

Regulatory Matters

Informed consent in emergency situations

United States of America — Freely elicited informed consent and independent peer review are the dual safeguards applied to protect the interests of subjects involved in biomedical research. The limited application of the informed consent procedure, and its vulnerability to abuse, render it inadequate as an exclusive means of protecting the human rights and welfare of research subjects, and it fails most decisively when the population from which the subjects are drawn are most vulnerable. Not least, this limitation applies to research conducted in emergency circumstances.

Patients with such conditions as traumatic brain injury, occlusive stroke, cardiac arrest, life-threatening arrhythmias, myocardial infarction, haemorrhagic shock, pulmonary embolism, status epilepticus and poisoning are acutely and gravely ill and face severe disability or death. Nearly always they are cognitively and physically unable to consent to participate in a research programme and it is often not feasible to obtain proxy consent from a responsible relative within practicable time limits. It has been contended that, as a result of varying interpretations of the existing regulations, some important research proposals have been substantially delayed. In some cases institutional review boards (or ethics review committees) have delayed or disapproved protocols calling for a waiver of informed consent on the basis of their interpretation of Federal regulations. In other cases these bodies have approved protocols only to be instructed by a Federal agency that the protocols do not comply with the requirements of the regulations.

A public forum, co-sponsored by the Food and Drug Administration and the National Institutes of Health, was consequently held in January 1995 to explore the ethical, legal, and operational aspects of obtaining informed consent in research conducted in emergency circumstances (1, 2). All the participants agreed that regulations need to be developed that accommodate the possibility of conducting research in emergency circumstances, while at the same time securely protecting the

interests of the subjects. Some felt that current regulations overemphasize the principle of autonomy for the subject at the expense of the principles of beneficence and justice. They argued that when the expected outcome of standard therapy is dismal, the principle of beneficence — that is, seeking what is best for the target population of subjects — should outweigh the principle of autonomy.

Considerable weight was accorded to a consensus statement prepared in October 1994 by US investigators active in this field (3), which contends that “the risk of not doing emergency research is denying promising new treatments to individual patients with conditions that currently have no effective therapy, or to future patients with the same devastating conditions.” The public forum considered that serious consideration should be given by Federal Agencies to the recommendations in the consensus statement which are set out in full below:

1. Federal regulations must be developed that explicitly address the investigation of emergency therapies for patients unable to give informed consent. This population of patients should be identified as a vulnerable population and specific safeguards should be implemented to protect them from research risks without excluding them from research benefits.
2. The Federal regulations that are developed should be complete and compatible. Institutional review boards (IRB) should receive clear guidance from the regulatory agencies to allow consistent interpretation and application of the new regulations.
3. A new category, termed “Appropriate Incremental Risk” should be defined for studies that propose to forgo consent in emergency research. Incremental risk is defined as the increased risk of participating in the research protocol relative to the natural consequences of the medical condition, or the increased risk of receiving the experimental intervention relative to receiving the standard treatment for the medical condition. Appropriate incremental risk is an amount of incremental risk that is acceptable to the vast majority of potential patients.

4. Federal regulations that are developed to provide for the emergency studies that forgo informed consent should include the following elements. Emergency research protocols which propose to forgo informed consent should also include these elements:

- a. the potential subject enters into the clinical condition under study unexpectedly and suddenly;
- b. once the clinical condition develops the potential subject cannot give consent as a result of the condition;
- c. the legally-authorized representative is not available to give proxy permission;
- d. to be effective, the intervention under study must be administered before consent from the legally authorized representative is feasible;
- e. the experimental intervention poses no more than Appropriate Incremental Risk;
- f. the research could not practicably be carried out without forgoing consent;
- g. the research hypothesis is based on a foundation of valid scientific studies that support a realistic possibility of a benefit over standard care;
- h. the state of knowledge has reached the point where necessary answers can be best obtained through human trials; and
- i. when possible, and at the earliest reasonable opportunity, the patient or his/her legally authorized representative will be informed of the patient's inclusion in the study. Informed consent should be obtained for continuation in the protocol and for subsequent examinations or tests related to the study. The patient or representative should also be informed that the patient may withdraw from the study at any time: upon withdrawal, the patient will receive only non-investigational treatment.

5. The interests, rights and welfare of potential subjects in emergency research trials, as a vulnerable population, must be protected by special safeguards applied by IRBs. These safeguards may include:

- a. additional scientific, medical, or ethical consultation;
- b. consultation with former or potential patients or community groups;

c. specialized monitoring procedures to be followed by Data Safety and Monitoring Boards;

d. careful review of how subjects are selected, including extraneous incentives to enroll patients in the study;

e. careful review of the relative risks and benefits of participation; and

f. careful consideration of the usefulness of the research.

6. IRB members should receive formal continuing education about the regulations applying to studies which propose to forgo consent, and the ethical principles upon which these regulations are based.

7. Because local IRBs have good insight into local practice, the local patient population, and the capabilities of local researchers, institutions and resources, they should be the monitoring bodies primarily responsible for maintaining vigilant oversight of clinical trials of emergency research.

Sources

1. Public forum on informed consent in clinical research conducted in emergency circumstances: Notice of meeting. *US Federal Register*, 59: 65779, 21 December, 1994.
2. *Report on the public forum on informed consent in clinical research conducted in emergency circumstances*. Food and Drug Administration/National Institutes of Health, Washington, USA. May 1995.
3. *Informed consent in emergency research*. Consensus from the Coalition Conference of Acute Resuscitation and Critical Care Researchers. 25 October, 1994.

Natural remedies: requirements for registration

Sweden — From July 1996 natural remedies will be regarded as medicinal products. The approval of the Medical Products Agency will be required for their production and wholesale distribution. They are described as products that:

- contain active ingredients that consist of naturally-occurring vegetable, animal or mineral matter, bacterial cultures, a salt or salt solution and which are not processed "too highly" by chemical, biotechnical or other methods;

- are intended for general sale (not restricted to pharmacies); and
- are suitable for self-medication in accordance with "tested national tradition or tradition in countries close to Sweden with respect to drug usage."

Homoeopathic products and preparations intended for injection are subject to other regulations and are excluded from these requirements.

Applications will be assessed by the Medical Products Agency having regard to quality, efficacy and safety, while general rules regarding claims that can be made in advertising and other forms of product information will be determined by the Swedish Board for Consumer Policies.

Manufacturers will be required to satisfy the Agency that they comply in all respects with Good Manufacturing Practice (GMP). This will be determined by an inspection of the manufacturing facilities and a review of documentation to determine whether the application provides sufficient chemical, microbiological and pharmaceutical data to ensure the product in question can be produced to a consistently high production standard. The preparation of dried plants, extracts and tinctures will be required to conform to currently existing guidelines.

The assessment of safety will be determined primarily on whether or not safety in use has been established by traditional use. If this evidence is not available, harmlessness must be established by submission of relevant pharmacological, toxicological and clinical data, as necessary.

Natural remedies may be marketed only for conditions that can be appropriately treated by self-medication. Reliable bibliographic data may suffice to establish the efficacy of well-documented traditional products. In other cases evidence of efficacy will need to be generated in accordance with existing guidelines.

Source: Medical Products Agency, Sweden. Press release, July 1995.

Starting materials: proposals for a regulatory framework

European Community — In the light of recommendations from its technical advisory bodies, the European Commission has issued a

concept paper that marks a decisive departure from the existing philosophy that the manufacturer of a finished pharmaceutical product should assume sole responsibility for the quality of its ingredients. The paper sets out a framework for the adoption of a licensing, inspection and certification scheme for starting materials.

At present — with the exception of biological products which are excluded from consideration within this paper — the legislative framework now operative within the European Union does not apply to the manufacture of starting materials. Although an inventory is still to be carried out, it is estimated that there are some 250 producers of pharmaceutical active substances within the countries of the Union and around 400 manufacturing sites. No authorization is currently required at Community level to manufacture starting materials — which are defined in the concept paper to include not only active substances, but also precursors, excipients and packaging materials — and in most member states there is no compulsory inspection scheme nor even the possibility to establish GMP certificates. Instead, routine tests, which must be defined in the marketing authorization for the finished product, are required to be carried out on each batch of starting material.

The testing of samples is no longer considered sufficient to ensure the quality of production batches of starting materials. It is emphasized that lack of consistency in the chemical or physical properties of the starting material, or impurities and contaminants not detected by routine analytical methods, could adversely affect the finished product. Controlling starting materials only at the end of the manufacturing process, it is concluded, is not consonant with the general principle of quality assurance: that quality should be "built into" a product throughout **all** the stages of manufacture.

The additional costs and administrative requirements involved in introducing the proposed scheme are acknowledged. It is noted, however, that some Member States (notably, Austria, Finland and Italy) have been inspecting producers of starting materials for years, that France and Germany are developing this capacity, and that some other Member States inspect these facilities on a voluntary basis when this is required as a condition of export. Moreover, it is noted that the United States Food and Drug Administration is working on standards for bulk pharmaceutical products (active ingredients) and has expressed its concern about foreign bulk manufacturing sites.

Several benefits are identified that would derive from the proposed common framework:

- an important shortcoming in the compilation of European Drug Master Files would be resolved. At present, active ingredient manufacturers contribute relevant data, but these data cannot be checked nor can manufacturing operations be inspected on premises that are not registered;
- the enactment of legal provisions to inspect companies submitting data to the European Pharmacopoeia (EP) would resolve a similar shortcoming in the system of certification of pharmacopoeial monographs;
- the exportation of starting materials from Member States would be facilitated — since manufacturers are often requested to submit GMP certificates — and the quality of imports would be better controlled; and
- the expensive and burdensome number of foreign inspections within the Member States of the Union would be reduced, since the proposed system would improve confidence in and use of the European Drug Master Files and the EP certification procedures.

It is proposed that the framework should initially be applied exclusively to active ingredients, although the need to extend the framework to other classes of starting materials should be established at the outset. The following aspects should be considered in the development of the framework:

- a system by which Member States grant manufacturing licences;
- a requirement for producers to observe appropriate GMP;
- adoption by the Commission, in consultation with Member States, of Community GMP for starting materials;
- provision for routine inspection of producers by the supervisory authorities at a frequency to be determined and for inspection reports to be drafted after each inspection;
- provision for additional targeted inspections, for example, when a new application for a marketing application is submitted;
- provision for supervisory authorities to inspect in third countries and for reciprocal agreements between the Community and third countries;

- provision to link the inspection services with both the European Drug Master File scheme and the EP certification scheme;
- a need to refer to the WHO certification scheme where appropriate;
- a need to set up and maintain a Community data base of manufacturers of active ingredients, and ultimately, all starting materials;
- if appropriate, a provision for the cost of inspections to be charged to the industry; and
- a requirement that manufacturers operating within the Community purchase only active ingredients manufactured in inspected and approved production facilities.

Interested parties are invited to offer comments, particularly on the proposed regulatory framework by 1 December 1995.

Source: European Commission (DG III/E-3 Pharmaceuticals, RP11 4/50). *Community regulatory framework on good manufacturing practice and certification of starting materials for the manufacture of medicinal products.* Concept paper addressed to the Pharmaceutical Committee and the Working Party on Control of Medicinal Products and Inspections. Brussels, 28 July 1995.

Medication errors: a new reporting initiative

United States of America — The Food and Drug Administration is encouraging the medical community to report serious medication errors that result, or could have resulted, in fatalities, disability, or hospitalization. If warranted, the agency will take appropriate action to change the design, name or packaging of a product. One manufacturer has already agreed to change the proprietary name of a prescription drug to avoid potential and serious confusion with a totally different product. The agency recommends, particularly when a possibility of confusion of names is known to exist, that prescriptions for drugs be printed or typed and that, whenever possible, the condition to be treated be entered on the prescription.

Within the same programme, the agency is collaborating with the Association for the Advancement of Medical Instrumentation to develop standard enteral feeding set connectors that are different in gauge and design from connectors and devices (such as intravenous lines and syringes)

used for parenteral administration. The FDA has received numerous reports of fatalities and serious injuries resulting from administration through an intravenous line of liquid medicines and enteral solutions intended for a gastric tube. It has been recommended during this interim period that the distal end of every catheter be clearly labelled to decrease the possibility of confusion.

Source: *FDA Medical Bulletin*, 25: 6 (1995).

Aminosalicylates and blood dyscrasias

United Kingdom — The Committee on Safety of Medicines has advised doctors that all marketed aminosalicylates share a potential to cause blood dyscrasias (1). Sulfasalazine, which is widely used in the management of rheumatoid arthritis and ulcerative colitis, is metabolised in the large bowel to mesalazine (5-amino-salicylic acid) and sulfapyridine. It has been assumed that the sulfonamide moiety, which has been claimed to be responsible for the beneficial effects of sulfasalazine in rheumatoid arthritis, is solely responsible for the blood dyscrasias associated with its use.

The other component, mesalazine, has been marketed as a single-component anti-inflammatory substance for the management of inflammatory bowel disease while, more recently, olsalazine — which consists of two mesalazine molecules linked by a diazo bond which is cleaved in the gut — has also become available. An initial review of adverse reaction reports provided no clear indication that these substances carried any risk of blood dyscrasias (2). This is no longer the case. The UK Medicines Control Agency has now received a total of 49 haematological reactions associated with mesalazine therapy, 3 of which were fatal. These include 5 patients with aplastic anaemia, 11 with leukopenia, 17 with thrombocytopenia and one with agranulocytosis. A further four reports associate olsalazine with such events.

The Committee notes that the reporting rates for blood dyscrasias associated with sulfasalazine, mesalazine and olsalazine are of similar order. It suggests, however, that events related to use of sulfasalazine are less likely to be reported because its adverse effects on the bone marrow are well recognized.

This expectation is consonant with results obtained in a comparative post-marketing study involving some 14 000 patients. In patients with inflamma-

tory bowel disease, both sulfasalazine and mesalazine were associated with a risk of blood dyscrasias of less than 1:1000 users: in fact, no cases were associated with mesalazine within a sample of 4000 patients. In contrast, among patients with rheumatoid arthritis, the incidence of blood dyscrasias associated with sulfasalazine was some ten-fold higher at 6.1:1000 users. This relatively high incidence possibly reflects an intrinsic sensitivity among patients with this disease.

The Committee recommends that patients receiving an aminosalicylate drug should be advised to report any unexplained bleeding, bruising, purpura, sore-throat, fever or malaise that occurs during treatment. A blood count should be performed and the drug stopped immediately if there is suspicion of a blood dyscrasia.

Sources

1. Committee on Safety of Medicines. *Current Problems in Pharmacovigilance*, No. 19 (1993).
2. Committee on Safety of Medicines. *Current Problems in Pharmacovigilance*, No. 21 (1995).

Antimicrobial susceptibility tests: unreliable performance

United States of America — The Food and Drug Administration has notified users that some commercial antimicrobial susceptibility tests may not reliably detect resistance in some pathogens, notably pneumococci and enterococci. These bacteria are slow-growing, whereas the systems in question — which were developed before the emergence of resistance in these pathogens — were designed for testing rapidly-growing bacterial isolates.

The FDA stresses the vital need for these tests to be reliable. The results that they offer determine not only the therapeutic management of individual patients, but also the strategies to be employed in surveillance and prevention.

The unreliability of penicillin (and other beta-lactam) disk diffusion systems for screening susceptibility in pneumococci has led the National Committee for Clinical Laboratory Standards (NCCLS) to recommend an oxacillin disk screen for this purpose. If this screen suggests resistance, a standardized minimum inhibitory concentration (MIC) test method is recommended to detect resistance to penicillin and other individual beta-lactam drugs.

To detect vancomycin-resistant enterococci, NCCLS recommends agar or broth microdilution, MIC, or disk diffusion testing allowing incubation for a full 24 hours, or a vancomycin agar test screen. For detection of penicillin/ampicillin resistance, agar or broth dilution tests and a nitrocefin-based beta-lactamase test are recommended.

Source: *FDA Medical Bulletin*, 25: 2 (1995).

Coumarin: a strong association with hepatotoxicity

Australia — The benzopyrone, coumarin, which is used in the control of lymphoedema and other high protein oedemas, was introduced in Australia in mid-1993. Over a period of little more than one year the regulatory authority received a total of 10 adverse reaction reports citing the drug (1). Six of these describe jaundice — which in one case progressed to fatal hepatic necrosis — occurring in women aged 49 years or more. The one liver biopsy that has been obtained showed periportal and lobular necrosis. Each of the women had been taking coumarin in a daily oral dose of 400 mg for periods ranging from one to four months, and in no case was any other cause of jaundice apparent. In all but one instance coumarin was the only suspected causal agent, the 5 surviving patients recovered after coumarin was withdrawn, and in one of these jaundice recurred on rechallenge.

No restriction on the availability of coumarin has been announced, but these cases suggest that the frequency of hepatotoxicity among treated patients is at least 34 : 10 000. This is considerably higher than has been demonstrated for flucloxacillin — which has recently been associated in Australia with cholestatic jaundice (2) — and other generally-available hepatotoxic compounds.

Sources

1. *Australian Adverse Drug Reactions Bulletin*, 14: 11 (1995).
2. Jick, H., Derby, L., Dean, A., Henry, D. Flucloxacillin and cholestatic hepatitis. *Medical Journal of Australia*, 160: 525 (1994).

Clomifene and ovarian cancer

United Kingdom — In the light of published evidence associating prolonged use of clomifene for infertility with a small increase in absolute risk of

ovarian cancer (1), the Committee on Safety of Medicines has recommended that treatment should not normally be extended beyond six cycles (2). Within this limit there is no evidence of increased carcinogenic risk.

The Committee considers that further studies are needed to investigate the possible association between clomifene and ovarian cancer. For women aged between 20 and 30 years, the overall incidence of this cancer in non-users is around 2 cases per 100 000 women per year. The risk increases tenfold during the fifth decade and is greater in nulliparous women.

Sources

1. Rossing, M., Daling, J.R., Weiss, N.S. et al. Ovarian tumors in a cohort of infertile women. *New England Journal of Medicine*, 331: 771-776 (1994).
2. Committee on Safety of Medicines. *Current Problems in Pharmacovigilance*, No. 21 (1995).

Iron-containing drugs and supplements: accidental poisoning

United States of America — Since 1986 more than 110 000 reports of children who had accidentally swallowed iron tablets have been received nationwide by poisons control centres. Throughout this period, the overall frequency of these reports and the number of associated fatalities has more than doubled. During the mid-1980s, up to 5% of children's deaths reported to these centres were attributed to iron-containing drugs and supplements. This proportion has now risen to approximately 17%. In some cases death has resulted from ingestion of no more than 5 tablets.

Current regulations require any product containing a total of 250 mg or more of iron in an orally-administered form to be sold in child-resistant packaging. FDA now proposes that dosage units (tablets and capsules) containing 30 mg or more of iron should be wrapped individually, as in blister packs, and that warning statements be carried on packaging of solid oral-dosage forms of iron-containing drugs and dietary supplements. It is proposed that these statements include the message that an overdose of iron may kill or harm a child; that the product should be kept in the original container, tightly closed and out of reach of children; and that medical help should be sought

immediately if a child accidentally swallows any of the product.

Source: *FDA Medical Bulletin*, 25: 3 (1995).

Quinolones and tendon rupture

United Kingdom — The Committee on Safety of Medicines has received a total of 21 reports of tendon damage associated with use of the quinolone antibiotics, ciprofloxacin and ofloxacin (1). In 15 of these cases — which ranged in severity from tendonitis to partial or complete tendon rupture — the Achilles' tendon was involved. Similar cases reported in other countries suggest that this is a class-effect shared by all quinolones, and that the risk increases with age or when steroids are taken concomitantly.

The Committee advises doctors that, at the first sign of pain or inflammation, patients taking quinolones should discontinue treatment and rest the affected limb until the symptoms have resolved.

Source: Committee on Safety of Medicines. *Current Problems in Pharmacovigilance*, No. 21 (1995).

Tocolytics and pulmonary oedema

United Kingdom — The Committee on Safety of Medicines has received several reports of maternal pulmonary oedema developing during the infusion of β -receptor agonist tocolytics (ritodrine, salbutamol and terbutaline). These drugs are used in pre-term labour (24–33 weeks) to delay delivery temporarily, allowing time to administer glucocorticoids and to take other measures to improve perinatal survival.

The Committee acknowledges that several risk factors are operative in these circumstances, including multiple pregnancy, pre-existing cardiac disease and maternal infection. It emphasizes, however, that fluid overload is the single most important predisposing factor, and that this risk is substantially reduced when these drugs are diluted with 5% dextrose (rather than saline) and when the rate of infusion is accurately controlled by using a syringe pump or similar device. In all cases, the mother's state of hydration must be closely monitored and, should signs of pulmonary oedema develop, the beta-agonist should be withdrawn immediately and diuretic therapy instituted.

Source: Committee on Safety of Medicines. *Current Problems in Pharmacovigilance*, No. 21 (1995).

Selegiline and antidepressants: risk of serious interactions

United States of America — The Food and Drug Administration has modified the labelling for selegiline hydrochloride, a selective monoamine oxidase (MAO) inhibitor which prevents dopamine breakdown in the brain, and which potentiates and prolongs the effect of levodopa in the treatment of parkinsonism. A warning will now be carried to reflect the risk of serious adverse effects when the drug is used in patients taking tricyclic antidepressants or selective serotonin reuptake inhibitors (SSRIs). These effects, which are variable, are in some instances similar to the potentially fatal syndromes reported when tricyclic or SSRI-type antidepressants are prescribed together with nonselective MAO inhibitors.

Thus far, at least two deaths have been attributed to use of a combination of selegiline and tricyclic antidepressants. One of these, which was associated with use of amitriptyline, had the characteristics of the acute encephalopathy associated with concomitant use of tricyclics and nonselective MAO inhibitors: death was preceded by acute, severe central nervous toxicity and hyperpyrexia. In the other, which involved protriptyline, the patient developed tremors, became agitated and restless, and died after two weeks. Reports involving other tricyclics cite a variety of signs including hypertension, syncope, asystole, sweating, seizures, muscular rigidity and changes in behaviour.

Signs that have been reported when selegiline is combined with the selective serotonin reuptake inhibitors, fluoxetine, paroxetine and sertraline, include hyperthermia, rigidity, myoclonus, autonomic instability with rapid fluctuations in vital signs, and behavioural changes that range from agitation to delirium and coma. Some of the reactions involving fluoxetine have resulted in death.

The FDA consequently advises that every care should be taken to avoid these potentially dangerous interactions involving selegiline. In general, at least 14 days should elapse between discontinuation of selegiline and subsequent treatment with a tricyclic antidepressant or a selective serotonin reuptake inhibitor. Conversely, selegiline should not be prescribed to any patient who has recently received these drugs. Sufficient time should elapse for the drugs to be completely metabolized or excreted. In the case of fluoxetine, which has a

particularly long half-life, this period should not be less than 5 weeks.

Source: *FDA Medical Bulletin*, 25: 6 (1995).

Simvastatin and endocrine effects in men

Australia — Simvastatin was the first of the co-enzyme A reductase inhibitors to become available in Australia for treating hypercholesterolaemia. Since it was introduced in 1990 it has been associated with a small but appreciable number of reports of gynaecomastia and impotence.

Eleven men, all over 50 years of age, are reported to have developed gynaecomastia after having received the drug for periods ranging from 2 to 10 months. Five of these patients had not received any other drugs in the recent past, and in at least 4 of the other cases the temporal relationship and other considerations suggested that simvastatin was the most likely cause. Regression of the condition subsequent to withdrawal of treatment has been reported in only one of the patients. However, it is noted that gynaecomastia is a condition that is often slow to resolve.

The temporal relationship is less persuasive in the 28 reports of impotence reported in men aged 45 to 72 years who were taking simvastatin. Onset of the complaint occurred from 48 hours to 27 months (median about 4 weeks) after starting treatment. However, in 24 cases, simvastatin was the only drug implicated; function was restored in 12 of these patients after withdrawal of treatment; and, in 4 instances, the problem was again reported on rechallenge. A further 9 patients reported no improvement on withdrawal of treatment.

Source: *Australian Adverse Drug Reactions Bulletin*, 14: 10 (1995).

Tacrolimus and cardiomyopathy

United Kingdom — The Committee on Safety of Medicines has advised doctors that cases of hypertrophic cardiomyopathy have developed in children undergoing organ transplants who have been treated with tacrolimus, a new immunosuppressant agent introduced in the UK late in 1994 (1).

A series of 5 such cases has recently been published (2), and a total of 29 suspected cases has

now been reported worldwide. Most relate to children aged 5 years or less who have received transplants of liver, small bowel, colon or a combination of these organs. In at least some of these cases trough blood concentrations of tacrolimus exceeded the recommended maximum level of 25 ng/ml, and in most cases the myopathy regressed when the drug was withdrawn or the dosage reduced.

This finding is unanticipated and unexplained. The product information in the UK is being revised to emphasize that patients receiving tacrolimus should be monitored carefully by echocardiography for hypertrophic changes, and that the drug should be either withdrawn or reduced in dosage should these be detected.

Sources

1. Committee on Safety of Medicines. *Current Problems in Pharmacovigilance*, No. 21 (1995).
2. Atkinson, P., Joubert, G., Barron, A. Hypertrophic cardiomyopathy associated with tacrolimus in paediatric transplant patients. *Lancet*, 345: 894-896 (1995).

Trimethoprim/sulfamethoxazole: restriction of previously-approved indications

United Kingdom — The Committee on Safety of Medicines has decided to restrict the approved indications for preparations of the combination antibiotic trimethoprim/sulfamethoxazole on the grounds that "its place in therapy has changed", and particularly because trimethoprim alone is now widely used for urinary tract and chest infections (1).

The Committee considers that the use of the combination product remains unchallenged in the treatment and prophylaxis of three opportunistic infections commonly associated with HIV infection: *Pneumocystis carinii* pneumonia, toxoplasmosis and nocardiasis.

However, the combination is now approved for use in acute exacerbations of chronic bronchitis and infections of the urinary tract only when there is bacteriological evidence of sensitivity and when there is "good reason to prefer this combination of drugs to a single antibiotic." Similarly, it is approved for use in acute otitis media in children "when there is good reason to prefer this combination."

In announcing this decision, the Committee emphasizes that it has no newly-founded concerns about the safety of the combination products. Spontaneously reported adverse reactions continue to conform to long-established patterns (2), and the profile of these reactions has been shown to be similar to that associated with trimethoprim when it is administered alone. This implies that there is no evidence that the sulfonamide component significantly augments any known risk associated with treatment.

The most serious reactions — blood dyscrasias and generalized skin disorders which occur predominantly in elderly patients — are associated with both the combination products and with trimethoprim. The Committee cites a recent large post-marketing study (3) which confirms that these reactions are very rare, and which fails to demonstrate any significant difference in the frequency with which serious hepatic, renal, blood and skin disorders are associated with the combination products and trimethoprim alone.

Sources

1. Committee on Safety of Medicines. *Current Problems in Pharmacovigilance*, No. 21 (1995).
2. Committee on Safety of Medicines. *Current Problems in Pharmacovigilance*, No. 15 (1985).
3. Jick, H., Derby, L. Is co-trimoxazole safe? *Lancet*, 345: 1118-1119 (1995).

Macrolide antibiotics interfere with response to warfarin

Australia — Within the past two years the Adverse Drug Reaction Advisory Committee has received over 20 reports indicating that intercurrent use of a macrolide antibiotic interferes with the therapeutic action of warfarin on coagulation factors. Half the cases were associated with use of erythromycin and half with roxithromycin.

The changes occurred in patients who had been on stable doses of warfarin for prolonged periods and within a few days of starting antibiotic therapy. In nearly all cases the prothrombin time rose considerably above the accepted therapeutic range. Spontaneous bleeding occurred in patients who received roxithromycin and three required transfusion.

The Committee concludes that a clear causal relationship exists and it stresses the need for careful

monitoring when either erythromycin or roxithromycin is administered to a patient receiving warfarin. It lacks evidence to indicate whether the effect results from a direct interaction with warfarin, or from an independent effect of the antibiotic such as reduced synthesis of vitamin K resulting from changes in the gut flora. The Committee does not comment on possible reasons for the apparent clustering of these reports within the past two years, or whether, as is possible, they have resulted from a targeted screening programme undertaken in one or more hospital laboratories rather than from spontaneously-generated reports submitted by clinicians.

Source: *Australian Adverse Drug Reactions Bulletin*, 14: 11 (1995).

Cyproterone acetate: further restrictive action

European Commission — The German health authorities have recently referred to the Committee for Proprietary Medicinal Products (CPMP) of the European Commission data suggesting that the synthetic anti-androgen, cyproterone acetate, is a genotoxic substance which may have carcinogenic potential. Concern was raised specifically about a possible association with primary hepatic cancer. Thus far, however, it seems that only one case possibly attributable to use of cyproterone acetate has been cited (1).

Although the CPMP considers that an association with hepatic cancer remains unproven, it has concluded that use of cyproterone acetate is associated with significant hepatotoxicity, particularly when it is administered at relatively high doses over extended periods of time to patients with prostatic carcinoma (2). A similar conclusion was announced by the UK Committee on Safety of Medicines early in 1995 (3, 4). Its use in this condition is still considered justified in long-term palliative treatment of prostatic cancer when surgery has failed or when LHRH analogues are ineffective, contraindicated or poorly tolerated.

Given this finding, the CPMP has advised that the approved indications for products containing cyproterone acetate should be restricted to serious conditions. It should no longer be contained, it is suggested, even at low dosage, in products promoted solely for contraception, nor should it be indicated for the treatment of precocious puberty, or

for less severe forms of acne, hirsutism and other androgen-induced changes in women.

Sources:

1 Rüdiger, T., Beckmann, J., Queisser, W. Hepatocellular carcinoma after treatment with cyproterone acetate combined with ethinyloestradiol. *Lancet*, **345**: 452 (1995).

2. Committee for Proprietary Medicinal Products, European Commission. *Pharmacovigilance opinion No. 19: cyproterone acetate*. Meeting of 13–14 December 1994.

3. Committee on Safety of Medicines. *Current Problems in Pharmacovigilance*, No. 21, 1995.

4. Cyproterone acetate and hepatic reactions. *WHO Drug Information*, **9**: 30 (1995).

Spermicide contraceptives: do they really work?

United States of America — The Food and Drug Administration has proposed that manufacturers of over-the-counter spermicidal products should generate data in prospective clinical studies to demonstrate the extent to which the final formulations are effective as contraceptives. The products at issue, nonoxinol-9 and, less commonly octoxinol-9, are polymers of substituted phenoxyethyl alcohol with surfactant properties.

The agency has evidence that some of these formulations may rapidly lose effectiveness *in situ*, and that they sometimes cause vaginal irritation which may facilitate transmission of infections. Manufacturers have been asked to collect information on the occurrence of vaginal irritation in the course of the required clinical studies.

Conversely, these products have also been shown to possess antimicrobial activity *in vitro* which may provide a tangible degree of protection in normal use against sexually transmitted diseases, including, perhaps, HIV infection. In addition to the requirements imposed by its formal proposal, the

FDA is encouraging companies to evaluate this antimicrobial potential in separate clinical trials.

The marketing status of existing products will not be immediately affected by the proposed rule but, to assure continued availability of these products once the rule is adopted, the FDA is encouraging companies to conduct the required clinical studies as quickly as possible. Products that fail to meet the requirements of the final rule will be subject to regulatory action.

Source: *United States Federal Register*, 3 February 1995.

Towards one strength of insulin (IU100)

The International Diabetes Federation (IDF), representing 130 diabetes associations in 108 countries, recommends that all countries change to IU100 insulin before the end of the century. This target is proposed in the knowledge that major insulin-consuming countries of the world have either already changed to one common insulin concentration of 100 u/ml (IU100) or will do so within the next 24 months. Continuing availability of other strengths (IU40 and IU80) is claimed to be confusing, costly and potentially dangerous.

Experience in many countries over the past two decades has shown that the withdrawal of redundant strengths of insulin and injection equipment can be undertaken safely, and without arousing significant concern among persons with diabetes. However, the IDF stresses that these changes have to be carefully planned at all levels to ensure that both patients and health professionals are adequately informed of their nature and timing.

IDF has consulted with the World Health Organization and the major insulin manufacturers who agree that other strengths, including IU40 and IU80, should be removed from the market before 31 December 1999.

Source: Statement from International Diabetes Federation transmitted to WHO, dated 23 May 1995.