canadian Health Protection Branch have jointly reviewed and approved for marketing a new antimicrobial substance, atovaquone (Mepron®, Burroughs Wellcome) for treating mild to moderate *Pneumocystis* pneumonia in patients who are intolerant of the standard therapy, trimethoprim/sulfamethoxazole.

In a multicentre comparative study, sustained improvement was recorded in about two-thirds of patients receiving each treatment. One quarter of the patients receiving trimethoprim/sulfamethoxazole — and one tenth of those receiving atovaquone — were intolerant of treatment, whereas the proportion of patients who either died or did not respond to treatment was significantly greater among those receiving atovaquone.


### Finasteride for benign prostatic hyperplasia

**United States of America** — The Food and Drug Administration has announced that it has approved the first drug intended for the treatment of patients with symptoms of benign prostatic hyperplasia. In premarketing trials, urinary flow increased significantly and other symptoms regressed in about half the patients taking finasteride (Merck and Co) 5 mg daily over 12 months. Prostate size as measured by ultrasound was reduced in most of the patients treated. It is estimated that treatment needs to be continued for 6-12 months before a clinical response can be expected.

### References


Seven of a total of 543 patients discontinued treatment prematurely. The most common adverse effects were loss of libido, impotence and disorders of ejaculation. Caution is advised in treating patients with hepatic dysfunction since the drug is extensively metabolized in the liver.

The product information emphasizes that prostatic stricture, infection, cancer, hypotonic bladder and other neurogenic disorders should be excluded before treatment is started. It also notes that finasteride also reduces plasma concentrations of prostate-specific antigens which are sometimes measured as a screening test for prostatic cancer.


Diethylene glycol: yet another tragedy

Within the past three years the World Health Organization has been notified of three apparently dissociated events in which many children are reported to have died after having taken locally formulated medicinal syrups. The products implicated were:

• paracetamol syrup (Nigeria, September 1989);

• a tonic preparation — Propoleo®, Laboratorios Huilen — (Argentina, August 1992); and

• several local formulations of paracetamol syrup (Bangladesh, November 1992).

A common factor in these events is evidence that diethylene glycol rather than propylene glycol was used as a solvent during the manufacture of these products. Diethylene glycol, which is used widely in industry as a solvent and an antifreeze, is acutely toxic to the kidneys and liver. It has been responsible for at least two earlier serious tragedies, one in the United States of America in 1938, and one in India in 1986, both resulting in the deaths of many infants.

In the light of this information all national regulatory authorities have been advised to consider consequential action. Where there is any doubt about the implementation of Good Manufacturing Practices within the manufacturing facilities, they have been reminded of the need to:

1. Obtain all possible information on suppliers and channels of distribution of propylene glycol — both locally manufactured and imported.

2. Review inspection reports of manufacturers of all registered products that contain propylene glycol as a declared ingredient.

3. Check relevant documentation and/or chemical analyses of products/materials as appropriate.

WHO has appealed to all national authorities to share any information that might assist in any way in preventing such tragedies.
Consultative Document

These proposed guidelines remain subject to consultation. Comments, which are invited from all interested parties, should be referred by 15 March 1993 to:
The Division of Drug Management & Policies
World Health Organization, 1211 Geneva 27, Switzerland

Proposed WHO Guidelines for Good Clinical Practice (GCP) for trials on pharmaceutical products

INTRODUCTION
The purpose of these WHO Guidelines for Good Clinical Practice (GCP) for trials on pharmaceutical products is to set globally applicable standards for the conduct of biomedical research on human subjects. They are based on provisions already promulgated in a number of highly-developed countries including Australia, Canada, EC Countries, Japan, Nordic Countries and the United States. These guidelines inevitably vary somewhat in content and emphasis, but all are consonant with regard to the prerequisites to be satisfied and the principles to be applied as a basis for assuring the ethical and scientific integrity of clinical trials. Indeed, they have provided a formal basis for mutual recognition of clinical data generated within the interested countries.

Every care has been taken, in developing the WHO Guidelines as a practicable administrative tool for the broader constituency of WHO's Member States, to assure their compatibility with existing national and other provisions. It is hoped, on the basis of further consultation, to seek formal acceptance of the WHO Guidelines by Member States as a contribution to harmonizing standards internationally and to facilitating movement of pharmaceutical products in international commerce. No question arises, however, of challenging or usurping existing national regulations or requirements. The objective is to provide a complementary standard with international validity.

The guidelines are addressed not only to investigators, but also to ethics review committees, pharmaceutical manufacturers and other sponsors of research and drug regulatory authorities. By providing a basis both for the scientific and ethical integrity of research involving human subjects and for generating valid observations and sound documentation of the findings, these Guidelines not only serve the interests of the parties actively involved in the research process, they protect the rights and safety of subjects, including patients, and they ensure that the investigations are directed to the advancement of public health objectives.

The Guidelines are applicable specifically to studies undertaken in the cause of commercial drug development both prior to and subsequent to product registration. None the less, many of the elements are of wider relevance to biomedical research. They should also provide a resource for editors to determine the acceptability of reported research for publication and, specifically, of any study that could influence the use or the terms of registration of a pharmaceutical product. Not least, they provide an educational tool that should become familiar to everyone engaged in biomedical research and to every newly-trained doctor.

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

Adverse Event
Any untoward medical occurrence that may present itself during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment.
Adverse Reaction
A response to a pharmaceutical product which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function. In clinical trials, injuries caused by overdosing, abuse/dependence and interactions with any other product should be considered as an adverse reaction.

Audit
A systematic examination, carried out independently of those directly involved in the trial, to determine whether the conduct of a trial complies with the agreed protocol and whether the data reported are consistent with the records on site, e.g., whether data reported or recorded in the case report forms (CRF) are consonant with those found in hospital files and other original recordings.

Case Report Form (CRF)
A document designed to record data on each trial subject during the course of the trial, as defined by the protocol. The data should be collected by procedures which guarantee preservation, retention and retrieval of information and allow easy access for verification and audit.

Clinical Trial
Any systematic study on pharmaceutical products in human subjects whether in patients or non-patient volunteers in order to discover or verify the effects of and/or identify any adverse reaction to investigational products, and/or to study absorption, distribution, metabolism and excretion of the products with the object of ascertaining their efficacy and safety.

Clinical trials are generally classified into Phases I to IV. It is not possible to draw distinct lines between the phases, and diverging opinions about details and methodology exist. Brief description of the individual phases, based on their purposes as related to clinical development of pharmaceutical products, are given below:

a) Phase I
These are the first trials of a new active ingredient or new formulations in man, often carried out in healthy volunteers. Their purpose is to establish a preliminary evaluation of safety, and a first outline of the pharmacokinetic/pharmacodynamic profile of the active ingredient in humans.

b) Phase II
The purpose of these therapeutic pilot studies is to demonstrate activity and to assess short-term safety of the active ingredient in patients suffering from a disease or condition for which the active ingredient is intended. The trials are performed in a limited number of subjects and are often, at a later stage, of a comparative (e.g., placebo-controlled) design. This phase also aims at the determination of appropriate dose ranges/ regimens and (if possible) clarification of dose/response relationships in order to provide an optimal background for the design of extensive therapeutic trials.

c) Phase III
Trials in larger (and possibly varied) patient groups with the purpose of determining the short- and long-term safety/efficacy balance of formulation(s) of the active ingredient, as well as to assess its overall and relative therapeutic value. The pattern and profile of any frequent adverse reactions must be investigated and special features of the product must be explored (e.g., clinically-relevant drug interactions, factors leading to differences in effect such as age, etc.). The design of trials should preferably be randomized double-blind, but other designs may be acceptable, e.g., long-term safety studies. Generally, the circumstances of the trials should be as close as possible to normal conditions of use.

d) Phase IV
Studies performed after marketing of the pharmaceutical product. Trials in phase IV are carried out on the basis of the product characteristics on which the marketing authorization was granted and are normally in the form of post-marketing surveillance, assessment of therapeutic value or treatment strategies. Although methods may differ, phase IV studies should use the same scientific and ethical standards as applied in premarketing studies. After a product has been placed on the market, clinical trials designed to explore new indications, new methods of administration or new combinations, etc. are normally considered as trials for new pharmaceutical products.

Contract
A document, dated and signed by the investigator/institution and the sponsor that sets out any agreements on financial matters and delegation/distribution of responsibilities. The protocol may also serve as a contract when it contains such information.
Contract Research Organization (CRO)
A scientific organization (commercial, academic or other) to which a sponsor may transfer some of its tasks and obligations. Any such transfer should be defined in writing.

Ethics Committee
An independent body (a review board or a committee, institutional, regional or national), constituted of medical professionals and non-medical members, whose responsibility is to verify that the safety, integrity and human rights of the subjects participating in a particular trial are protected and to consider the general ethics of the trial, thereby providing public reassurance.

Final Report
A comprehensive description of the trial after its completion including a description of experimental (including statistical) methods and materials, a presentation and evaluation of the results, statistical analyses and a critical, ethics, statistical and clinical appraisal.

Good Clinical Practice
Good Clinical Practice is a standard for clinical studies which encompasses the design, conduct, termination, audit, analyses, reporting and documentation of the studies and which ensures that the studies are scientifically and ethically sound and that the clinical properties of the diagnostic/therapeutic/prophylactic product under investigation are properly documented.

Good Manufacturing Practice (GMP)
That part of pharmaceutical quality assurance which ensures that products are consistently produced and controlled in conformity with quality standards appropriate for their intended use and as required by the product specification. Any reference to GMP in this document should be understood as a reference to the current WHO GMP Guidelines.

Informed Consent
A subject’s voluntary confirmation of willingness to participate in a particular trial, and the documentation thereof. This consent should only be sought after all appropriate information has been given about the trial including an explanation of its status as research, its objectives, potential benefits, risks and inconveniences, alternative treatment that may be available, and of the subject’s rights and responsibilities in accordance with the current revision of the Declaration of Helsinki.

Inspection
An officially-conducted examination (i.e., review of the conduct of the trial, including quality assurance, personnel involved, any delegation of authority and audit) by relevant authorities at the site of investigation and/or at the site of the sponsor in order to verify adherence to Good Clinical Practice as set out in this document.

Investigational Product
Any pharmaceutical product (see definition) or placebo being tested or used as reference in a clinical trial.

Investigator
A person responsible for the trial and for the rights, health and welfare of the subjects in the trial. The investigator must be an appropriately qualified person legally allowed to practice medicine/dentistry.

Investigator’s Brochure
A collection of data for the investigator consisting of all the relevant information on the investigational product(s) known prior to the onset of a clinical trial including chemical and pharmaceutical data and toxicological, pharmacokinetic and pharmacodynamic data in animals as well as in man and the results of earlier clinical trials. There should be adequate data to justify the nature, scale and duration of the proposed trial and to evaluate the potential safety and need for special precautions. If new data are generated, the information must be updated.

Monitor
A person appointed by the sponsor, and responsible to the sponsor, for the monitoring and reporting of progress of the trial and for verification of data.

Patient Files
Hospital files, consultation records or special subject file allowing the authenticity of the information presented in case record forms to be verified and, where necessary, allowing them to be completed or corrected. The conditions regulating the use and consultation of such documents must be respected.

Pharmaceutical Product
Any substance or combination of substances which has a therapeutic, prophylactic or diagnostic purpose, or is intended to modify physiological functions, and presented in a dosage form suitable for administration to humans.
Principal Investigator
The investigator serving as coordinator for certain kinds of clinical trials, e.g., multicentre trials.

Protocol
A document which states the background, rationale and objectives of the trial and describes its design, methodology and organization, including statistical considerations, and the conditions under which it is to be performed and managed. The protocol should be dated and signed by the investigator/institution involved and the sponsor. It can, in addition, function as a contract.

Quality Assurance relating to Clinical Trials
Systems, processes and quality control procedures which have been established to ensure that the trial is performed and the data are generated in compliance with Good Clinical Practice. These include procedures to be followed which apply to ethical and professional conduct, standard operating procedures (SOP), reporting, and professional/personnel qualifications.

Raw Data
Raw data refer to all records or certified copies of original observations, clinical findings or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Such material includes laboratory notes, memoranda, calculations and documents, recorded data from automated instruments or exact, verified copies in the form of photocopies, microfiches, etc. The term can also include photographic negatives, microfilm or magnetic media.

1. Provisions and prerequisites for a clinical trial

1.1 Justification for the trial
It is important for anyone preparing a trial of a medicinal product in humans that the specific aims, problems and risks/benefits of a particular clinical trial be thoroughly considered and that the chosen solutions be scientifically sound and ethically justified.

1.2 Ethical principles
All research involving human subjects should be conducted in accordance with four basic ethical principles, namely justice, respect for persons, beneficence and non-maleficence as defined by the current revisions of the Declaration of Helsinki and the International Ethical Guidelines for Biomedical Research Involving Human Subjects issued by the Council for International Organizations of Medical Sciences (CIOMS). These principles must be fully known and followed by all engaged in conducting clinical trials throughout all phases (see sections 3 and 4).

1.3 Investigational product
Preclinical studies that provide sufficient evidence of potential safety and eventual clinical application of a pharmaceutical product are a necessary prerequisite for a clinical trial. Similarly, the chemical and pharmaceutical studies prior to a clinical trial should establish adequate quality of the trial product. The pharmaceutical, preclinical and clinical data should be adapted to

Serious Event
An event that is associated with death, inpatient hospitalization, prolongation of hospitalization, persistent or significant disability or incapacity, or is otherwise life-threatening in connection with a clinical trial.

Sponsor
An individual, a company, an institution or an organization which takes responsibility for the initiation, management and/or financing of a clinical trial. When an investigator independently initiates and takes full responsibility for a trial, the investigator then also assumes the role of the sponsor.

Standard Operating Procedures (SOP)
Standard, detailed, written instructions for the management of any defined situation occurring during the clinical trial. They provide a general framework enabling the efficient implementation and performance of all the functions and activities for a particular trial as described in this document.

Trial Subject
The trial subject may be:
1) a healthy person volunteering in a trial,
2) a person with a condition unrelated to the use of the investigational product,
3) a person (usually a patient) whose condition is relevant to the use of the investigational product who participates in a clinical trial, either as a recipient of the pharmaceutical product under investigation or as a control.
the appropriate phase of the trial. In addition, a compilation of information on safety and efficacy collected in previous and ongoing clinical trials elsewhere with the investigational product is vital for the planning and conduct of subsequent trials.

1.4 Investigator and site(s) of investigation
All investigators should have appropriate expertise, qualifications and competence to undertake a proposed study. Prior to the trial, agreement on monitoring and auditing procedures, and also on standard operating procedures (SOP), should be established. The logistics and premises of the trial site should comply with requirements for the safe and efficient conduct of the trial (see section 4).

1.5 Regulatory requirements
Countries in which clinical trials are performed should have regulations by which these studies can be conducted. All parties involved in a clinical trial should comply fully with the existing national regulations or requirements. In those countries where regulations do not exist or require supplementation, the competent government officials may designate, in part or in whole, the present WHO Guidelines for Good Clinical Practice as the basis on which clinical trials will be conducted. The use of these guidelines should not prevent their eventual adaptation into national regulatory law. Neither should they be used to supersede an existing national requirement in those cases where the national requirement is more rigorous.

2. The protocol
The clinical trial should be carried out in accordance with a protocol agreed and signed by the investigator and sponsor. Any change(s) appearing later should be appended as amendments and be similarly agreed on and signed by the investigator and sponsor.

The protocol should state the aim of the trial and the procedures to be used; the reasons for proposing that it should be undertaken on human subjects; the nature and degree of any known risks; the groups from which it is proposed that trial subjects be selected and the means for ensuring that they are adequately informed before they give their consent.

The protocol should be scientifically and ethically appraised by one or more suitably constituted review bodies, independent of the investigator(s) and sponsor.

A model list of items to be contained in a protocol is given in Appendix I.

3. Protection of trial subjects
The personal integrity and welfare of the trial subjects as defined in the Declaration of Helsinki is the ultimate responsibility of the investigator who must also take into consideration the scientific validity of the trial for which all involved are responsible.

3.1 Declaration of Helsinki
The current revision of the Declaration of Helsinki (Appendix 2) is the accepted basis for clinical trial ethics, which must be fully known and followed by all engaged in research on human beings. Independent assurance that subjects are protected can only be provided by an ethics committee and freely-obtained informed consent.

3.2 Independent ethics review board/committee
The aim of the work of the ethics committee is to ensure the protection of the rights and welfare of human subjects involved in research, and provide public reassurance, inter alia by previewing trial protocols. The work of the ethics committee should be guided by the Declaration of Helsinki and governed by national and other relevant international requirements.

The ethics committee should have documented policies and procedures as a basis for its work, which should include the authority under which the committee is established, the number and qualifications of members elected, a definition of what it will review and its authority to intervene and maintain records of its activities. The frequency of meetings and how it interacts with the investigator and/or sponsor should be defined.

The sponsor and/or investigator must consult the relevant ethics committee(s) regarding suitability of a proposed clinical trial protocol (including annexes) and of the methods and material to be used in obtaining and documenting informed consent of the subjects. The ethics committee must be informed of all subsequent protocol amendments and of any serious adverse events occurring during the trial, likely to affect the safety of the subjects or the conduct of the trial. The ethics committee should be asked for its opinion if a re-evaluation of the ethical aspects of the trial appears to be called for.

Subjects must not be entered into the trial until the relevant ethics committee(s) has issued its favourable opinion on the procedures and documentation in writing.
When receiving the submission for a clinical trial the ethics committee should consider the following:

a) the acceptability of the investigator for the proposed trial, on the basis of sufficient information made available to the committee, in terms of his/her qualifications, experience, supporting staff, and available facilities.

b) the suitability of the protocol in relation to the objectives of the study and the justification of predictable risks and inconveniences weighed against the anticipated benefits for the subjects and/or others, as well as the efficiency of its design, i.e. the potential for reaching sound conclusions with the smallest possible exposure of subjects.

c) the means by which patients will be admitted and by which necessary/appropriate information will be given, and by which consent is to be obtained.

d) the adequacy and completeness of the information in lay language to be given to the subjects, their relatives, guardians and, if necessary, legal representatives presented in writing to the ethics committee. All written information for the subject and/or legal representative must be submitted in its final form.

e) provision for compensation/treatment in the case of death or other loss or injury of a subject, if attributable to a clinical trial, and details of any insurance or indemnity to cover the liability of the investigator and sponsor.

f) the extent and form of payment through which the sponsor will remunerate/compensate organizations, investigators, and trial subjects involved.

g) acceptability of major amendments in the protocol.

The ethics committee should give its opinion and advice in writing within a reasonable time, clearly identifying the trial protocol, the documents studied and date of review. A list of those present at the committee meeting, including their professional status, should be attached.

3.3 Informed consent

The principles of informed consent in the current revision of the Declaration of Helsinki should be implemented in each clinical trial.

a) Information should be given in both oral and written form whenever possible. No subject should be obliged to participate in the trial. Subjects, their relatives, guardians or, if necessary, legal representatives must be given ample opportunity to enquire about details of the trial. The information must make clear that the trial is a research procedure, participation is voluntary and that refusal to participate or withdraw from the trial at any stage is without prejudice to the subject's care and welfare. Subjects must be allowed sufficient time to decide whether or not they wish to participate.

b) The subject must be made aware and consent that personal information may be scrutinized during audit/inspection by competent authorities and properly authorized persons/sponsor, and that participation and personal information in the trial will be treated as confidential and will not be publicly available.

c) The subject must have access to information about insurances and other procedures for compensation and treatment should he/she be injured/disabled by participating in the trial. The subject should know the circumstances under which the investigator or the sponsor might terminate the subject's participation in the study.

d) If a subject consents to participate after a full and comprehensive explanation of the study (including its aim, expected benefits for the subjects and/or others, reference treatment/placebo, risks and inconveniences — e.g., invasive procedures — and, where appropriate, an explanation of alternative, recognized standard medical therapy), this consent should be appropriately recorded. Consent must be documented either by the subject's dated signature or by the signature of an independent witness who records the subject's assent (consent). In either case, the signature confirms that the consent is based on information which has been given, and that the subject has freely chosen to participate without prejudice to legal and ethical rights while reserving the right to withdraw at his/her own initiative from the study at any time, without having to give any reason. However, in case the reason for withdrawal relates to adverse event(s) the investigator should be informed.

e) Careful consideration should be given to members of a group with a hierarchical structure — such as medical, pharmacy and nursing students, subordinate hospital and laboratory personnel, employees of the pharmaceutical industry, and members of the armed forces. In such cases the willingness to volunteer may be unduly influenced by the expectation, whether justified or not, of benefits or that refusal might provoke a retaliatory response from senior members of the hierarchy. Other vulnerable people whose mode of consent also needs special consideration include
patients with incurable diseases, persons in nursing homes, unemployed or impoverished persons, patients in emergency rooms, some ethnic minority groups, homeless persons, nomads and refugees.

(f) If the subject is incapable of giving personal consent (e.g., unconscious or suffering from severe mental illness or disability), the inclusion of such patients in a trial may be acceptable if the ethics committee is, in principle, in agreement and if the investigator is of the opinion that participation will promote the welfare and interest of the subject. The agreement of a legally valid representative that participation will promote the welfare and interest of the subject should also be recorded by a dated signature. If neither signed informed consent nor witnessed signed verbal consent are possible, this fact must be documented stating reasons by the investigator.

Only (open-label) emergency treatment with the investigational product may be appropriate in those cases where consent cannot be obtained.

g) In a non-therapeutic study, i.e., when there is no direct clinical benefit to the subject, consent must always be given by the subject or that of a legally valid representative and their signature obtained.

(h) The trial subjects should be informed that they have access to appropriate (indicated) persons to obtain further information, if necessary.

(i) Any information becoming available during the trial which may be of relevance for the trial subjects must be made known to them by the investigator.

4. Responsibilities of the investigator

4.1 Medical care of trial subjects
The investigator is responsible for adequate and safe medical care of those subjects who participate for the duration of the trial and the investigator must ensure that appropriate medical care is maintained after the trial for a period that is dependent upon the nature of the disease and the trial and the interventions made.

4.2 Qualifications
The investigator should:
• be an appropriately-qualified person legally allowed to practice medicine/dentistry;
• have good knowledge and experience of the field of medicine defined by the protocol;
• have the qualifications and competence in accordance with national regulations as evidenced by an up-to-date curriculum vitae and other credentials;
• be experienced in clinical trial research methods or receive scientific support from an experienced colleague;
• be aware of available relevant data and literature and all information provided by the sponsor;
• have access to human and other resources to assume full responsibility for the proper conduct of the trial.
• be aware of and comply with national regulatory and legal requirements.

4.3 Selection of trial subjects
The investigator is responsible for ensuring the equitable selection and adequate number of suitable subjects. It may be necessary to secure the cooperation of other physicians in order to obtain a sufficient number of subjects.

In order to assess the probability of an adequate recruitment rate for subjects for the study it may be useful to determine prospectively or to review retrospectively the availability of the subjects. A check should be made by the investigator whether subjects so identified could be included according to protocol.

4.4 Compliance with the protocol
The investigator should agree and sign the protocol with the sponsor and confirm in writing that he/she has read, understands and will work according to the protocol and Good Clinical Practice.

The investigator is responsible for ensuring that the protocol is strictly followed. The investigator should not make any changes in the study without the agreement of the sponsor, except when necessary to eliminate an apparent immediate hazard or danger to the trial subjects. Any change should be in the form of a protocol amendment, appended to the original protocol and signed by the investigator and sponsor. Major amendments, with justification, should be submitted to and implemented after approval of the ethics committee (see Section 3.2) and drug regulatory authority.

4.5 Information to subjects and informed consent
The investigator is responsible for giving adequate information to subjects about the trial. The current version of the Declaration of Helsinki (Appendix 2), and International Ethical Guidelines for Biomedical Research Involving Human Subjects issued by the Council for International Organizations of Medical Sciences (CIOMS) should be followed. The nature of the information that should be given is dependent on
the complexity of the study, the nature of the investiga­tional pharmaceutical product and its stage of de­velopment.

Information should be given in both oral and written form in the language understandable to the subject. It should be noted in the protocol how it is to be recorded that information has been given and when and by whom it will be given.

Informed consent should be obtained according to the principles as described in Section 3.3.

The investigator should supply subjects with, and encourage them to carry with them, information about their participation in the trial and information about contact personnel who can assist in an emergency situation.

4.6 The investigational product
The investigator should be thoroughly familiar with the properties, effects, and safety, including pre-trial data, of the investigational pharmaceutical product(s) as described in the investigator's brochure or in the literature. The investigator should be aware of all relevant new data on the product that appears during the course of the trial as required.

4.7 Site of the trial, facilities and staff
Clinical trials must be carried out under conditions which ensure adequate safety for the subjects. Selection of the site is dependent on the stage of development of the product and the potential risks involved. The trial site must have adequate facilities, including laboratories, equipment and sufficient medical, paramedical, and clerical staff to support the trial as required.

Facilities should be available to meet all possible emergencies.

The investigator should ensure that he/she has sufficient time to conduct and complete the trial, and that other commitments or trials do not divert essential subjects or facilities away from the trial in hand.

The investigator should provide adequate information to all staff involved in the trial.

The investigator should notify or obtain approval for the trial from relevant local hospital (medical, administrative) management in compliance with existing regulations.

4.8 Notification to drug regulatory authority
As governed by national regulations, the investigator, sponsor, or investigator jointly with the sponsor, should give notification of the trial to, or obtain approval from, the drug regulatory authority. The investigator should ensure that any submission must be in writing, be dated and contain sufficient information to identify the protocol.

4.9 Review by an ethics committee
Prior to its commencement, the investigator must ensure that the proposed trial has been reviewed and accepted by an independent ethics committee (see Section 3.2).

4.10 Serious adverse events/reactions
As governed by national regulations, the investigator is responsible for notifying (with documentation) the health authorities, the sponsor and, when applicable, the ethics committee immediately in the case of serious adverse events/reactions, and must take appropriate measures to safeguard subjects (see also Section 7).

4.11 Financing
The relationship between the investigator and the sponsor (in matters such as financial support, fees, honorarium payments in kind, etc.) must be stated in writing in the protocol or contract.

4.12 Monitoring, auditing and inspection
The investigator must accept and be available for periodic visits by the monitor/s and accept the implications thereof (see also Section 6). In addition, the investigator must accept the auditing and/or inspection procedures by the authorities and by persons appointed by the sponsor for quality assurance.

4.13 Record keeping and handling of data (see Section 8).

4.14 Handling and accountability of pharmaceutical products for trial (see Section 10).

4.15 Termination of trial and final report
In the case of premature termination of the trial, the investigator must inform the drug regulatory authority and ethics committee where applicable. Reasons for termination must be stated.
After completion of the trial, a final report must be drawn up. The report should be dated and signed by the investigator to verify responsibility for the validity of the data.

5. Responsibilities of the sponsor

5.1 General role of the sponsor
The sponsor may be a pharmaceutical company, but may also be an investigator, a principal investigator or an independent institution or organization that initiates, funds, organizes and oversees the conduct of a trial. When the sponsor is a foreign company or organization it should have a local representative to fulfill the appropriate local responsibilities as governed by national regulations.

The sponsor is responsible for the overall adequacy and reliability of the data and information that are presented to the investigator before the start of the clinical trial or that become available during the trial, as well as responsible for the pharmaceutical product(s) involved.

The sponsor, investigator, or both, are responsible as stipulated in the national regulations for the necessary contacts with the drug regulatory authority and independent ethics committee, such as notification or submission of the trial protocol, reporting adverse events and submitting reports on the trial.

In clinical trials in which the investigator is a sponsor, he/she is responsible for the corresponding functions, including monitoring.

The sponsor should set up a system of quality assurance (including independent auditing) for the conduct of the trial as defined in Section 13. Such a system should operate independently of those conducting the trial.

The sponsor must establish written detailed standard operating procedures (SOP) to comply with Good Clinical Practice.

The sponsor should agree and prepare a written contract/agreement with the investigator prior to the trial, setting out the distribution of responsibilities.

Both the sponsor and investigator must agree on and sign the protocol as an agreement of the details of the clinical trial and the means of data recording (e.g. case report form (CRF)). Any major amendment to the protocol should be submitted with its justification to the ethics committee and drug regulatory authority, should be approved by the ethics committee, and should be agreed to by both the sponsor and the investigator before the amendment is implemented; any such agreement should be documented.

The sponsor may transfer responsibilities for any or all obligations to a scientific body (commercial, academic or others), or to a contract research organization (CRO). Any such transfer should be stated in writing.

5.2 Particular responsibilities of the sponsor
a) To select the investigator, taking into account the appropriateness and availability of the trial site and facilities, and be assured of the investigator's qualifications and availability for the entire duration of the study; to assure the investigator's agreement to undertake the study as laid down in the protocol, and according to these guidelines of Good Clinical Practice, including the acceptance of verification procedures, audit and inspection.

b) To inform the investigator of the chemical/pharmaceutical, toxicological, pharmacological and clinical data (including previous and on-going trials), which should be adequate to justify the nature, scale and duration of the trial, as a prerequisite to planning the trial and to bring to the attention of the investigator any relevant new information arising during the trial. All relevant information must be included in the Investigator's Brochure which must be supplemented and/or updated by the sponsor whenever new pertinent information is available.

c) To submit notifications/applications to the relevant authorities (where required) and to ensure the submission of any necessary documents to the ethics committee, and to ensure communication of any modification, amendment or violation of the protocol, if the change may have impact on the subject's safety or the outcome of the trial, and to inform the investigator and relevant authorities about discontinuation of the trial and the reasons for discontinuation.

d) To provide and supply the fully characterized, properly coded and labelled investigational pharmaceutical product(s) prepared in accordance with principles of Good Manufacturing Practice (GMP), and suitably packaged in such a way as to protect the product from deterioration, and that any blinding procedure is ensured.

Sufficient samples of each batch and a record of analyses and characteristics must be kept for reference so that if necessary an independent laboratory is able to re-check the investigational product(s), e.g. for quality control or bioequivalence.
Records of the quantities of investigational pharmaceutical products supplied must be maintained with batch/serial numbers. The sponsor must ensure that the investigator within his/her institution is able to establish a system for adequate and safe handling, storage, use, return and destruction of the investigational product(s).

e) To appoint and ensure the on-going training of suitable and appropriately trained monitors and their clinical research support personnel.

f) To appoint appropriate individuals and/or committees for the purpose of steering, supervising, data handling and verification, statistical processing and trial report writing.

g) To consider promptly, jointly with the investigator(s), all serious adverse events and take appropriate measures necessary to safeguard trial subjects, and to report to appropriate national authorities according to their requirements.

h) To inform promptly the investigator(s) of any immediately relevant information that becomes available during a trial and ensure that the ethics committee is notified by the investigator(s) if required.

i) To ensure the preparation of a comprehensive final report of the trial suitable for regulatory purposes whether or not the trial has been completed. Submissions of safety updates and annual reports may be required by the authorities.

j) To provide adequate compensation/treatment for subjects in the event of trial-related injury or death, and to provide indemnity (legal and financial cover) for the investigator, except for claims resulting from malpractice and/or negligence.

k) To agree with the investigator(s) on the allocation of responsibilities for data processing, breaking of the code, statistical handling, reporting of the results, and publication policy.

6. Monitor

6.1 General role of the monitor

The monitor is the principal communication link between the sponsor and the investigator. The monitor is appointed by the sponsor and should be accepted by the investigator. The number of monitors may depend on the complexity of the trial and types of centres involved.

The monitor should be appropriately trained and fully aware of all aspects of the drug under investigation and the requirements of the protocol, its annexes and amendments. The monitor should have adequate medical, pharmaceutical and/or scientific qualifications. The qualifications most appropriate for a monitor will depend on the type of trial and the type of product under investigation.

The monitor or some other responsible person who has been notified by the sponsor and is known to the investigator, should always be available at any time to the investigator for consultation or reporting of adverse events.

The monitor should follow a predetermined written set of standard operating procedures (SOP). The main responsibility of the monitor is to oversee progress of the trial and to ensure that this is conducted and reported in accordance with the protocol. A written record should be kept of the monitor’s visits, telephone calls and letters to the investigator.

Any unwarranted deviation from the protocol or any transgression of the principles embodied in Good Clinical Practice should be reported promptly by the monitor both to the sponsor and the interested ethics committee.

6.2 Particular responsibilities of the monitor

a) To work according to a predetermined standard operating procedure (SOP), visit the investigator before, during and after the trial to control adherence to the protocol and assure that all data are correctly and completely recorded and reported, and that informed consent is being obtained and recorded for all subjects prior to their participation in the trial.

b) To ensure, prior to the trial, that the trial site has adequate premises including laboratories, equipment, staff, and that an adequate number of trial subjects is likely to be available during the trial.

c) To ensure that all staff assisting the investigator in the trial have been adequately informed about, and will comply with the details of, the trial.

d) To enable/ensure prompt communication between the investigator and sponsor at all times.

e) To ensure that all CRFs are correctly filled out, in accordance with original observations and to clarify with the investigator any errors/omissions.
f) To ensure that all errors/omissions are corrected/commented on and that the investigator signs and dates the final edited CRFs. In addition, that these procedures are carried out continuously during the entire course of the trial.

g) To check that the supplies, storage, dispensing and return of investigational pharmaceutical product(s) are safe and adequate and properly documented and in accordance with local regulations and, where applicable, the trial protocol.

h) To assist the investigator in any necessary notification/application procedure.

i) To assist the investigator in reporting the data and results of the trial to the sponsor.

j) To submit a written monitor report to the sponsor (stating the findings and if actions were taken) after each visit and after all relevant telephone calls, letters and other contacts with the investigator (audit paper trail concept).

7. Safety monitoring

The occurrence of adverse events must be monitored carefully and recorded in detail during the course of the trial.

7.1 General requirements

The trial protocol should clearly state method(s) by which adverse events will be monitored. It should also describe how this information is to be handled and analysed by the investigator and sponsor, and their responsibilities to report to each other and to the regulatory authority(s). The sponsor should provide adverse event reporting forms.

National regulations may require the sponsor and/or the investigator to report certain types of adverse events/reactions (e.g. serious, previously unknown, etc.) to the regulatory authority and ethics committee. If required, all such reports should be accompanied by an assessment of causality and possible impact on the trial and on future use of the product.

7.2 The investigator

The investigator has to report adverse events to the sponsor immediately and to the regulatory authority and the ethics committee in accordance with national regulations. Normally, adverse events associated with the use of the product must be reported to the regulatory authority within specified time limits.

Reports on adverse events submitted by the investigator to the drug regulatory authority should contain both subject and trial identification data (i.e. unique code number assigned to each subject in the trial).

When reporting adverse events to the sponsor, the investigator should not include the names of individual subjects, personal identification numbers or addresses. The unique code number assigned to the trial subject should be used in the report and the investigator should retain the code. The name of the investigator reporting the adverse events should be stated.

After the trial has ended, all recorded adverse events should be listed, evaluated and discussed in the final report.

7.3 The sponsor

During the conduct of the trial, the sponsor has to report adverse events/reactions to the drug regulatory authority according to national regulations.

The sponsor is responsible for reporting adverse events/reactions with the trial product to the local health authority as required by national regulations and to the other investigators involved in clinical trials of the same product.

The sponsor should also report as soon as possible to the investigator as well as internationally and nationally to drug regulatory authorities any trial with the same product that has been stopped anywhere in the world due to action taken by any regulatory authorities, or any other withdrawals from the market for safety reasons.

8. Record-keeping and handling of data

The aim of record-keeping and handling of data is to record, transfer, and where necessary convert efficiently and without error, the information gathered on the trial subject into data which can be used in the report.

All steps involved in data management should be documented in order to allow for a step-by-step retrospective assessment of data quality and study performance (audit paper trail concept). Documentation is facilitated by the use of check-lists and forms giving details of action taken, dates and the individuals responsible.

A basic aspect of the integrity of data is the safeguarding of “binding” with regard to treatment assignment.
It starts with the randomization of patients into treatment groups. It is maintained through all steps of data processing up to the moment when the decision to break the code is formally taken.

In the event of electronic data handling, confidentiality of the data base must be secured by safety procedures such as passwords and written assurances from all staff involved. Provision must be made for the satisfactory maintenance and back-up procedures of the data base.

8.1 Responsibilities of the investigator
a) The investigator undertakes to ensure that the observations and findings are recorded correctly and completely in the CRFs and signed by the appropriate person after delegation according to the protocol.

b) If trial data are entered directly into a computer, there must always be an adequate safeguard to ensure validation including a signed and dated print-out and back-up records. Computerized systems should be validated and a detailed description for their use be produced and kept up-to-date.

c) All corrections on a CRF and elsewhere in the hard copy raw data must be made in a way which does not obscure the original entry. The correct data must be inserted with the reason for the correction, dated and initialled by the investigator or the authorized person. For electronic data processing, only authorized persons should be able to enter or modify data in the computer and there should be a record of changes and deletions.

d) If data are altered during processing, the alteration must be documented.

e) Laboratory values with normal reference ranges, preferably together with the specificity and sensitivity of the methods used, should always be recorded on the CRF or be attached to it. Values outside a clinically accepted reference range or values that differ importantly from previous values must be evaluated and commented upon by the investigator.

f) Data other than those requested by the protocol acquired in the course of monitoring adverse events or recurrent or new illness may appear on the CRF clearly marked as additional/optional findings, and their significance should be described by the investigator.

g) Units of measurement must always be stated, and transformation of units must always be indicated and documented.

h) The final report of the trial should be drawn up as defined in the protocol and be signed by the sponsor/monitor/investigator(s) and the responsible statistician.

i) For a period of time defined by national regulations, the investigator should maintain a confidential record to allow the translation of the unambiguous code used to conceal the identity of the individual subjects of the trial (subject identification code).

8.2 Responsibilities of the sponsor and monitor
a) When using electronic data-handling the sponsor must use validated, error-free data processing programmes with adequate user documentation.

b) Appropriate measures should be taken by the monitor to avoid overlooking missing data or including inconsistencies. If a computer assigns missing values automatically, this should be made clear.

c) When electronic data-handling systems or remote electronic data entry are employed, SOPs for such systems must be available. Such systems should be designed to allow correction after loading, and the corrections made must appear in an audit file.

d) The sponsor must ensure the greatest possible accuracy when processing data. If data are transformed during processing, the transformation must be documented and the method validated. It should always be possible to compare the data print-out with the original observations and findings.

e) The sponsor must be able to identify all data entered pertaining to each subject by means of an unambiguous code.

f) The sponsor must maintain a list of persons authorized to make corrections, and protect access to the data by appropriate security systems.

8.3 Archiving of data
The investigator must arrange for the retention of the subject identification codes for a sufficient period of time for reasons of safety and efficacy as instructed by the national regulations. Patient files and other source data must be kept for a period of time required by the local rules for hospitals, institutions or private practice. The sponsor or owner of the product must make appropriate arrangements for retention of all other documentation pertaining to the trial in a form which can be retrieved for future reference. Archived data may be held on microfiche or electronic record, provided that hard copy is available.
The protocol, documentation, approvals and all other documents related to the trial, including certificates that satisfactory audit and inspection procedures have been carried out, must be retained by the sponsor. Data on adverse events must always be included.

All data and documents should be made available if requested by relevant authorities.

9. Statistics and calculations

The use of qualified biostatistical expertise is necessary before and throughout the entire trial procedure, commencing with the design of the protocol and CRFs and ending with completion of the final report and/or publication of results.

Where and by whom the statistical work should be carried out is agreed upon between the sponsor and the investigator and recorded in the protocol.

9.1 Experimental design

The scientific integrity of a clinical trial and the credibility of the data produced depend first on the design of the trial. In the case of comparative trials, the protocol should, therefore, describe:

a) an a priori rationale for the targeted difference between treatments which the trial is being designed to detect, and the power to detect that difference, taking into account clinical and scientific information and professional judgement on the clinical significance of statistical differences;

b) measures taken to avoid bias, particularly methods of randomization, when relevant, and selection of patients.

9.2 Randomization and blinding

In case of randomization of subjects the procedure must be documented. Where a sealed code for each individual treatment has been supplied in a blinded, randomized study, it should be kept both at the site of the investigation and with the sponsor.

In the case of a blinded trial the protocol must state the conditions under which the code is allowed to be broken and by whom. A system is also required to enable access to the information on treatment received by individual subjects in the case of an emergency. The system must only permit access to the treatment schedule of one trial subject at a time. If the code is broken, it must be justified and documented in the CRF.

9.3 Statistical analysis

The type(s) of statistical analyses to be used must be specified in the protocol, and any other subsequent deviations from this plan should be described and justified in the final report of the trial. The planning of the analysis and its subsequent execution must be carried out or confirmed by an identified, appropriately qualified and experienced statistician. The possibility and circumstances of interim analyses must also be specified in the protocol.

The investigator and monitor must ensure that the data are of the highest quality possible at the point of collection and the statistician must ensure the integrity of the data during processing.

The results of analyses should be presented in such a manner as to facilitate interpretation of their clinical importance, e.g. by estimates of the magnitude of the treatment effect/difference and confidence intervals, rather than sole reliance on significance testing.

An account must be made of missing, unused or spurious data excluded during statistical analyses. All such exclusions must be documented so that they can be reviewed if necessary.

10. Handling and accountability of pharmaceutical products

The sponsor is responsible for ensuring that the pharmaceutical product(s) supplied for the trial (investigational product, or reference products including placebo) are of appropriate quality and subject to quality assurance procedures (see 5.2 d).

10.1 Supply and storage

The arrangements made by the sponsor to supply the investigator with investigational pharmaceutical products for the trial should be described in the protocol. The manner in which investigational products are recorded, delivered, dispensed and stored should be detailed. Records should contain information about the shipment, delivery, receipt, disposition, return and destruction of any remaining pharmaceutical products. The investigator must not supply the investigational product to any person not targeted to receive it. Preferably a local pharmacy or the pharmacy department of the hospital should assume responsibility for storage, delivery, return and keeping records of the investigational pharmaceutical product(s). If it does, the procedure in the pharmacy must be documented to make auditing possible.
10.2 Packaging and labelling
The sponsor is responsible for the correct packaging and labelling of the pharmaceutical products used. The investigational products should be labelled in compliance with instructions from the national drug regulatory authority and the label should state that the product is for clinical research purposes only.

In blinded trials, the package should be labelled in a way that does not reveal the identity of the product. In an emergency it must be possible to determine the identity of the actual treatment received by an individual subject.

In blinded trials all investigational product(s), including reference products and placebos used, should be indistinguishable by appearance, taste, smell and other physical characteristics. If changes are made to the control product formulation, the need for a comparative in vivo bioavailability and dissolution test or other in vitro studies should be considered.

10.3 Responsibilities of the investigator
The investigator is responsible for ensuring:

- safe handling of the investigational products during and after the conduct of the trial, preferably in cooperation with a pharmacy or hospital pharmacy;

- that the investigational product is used only in accordance with the protocol and only for subjects included in the trial and by designated staff responsible to the investigator;

- that dosage and instructions for use are correct and that every subject involved understands them properly;

- that unused investigational products are returned to the pharmacy or sponsor or destroyed, and that records of these activities are kept according to the protocol.

10.4 Responsibilities of the sponsor and monitor
The sponsor is responsible for:

- ensuring that the package of investigational product(s) is of a size suitable for the trial and adequate for the trial subjects;

- keeping sufficient samples from each batch used in the trial as a reference for future re-checking and control and as provided in national regulations.

During the study visits the monitor should check:

- that the pharmaceutical products for the trial are used exclusively within the limits defined by the protocol;

- that supply records of investigational products are in order and that there are sufficient supplies;

- the expiry dates of batches;

- storage conditions of the pharmaceutical products for the trial;

- the handling of returned and/or unused pharmaceutical products.

11. Role of the drug regulatory authority
The role of governments is to provide the legal framework for clinical trials. The aim should be twofold; to protect the safety and rights of the subjects participating in a trial and to allow only trials which may lead to conclusive data. This could be done by several means, including the specification of the competence needed for investigators and the demand for approval by relevant scientific/ethics committees. Regulatory authorities should have a mandate to revise or terminate trials. The system must allow for on-site inspection of the quality of the data obtained, with due concern to subject confidentiality.

11.1 General responsibilities
The national drug regulatory authority should ensure that the protocols of clinical trials, submitted in advance for its review, are in accordance with existing national regulations and instructions.

Under national regulations and on the basis of its review of clinical trial protocols and/or reports, the regulatory authority may propose revisions or request additional data on a clinical trial or may terminate a trial.

The regulatory authority should be able to check on supervision of the conduct of the trial by requesting reports on the monitor's interaction with the investigator.

It should also be possible for the authorities to check the reliability and quality of reported results.

The drug regulatory authority should file the subject identification code list submitted by the investigator/sponsor at the same time as the signed final report.
National regulations should stipulate ways to report and handle misconduct discovered in connection with clinical trials.

11.2 Inspections
Under national regulations the regulatory authority might inspect the conduct of a clinical trial by on-site visits. Such an inspection should consist of a comparison of the procedures and practices of the clinical investigator with the commitments set out in the protocols and reports submitted to the drug regulatory authority by the investigator or the sponsor.

Inspections may be carried out either routinely, randomly or for specific reasons.

The inspection should determine whether the investigator has custody of the required records or, if not, who has assumed this responsibility. The data archives should be tested for retrieval.

12. Quality assurance for conduct of clinical trial
The sponsor is responsible for the implementation of a system of quality assurance in order to ensure that all sites, data and documents are available for verification.

All observations and findings should be verifiable in order to ensure the credibility of data and to assure that the conclusions presented are derived correctly from the raw data. Verification processes must, therefore, be specified and justified. Statistically controlled sampling may be an acceptable method of data verification in a trial.

Quality control must be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

The sponsor’s audit should be conducted by persons/facilities independent of those carrying out the trial.

Any or all of the recommendations, requests or documents addressed in this Guideline or in national regulations may be subject to, and must be available for, an audit through the sponsor or a nominated independent organization and/or competent authorities (inspection).

Sponsor and investigational sites, facilities and laboratories, and all data (including patient files) and documentation must be available for institutional and independent sponsor audit as well as for inspection by competent authorities.

13. Considerations for multicentre trials
Because a multicentre trial is conducted simultaneously by several investigators at different sites following the same protocol, some special administrative arrangements are normally needed. Ideally, the trial should begin and end simultaneously at all sites.

A number of aspects are rendered more complex in multicentre trials such as:
- the elaboration, discussion and written acceptance of the protocol and its annexes by all investigators;
- ethics committee(s), and the number of committees to be consulted;
- the organization of initial and intermediary meetings of parties involved;
- implementation of the trial;
- the randomization procedure;
- ensuring that the quality of the product is maintained during distribution and storage in different locations;
- the training of investigators to follow the same protocol;
- standardization of methods for evaluation and analyses of laboratory and diagnostic data (e.g. set-up of an external quality control system for laboratory assays);
- control of adherence to the protocol including measures to terminate participation of sites if necessary;
- role of monitor(s);
- centralized data management and analysis;
- drafting of the final report;
- publication.

A multicentre trial therefore may require a special administrative system, the scale of which will depend on the number of trial sites involved, study end-points and present knowledge of the investigational pharmaceutical product. One or several committees may be set up or the necessary functions may be performed by one or more designated person(s). The functions, responsibilities and mandate of the committee(s) or
person(s) should be described in the trial protocol, as should the procedure for nomination.

The responsibility for commencement and overall performance of the trial could be the task of a committee/person. A second committee/person could be appointed to provide advice on policy matters and supervision of data. A third committee/person should have access to the results obtained in the trial, including adverse events. It should be stated in the protocol if and under what circumstances and how this committee/person can break the code. Interaction between these committee(s)/person(s) is necessary.

A coordinating committee could also be set up or a coordinator appointed with responsibility for the control of the practical performance and progress of the trial and maintaining contacts with the regulatory authorities and ethics committees.

This system will provide adequate assurance that the study will be planned and conducted according to acceptable scientific standards.

**APPENDIX I**

**Model List of Items to be contained in a Clinical Trial Protocol**

The trial protocol should, where relevant, be required to cover the following points:

1. Title and justification for the trial.
2. Statement of rationale, objectives and purpose of trial.
3. Site of the trial, name and address of the sponsor.
4. Name, address and qualifications of each investigator.
5. Description of the type of trial (controlled, open), trial design (parallel groups, cross-over technique), blinding technique (double-blind, single-blind), randomization (method and procedure).
6. Description of trial subjects. Criteria for inclusion and exclusion of potential trial subjects and process of recruitment, types, methods and time of allocation of subjects.
7. Number of trial subjects needed to achieve the trial objective based on statistical considerations.
8. Description of and justification for route of administration, dosage, dosage interval and treatment period for the pharmaceutical product being tested and the product being used as a control.
9. Any other treatment that may be given or permitted concomitantly.
10. Clinical and laboratory tests, pharmacokinetic analysis, etc., that are to be carried out.
11. Description of how responses are recorded. Description and evaluation of methods of measurement, times of measurements, follow-up procedures.
12. Discontinuation criteria for trial subjects and instructions on terminating the whole study or a part of the study.
14. Procedures for the maintenance of subject identification code lists, treatment records, randomization list and/or case report form (CRF). Records should permit easy identification of individual patients/participants and the auditing and reconstruction of data.
15. Information on establishment of the trial code, where it will be kept and when, how and by whom it can be broken in the event of an emergency.
16. Measures to be implemented to ensure the safe handling and storage of pharmaceutical products, and to promote and control compliance with the prescribed and other instructions.
17. Description of methodology on the evaluation of results, (e.g., statistical methods) and on the report on patients/participants withdrawn from the trial.
18. Time schedule for completion of the trial.
19. Information to be presented to the trial subjects including how trial subjects will be informed about the trial and how and when consent will be obtained.
20. Staff instructions, i.e., statement of how the staff involved are to be informed about the way the trial is to be conducted and about the procedures for drug usage and administration.
21. Ethical considerations and measures relating to the trial.
22. Medical care after the trial and modalities of post-trial treatment should be defined.

23. Statements regarding financing, insurance, liability, and delegation/distribution of responsibilities, i.e., when serving as a contract.

24. List of literature referred to in the protocol.

APPENDIX 2

WORLD MEDICAL ASSOCIATION

Declaration of Helsinki

Recommendations guiding physicians in biomedical research involving human subjects

Adopted by the 18th World Medical Assembly, Helsinki, Finland, in June 1964. Amended by the 29th World Medical Assembly, Tokyo, Japan, in October 1975. 35th World Medical Assembly, Venice, Italy, in October 1983 and 41st World Medical Assembly, Hong Kong, in September 1989.

I. Basic principles

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on thorough knowledge of the scientific literature.

2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.

3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.
4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.

5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.

6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

7. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.

8. In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely-given informed consent, preferably in writing.

10. When obtaining informed consent for the research project, the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.

11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation.

Whenever the minor child is in fact able to give a consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.

12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II. Medical research combined with professional care (clinical research)

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgement it offers hope of saving life, reestablishing health or alleviating suffering.

2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.

3. In any medical study, every patient — including those of a control group, if any — should be assured of the best proven diagnostic and therapeutic method.

4. The refusal of the patient to participate in a study must never interfere with the physician-patient relationship.

5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (1, 2).

6. The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.
III. Non-therapeutic biomedical research involving human subjects
(non-clinical biomedical research)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.

2. The subjects should be volunteers — either healthy persons or patients for whom the experimental design is not related to the patient's illness.

3. The investigator or the investigating team should discontinue the research if in his/her or their judgement it may, if continued, be harmful to the individual.

4. In research on man, the interest of science and society should never take precedence over considerations related to the well-being of the subject.

Acknowledgements
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Infectious disease: an ominous and unpredictable threat

Over the past six years, this journal has been pointing to the threats posed by infectious disease in an ever more densely populated world. Complacency induced by the development of successive generations of novel antibiotics and insecticides has allowed governments to cut back on the staple surveillance and reporting mechanisms that are the foundations of public health medicine. The emergence of AIDS has jolted this complacency and unleashed a frenzied effort to develop drugs and vaccines to combat this particular disease. But, perhaps because it is not transmitted by casual contact or sneezing, its appearance has failed to sensitize policy-makers to the possibility of further — and perhaps more devastating — pre-emptive microbial attacks. Far less has it established awareness of an urgent need for worldwide monitoring of patterns of infective disease and the spread of antibiotic-resistant organisms.

The warning signals are clear enough. Notwithstanding contrary trends in some developed countries, and impressive developments in methods of contraception (1), the world population has continued to grow at a rate that exceeds predictions (2). Civilizations are venturing into environments and risking contact with viruses and other microorganisms previously existent only in animal populations. The genetic variability of retroviruses and other microorganisms increases their ability to adapt to new environments and new hosts. These microorganisms possess the potential to develop resistance to widely-used antimicrobial drugs. In many cases the genetic apparatus responsible for these changes can be transferred from species to species by plasmids which have the ability to encode for resistance to several antibiotics. Longer-term climatic trends may encourage the spread and enhance the transmissibility of diseases endemic in tropical climates (3, 4). The mosquitoes and other vectors responsible for the transmission of many of these diseases have similarly developed resistance to widely available insecticides. Modern international travel provides for rapid spread of both pathogens and vectors.

These concerns, as perceived from within the USA, are starkly reflected within a report on "Emerging Infections" published by the Institute of Medicine which emphasizes the immediacy of the risks and calls for a sense of urgency within governments (5). It points to the current resurgence of tuberculosis and measles within the USA; the speed with which Lyme disease has become the most common vector-borne disease within the country; and the vulnerability of the population to an influenza pandemic of the scale that killed 20 million people worldwide in 1918–19. Further afield it looks to a plethora of threats to human populations from microbial diseases that have until now been effectively controlled or localized.

It calls for the national and international disease surveillance activities of the Centers for Disease Control to be upgraded as a matter of highest priority. As yet, State and local health officials are required by law only to report tuberculosis and other diseases for which quarantine measures are enforced. But surveillance alone can never be sufficient. The report, more speculatively, calls for fresh thinking on means for responding efficiently to urgent community needs for new vaccines and drugs; for central government to maintain stockpiles of selected vaccines; and for manufacturers to develop — subject to government purchase guarantees — “surge capacity” for vaccine production to assure adequate supplies at the earliest phase of an epidemic. The very scale of the problem inhibits realistic discussion of their redressment in a global context. But global approaches there must be, if secure protective strategies are to be developed against these potentially catastrophic threats.

References


International Nonproprietary Names for Pharmaceutical Substances (INN)

Notice is hereby given that, in accordance with article 3 of the Procedure for the Selection of Recommended International Nonproprietary Names for Pharmaceutical Substances, the following names 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.

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 68 Proposed INN not later than 30 June 1993.

Proposed International Nonproprietary Names: List 68
Lists of proposed (1–65) and recommended (1–31) international nonproprietary names can be found in Cumulative List No. 8, 1992.

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*Action and Use: The statements in italics indicating the action and use are based largely on information supplied by the manufacturer. The information is 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 be neither revised nor included in the Cumulative Lists of INNs.
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<td>(+)-(6S,7S, biar-R)-5,6,7,8-tetrahydro-1,2,3,13-tetramethoxy-6,7-dimethylbenzo[3,4]cycloocta[1,2-f][1,3]benzodioxol-6-ol</td>
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<td>C_{23}H_{28}O_{7} 58546-54-6</td>
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<td>1,3-bis[2-[(S)-1-(chloromethyl)-1,6-dihydro-5-hydroxy-8-methylbenzo[1,2-b,4,3-b']dipyryl-3(2H)-yl]carbonyl]indol-5-yl]urea</td>
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<td>(6R,7R)-7-[(Z)-2-(2-amino-4-thiazolyl)-2-pentenamido]-3-(hydroxymethyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, carbamate (ester)</td>
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<td>(-)-7-[(2S,3R)-3-amino-2-methyl-1-azetidinyl]-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid</td>
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<td>cilansetronum</td>
<td>($^\cdot$)-(R)-5,6,9,10-tetrahydro-10-[[2-methylimidazol-1-yl]methyl]-4H-pyrido[3,2,1-(jk)]carbazol-11(8H)-one</td>
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<td>($^\cdot$)-methyl (3aS,5R,6R,6aS)-1,3a,4,5,6,6a-hexahydro-5-hydroxy-6-[(E)-(3S)-3-hydroxy-1-octenyl]-2-pentalenevalerate</td>
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<td>3-[(α,α,α-trifluoro-(m)-tolyl)oxy]-1-azetidinecarboxamide</td>
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<td>($^\cdot$)-dihydro-1H-pyrrolo[1,2-(\alpha)]imidazole-2,5(3H,6H)-dione</td>
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<td>($^\cdot$)-(S)-(\cdot)N-methyl-(\cdot)-(\cdot)-naphthoxy)-2-thiophenepropylamine</td>
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<td>N-[{(S)-α-(mercaptomethyl)hydrocinnamoyl]glycine, benzyl ester, acetate (ester)</td>
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ganefromycinum
ganefromycin

An antibiotic produced by *Streptomyces lydicus*. Ganefromycin is a complex antibiotic with two major components: α and β.

Component α

\[(2E,4E,6E)-7\{[(2R^*,3R^*,5R^*)-5\{[(3E,5E)-3\{[(2,6-dideoxy-3-O-methyl-\alpha-L-lyxo-hexopyranosyl]-5\{[(2,6-dideoxy-3-O-methyl-\beta-D-ribo-hexopyranosyl]-5\{[(2,6-dideoxy-3-O-methyl-\alpha-L-lyxo-hexopyranosyl]-oxy\}]\{[(2S^*,3S^*,4S^*,6R^*)-tetrahydro-2,3,4-trihydroxy-5,5-dimethyl-6\{[(1E,3Z)-1,3-pentadienyl]-2H-pyran-2\}y]propionamido]-2-methoxy-1,3-dimethyl-3,5-heptadienyl\}tetrahydro-3-hydroxy-2-furyl\}]-2,4,6-heptatrienoic acid, 2\{phenylacetate\}\}\] 114451-31-9

Component β

\[(2E,4E,6E)-7\{[(2R^*,3R^*,5R^*)-5\{[(3E,5E)-3\{[(2,6-dideoxy-3-O-methyl-\alpha-L-lyxo-hexopyranosyl]-5\{[(2,6-dideoxy-3-O-methyl-\beta-D-ribo-hexopyranosyl]-5\{[(2,6-dideoxy-3-O-methyl-\alpha-L-lyxo-hexopyranosyl]-oxy\}]\{[(2S^*,3S^*,4S^*,6R^*)-tetrahydro-2,3,4-trihydroxy-5,5-dimethyl-6\{[(1E,3Z)-1,3-pentadienyl]-2H-pyran-2\}y]propionamido]-2-methoxy-1,3-dimethyl-3,5-heptadienyl\}tetrahydro-3-hydroxy-2-furyl\}]-2,4,6-heptatrienoic acid, 2\{phenylacetate\}\}\] 114451-30-8

glemanserinum

glemanserin

\{(±\}1-phenethyl-\alpha-phenyl-4-piperidinemethanol\}

\[C_{20}H_{25}NO\]

107703-78-6

serotonin receptor antagonist

grepafloxacinum

grepafloxacin

\{(±\)1-cyclopropyl-6-fluoro-1,4-dihydro-5-methyl-7\{(3-methyl-1-piperazinyl\}4-oxo-3quinolinecarboxylic acid\}

\[C_{19}H_{23}FN_{2}O_{3}\]

119914-60-2

antibacterial
<table>
<thead>
<tr>
<th>Proposed International Chemical Name or Description, Molecular and Graphic formulae</th>
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<tr>
<td>gusperimus</td>
<td>(±)-N-[[4-[(3-aminopropyl)amino]butyl]carbamoyl]hydroxymethyl]-7-guanidinoheptanamide</td>
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<td>icodextrinum</td>
<td>dextrin, having more than 85% of its molecules with molecular masses between 1640 and 45000 with a claimed-average molecular mass of approximatively 20000</td>
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<td>(+)-α-[(E)-cinnamyl]-N-(cyclopropyl)methyl]-α-ethyl-N-methylbenzylamine</td>
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<td>C_{17}H_{37}N_{10}O_{9}</td>
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<td>C_{23}H_{29}N</td>
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</tbody>
</table>
**Proposed International Chemical Name or Description, Molecular and Graphic formulae**

**Nonproprietary Name Chemical Abstracts Service (CAS) registry number**

**Action and Use**

---

**iobitridolum**

iobitridol

*N,N*-bis(2,3-dihydroxypropyl)-5-[2-(hydroxymethyl)hydracrylamido]-2,4,6-triiodo-
N,N'-dimethylisophthalamide  
C$_{20}$H$_{28}$I$_{3}$N$_{3}$O$_{9}$  136949-58-1  contrast medium

---

**itasetronum**

itasetron

2-oxo-N-1$\alpha$H,5$\alpha$H-tropan-3$\alpha$-yl-1-benzimidazoline-1-carboxamide  
C$_{16}$H$_{20}$N$_{4}$O$_{2}$  123258-84-4  serotonin receptor antagonist

---

**leminoprazolum**

leminoprazole

(±)-2-[[o-(isobutyl)methylamino]benzyl]sulfinyl]benzimidazole  
C$_{19}$H$_{23}$N$_{3}$O$_{2}$S  104340-86-5  antiulcer

---

**levosimendanum**

levosimendan

mesoxalonitrile (-)$\cdot$[p][(R)-1,4,5,6-tetrahydro-4-methyl-6-oxo-3-
pyridazinyl]phenyl]hydrazone  
C$_{14}$H$_{12}$N$_{6}$O  141505-33-1  cardiac stimulant

---

**lomerizinum**

lomerizine

1-[bis(p-fluorophenyl)methyl]-4-(2,3,4-trimethoxybenzyl)piperazine  
C$_{27}$H$_{30}$F$_{2}$N$_{2}$O$_{3}$  101477-55-8  cerebral vasodilator
Proposed International Chemical Name or Description, Molecular and Graphic formulae
Nonproprietary Name
(Latin, English)

<table>
<thead>
<tr>
<th>Chemical Name or Description, Molecular and Graphic formulae</th>
<th>Chemical Abstracts Service (CAS) registry number</th>
<th>Action and Use*</th>
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<tbody>
<tr>
<td>monatepil monatepil</td>
<td>(±)-N-(6,11-dihydro dibenzo[b,e]thiepin-11-yl)-4-(p-fluorophenyl)-1-piperazinebutyramide</td>
<td>calcium channel blocker</td>
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<tr>
<td>nasaruplasum nasaruplase</td>
<td>prourokinase (enzyme-activating) (human clone pA3/pD2/pF1 protein moiety)</td>
<td>enzyme</td>
</tr>
<tr>
<td>niravolinum niravoline</td>
<td>N-methyl-2-(m-nitrophenyl)-N-[1'S,2'S]-2-(1-pyrrolidinyl)-1-indanylacetamide</td>
<td>diuretic</td>
</tr>
<tr>
<td>odapipam odapipam</td>
<td>(+)-(S)-8-chloro-5-(2,3-dihydro-7-benzofuranyl)-2,3,4,5-tetrahydro-3-methyl-1H-3-benzazepin-7-ol</td>
<td>dopamine D_1 receptor antagonist</td>
</tr>
<tr>
<td>orbifloxacinum orbifloxacin</td>
<td>1-cyclopropyl-7-(cis-3,5-dimethyl-1-piperazinyl)-5,6,8-trifluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid</td>
<td>antibacterial</td>
</tr>
</tbody>
</table>
**osateronum**  
**osaterone**  
\((+)-6\text{-chloro-17-hydroxy-2-oxapregna-4,6-diene-3,20-dione}\)  
\(C_{20}H_{25}ClO_{4}\)  
105149-04-0  
antiandrogen, progestogen

**paclitaxelum**  
**paclitaxel**  
\((2aR,4S,4aS,6R,9S,11S,12S,12aR,12bS)-1,2a,3,4,4a,6,9,10,11,12,12a,12b-dodecahydro-4,6,9,11,12,12b-hexahydroxy-4a,8,13,13-tetramethyl-7,11-methano-5H-cyclodeca[3,4]benz[1,2-b]oxet-5-one 6,12b-diacetate, 12-benzoate, 9-ester with (2R,3S)-N-benzoyl-3-phenylisoserine\)  
\(C_{47}H_{51}NO_{14}\)  
33069-62-4  
antineoplastic

**pidobenizonum**  
**pidobenzone**  
5-oxo-L-proline, p-hydroxyphenyl ester  
\(C_{11}H_{11}NO_{4}\)  
138506-45-3  
melanine synthesis inhibitor

**ramorelixum**  
**ramorelix**  
\(C_{74}H_{95}ClN_{16}O_{18}\)  
136639-71-9  
luteinizing-hormone-releasing-hormone inhibitor
<table>
<thead>
<tr>
<th>Proposed International Nonproprietary Name</th>
<th>Chemical Name or Description, Molecular and Graphic formulae</th>
<th>Chemical Abstracts Service (CAS) registry number</th>
<th>Action and Use*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>raxofelastum</strong></td>
<td>(±)-2,3-dihydro-5-hydroxy-4,6,7-trimethyl-2-benzofuranacetic acid, acetate</td>
<td>128322-14-4</td>
<td>antiasthmatic, anti-inflammatory</td>
</tr>
<tr>
<td><strong>safironilum</strong></td>
<td>N,N'-bis(3-methoxypropyl)-2,4-pyridinedicarboxamide</td>
<td>134377-69-8</td>
<td>collagen inhibitor</td>
</tr>
<tr>
<td><strong>sameridinum</strong></td>
<td>N-ethyl-1-hexyl-N-methyl-4-phenylisonpeotamide</td>
<td>143257-97-0</td>
<td>analgesic, local anaesthetic</td>
</tr>
<tr>
<td><strong>sanguinarii chloridum</strong></td>
<td>sanguinarine chloride or 13-methyl[1,3]benzodioxolo[5,6-c]-1,3-dioxolo[4,5-i]-phenanthroindinium chloride</td>
<td>5578-73-4</td>
<td>anti-inflammatory; antimicrobial; antifungal</td>
</tr>
<tr>
<td><strong>sebriplatinum</strong></td>
<td>(+)-cis-(1,1-cyclobutanedicarboxylato)[(2R)-2-methyl-1,4-butanediamine-N,N']platinum</td>
<td>110172-45-7</td>
<td>antineoplastic</td>
</tr>
<tr>
<td><strong>sepimostatum</strong></td>
<td>6-amidino-2-naphthyl-p-(2-imidazolin-2-ylamino)benzoate</td>
<td>103926-64-3</td>
<td>protease inhibitor</td>
</tr>
</tbody>
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Proposed International\nNonproprietary Name\n(Latin, English)\n
<table>
<thead>
<tr>
<th>Name</th>
<th>Molecular and Graphic formulae</th>
<th>Action and Use*</th>
</tr>
</thead>
<tbody>
<tr>
<td>siratiazem</td>
<td>((+)-(2S,3S)-2,3\text{-dihydro-3-hydroxy-5}\text{-}[2\text{-}(\text{isopropylmethylamino})\text{ethyl}]\text{-}2\text{-}(\text{p}-\text{methoxyphenyl})\text{-}1,5\text{-benzothiazepin-4(5H)-one}\text{ acetate (ester)})</td>
<td>antianginal, antihypertensive</td>
</tr>
<tr>
<td>siratiazem</td>
<td>(\text{C}<em>{24}\text{H}</em>{30}\text{N}<em>{2}\text{O}</em>{4}\text{S})\phantom{25}138778-28-6</td>
<td></td>
</tr>
<tr>
<td>sonermin</td>
<td>(3\text{-}157\text{-tumor necrosis factor (human)})</td>
<td>antineoplastic</td>
</tr>
<tr>
<td>sonermin</td>
<td>(\text{C}<em>{767}\text{H}</em>{1204}\text{N}<em>{210}\text{O}</em>{229}\text{S}_{2})\phantom{25}144916-42-7</td>
<td></td>
</tr>
<tr>
<td>sulopenem</td>
<td>((5S,6S)-6\text{-}[[1R]-1\text{-hydroxyethyl}]\text{-}7\text{-oxo-3}\text{-}[[3S]\text{-}\text{tetrahydro-3-thienyl}]\text{thio}]\text{-}4\text{-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid, (R)-S-oxide})</td>
<td>antibacterial</td>
</tr>
<tr>
<td>sulopenem</td>
<td>(\text{C}<em>{12}\text{H}</em>{15}\text{NO}<em>{5}\text{S}</em>{3})\phantom{25}120788-07-0</td>
<td></td>
</tr>
<tr>
<td>tallimustine</td>
<td>(N''\text{-}(2\text{-amidinoethyl})\text{-}4\text{-}[p\text{-bis(2-chloroethyl)amino}benzamido]-1\text{,}1\text{','}1\text{''-trimethyl-}N,4\text{'',}N,4''\text{-ter[pyrrole-2-carboxamide]})</td>
<td>antineoplastic</td>
</tr>
<tr>
<td>tallimustine</td>
<td>(\text{C}<em>{32}\text{H}</em>{38}\text{Cl}<em>{2}\text{N}</em>{10}\text{O}_{4})\phantom{25}115308-98-0</td>
<td></td>
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<tr>
<td>tarazepide</td>
<td>((-)-N\text{-}[(S)-2,3\text{-dihydro-1-methyl-2-oxo-5-phenyl-1H,1,4-benzodiazepin-3-yl}]\text{-}5,6\text{-dihydro-4H-pyrrolo[3.2.1-f]quinoline-2-carboxamide})</td>
<td>cholecystokinin inhibitor</td>
</tr>
<tr>
<td>tarazepide</td>
<td>(\text{C}<em>{28}\text{H}</em>{12}\text{N}<em>{2}\text{O}</em>{3})\phantom{25}141374-81-4</td>
<td></td>
</tr>
<tr>
<td>Proposed International Nonproprietary Name (Latin, English)</td>
<td>Chemical Name or Description, Molecular and Graphic formulae</td>
<td>Chemical Abstracts Service (CAS) registry number</td>
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<td>-------------------------------------------------------------</td>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td></td>
<td>C_{21}H_{25}N_{5}O_{4} 91441-48-4 antineoplastic</td>
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<tr>
<td>thymoctonanum thymoctonan</td>
<td>N-{N-{N-(\text{N}-\text{L}-leucyl-\text{L}-\text{a}-glutamyl})-\text{L}-\text{a}-aspartyl\text{glycyl})-\text{L}-prolyl\text{L}-lysyl\text{L}-phenylalanyl\text{L}-leucine</td>
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</tr>
<tr>
<td></td>
<td>C_{43}H_{67}N_{9}O_{13} 107489-37-2 immunomodulator</td>
<td></td>
</tr>
<tr>
<td>tiquesidum tiqueside</td>
<td>(25R)-5\text{a}-spirostan-3\text{b}-yl 4-\text{O}-\text{b}-\text{D}-glucopyanosyl\text{b}-\text{D}-glucopyranoside</td>
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</tr>
<tr>
<td></td>
<td>C_{39}H_{64}O_{13} 99759-19-0 antihyperlipidaemic</td>
<td></td>
</tr>
<tr>
<td>tirapazaminum tirapazamine</td>
<td>3-amino-1,2,4-benzotriazine 1,4-dioxide</td>
<td>C_{7}H_{6}N_{2}O_{2} 27314-97-2 antineoplastic</td>
</tr>
<tr>
<td>Proposed International Nonproprietary Name (Latin, English)</td>
<td>Chemical Name or Description, Molecular and Graphic formulae</td>
<td>Chemical Abstracts Service (CAS) registry number</td>
</tr>
<tr>
<td>------------------------------------------------------------</td>
<td>---------------------------------------------------------------</td>
<td>-------------------------------------------------</td>
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<tr>
<td>troglitazonum troglitazone</td>
<td>$(\pm)$-all-rac-5-$p$-[(6-hydroxy-2,5,7,8-tetramethyl-2-chromanyl)methoxy]benzyl]-2,4-thiazolidinedione</td>
<td>$C_{24}H_{27}NO_5S$ 97322-87-7</td>
</tr>
<tr>
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<td><img src="" alt="troglitazone structure" /></td>
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</tr>
<tr>
<td>valsartanum valsartan</td>
<td>$N$-$p$-[o-$1\text{H}$-tetrazol-5-ylphenyl]benzyl]-N-valeryl-L-valine</td>
<td>$C_{24}H_{27}N_5O_3$ 137862-53-4</td>
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<td><img src="" alt="valsartan structure" /></td>
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<tr>
<td>zamifenacinum zamifenacin</td>
<td>$(R)$-3-(diphenylmethoxy)-1-[3,4-(methylenedioxy)phenethyl]piperidene</td>
<td>$C_{27}H_{25}NO_3$ 127308-82-1</td>
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<tr>
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AMENDMENTS TO PREVIOUS LISTS

Chronicle of the World Health Organization Vol. 7, No. 10, 1953

**Proposed International Nonproprietary Names (Prop. INN): List 1**

p. 304  delete insert
corticotrophinum corticotropinum
corticotrophin corticotropin


**Proposed International Nonproprietary Names (Prop. INN): List 6**

p. 103  delete insert
corticotrophinum zinci corticotropinum zinci
hydroxydum hydroxydum
corticotrophin zinc hydroxide corticotropin zinc hydroxide

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

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

p. 14  icospiramidum icospiramide
replace the chemical name by the following:
\[ \text{cis-4-cyano-4-} \cdot \text{p-fluorophenyl)cyclohexyl}-1 \cdot \text{-p-fluorophenyl)-4-oxo-1,3,8-triazaspiro[4.5]decane-3-acetamide} \]


**Proposed International Nonproprietary Names (Prop. INN): List 63**

p. 4  delete insert
docetaxolum docetaxelum
docetaxol docetaxel

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

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

p. 13  leuciglumerum leuciglumer
replace the molecular formula and the graphic formula by the following:
\[ (\text{C}_6\text{H}_{13}\text{NO}_2 \cdot \text{C}_6\text{H}_7\text{NO}_4)_n \]

205
WHO Drug Information, Vol. 5, No. 4, 1991

Proposed International Nonproprietary Names (Prop. INN): List 66

p. 4 dextofosferinum
dextosferine replace the chemical name by the following:
(+)-1-serine dihydrogen phosphate (ester)

p. 6 ilatreotidum
ilatreotide include the following CAS registry number:
119719-11-8

WHO Drug Information, Vol. 6, No. 2, 1992

Proposed International Nonproprietary Names (Prop. INN): List 67

p. 9 satumomabum
satumomab include the following CAS registry number:
144058-40-2

p. 12 limaprostum
limaprost replace the chemical name by the following:
\((E)-7-[(1R,2R,3R)-3-hydroxy-2-[(E)-(3S,5S)-3-hydroxy-5-methyl-1-noneny]-5-oxocyclopentyl]-2-heptenoic acid\)

Procedure and Guiding Principles

The text of the Procedures for the Selection of Recommended International Nonproprietary Names for Pharmaceutical Substances and General Principles for Guidance in Devising International Nonproprietary Names for Pharmaceutical Substances will from now on be reproduced in uneven numbers of the proposed INN lists only.
## SELECTED WHO PUBLICATIONS OF RELATED INTEREST

<table>
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<tbody>
<tr>
<td><strong>The use of essential drugs</strong></td>
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<tr>
<td>Fourth report of the WHO Expert Committee</td>
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<tr>
<td>WHO Technical Report Series, No. 796</td>
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<tr>
<td>1990 (57 pages)</td>
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<tr>
<td><strong>WHO model prescribing information:</strong></td>
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<td>drugs used in anaesthesia</td>
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<td>1989 (53 pages)</td>
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<td>drugs used in parasitic diseases</td>
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<td>drugs used in mycobacterial diseases</td>
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<td>1991 (40 pages)</td>
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<tr>
<td><strong>Guidelines for developing national drug policies</strong></td>
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<tr>
<td>1988 (iv + 52 pages)</td>
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<tr>
<td><strong>The International Pharmacopoeia, third edition</strong></td>
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<tr>
<td>Volume 1: general methods of analysis. 1979 (223 pages)</td>
<td>24.–</td>
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<tr>
<td>Volume 2: quality specifications. 1981 (342 pages)</td>
<td>36.–</td>
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<tr>
<td>Volume 3: quality specifications. 1988 (407 pages)</td>
<td>64.–</td>
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<tr>
<td><strong>Basic tests for pharmaceutical substances</strong></td>
<td></td>
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<tr>
<td>1986 (vi + 204 pages)</td>
<td>34.–</td>
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<tr>
<td><strong>Basic tests for pharmaceutical dosage forms</strong></td>
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<tr>
<td>1991 (v + 129 pages)</td>
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<td><strong>International Nonproprietary Names (INN) for Pharmaceutical</strong></td>
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<tr>
<td>Substances, Cumulative List No. 8</td>
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<tr>
<td>1992 (xlii + 692 pages)</td>
<td>140.–</td>
</tr>
</tbody>
</table>

Further information on these and other World Health Organization publications can be obtained from Distribution and Sales, World Health Organization, 1211 Geneva 27, Switzerland

*prices in developing countries are 70% of those listed here.*