

# Regulatory Matters

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## Acetylsalicylic acid for the heart: warning against self-medication

**United States of America** — The Food and Drug Administration has proposed that the labelling of many over-the-counter drug products containing acetylsalicylic acid should bear a statement advising users to consult a doctor if they are considering embarking on long term self-medication in an attempt to reduce the risk of myocardial infarction or other cardiovascular illnesses.

Although there is strong evidence that such use of acetylsalicylic acid can reduce the risk of a second myocardial infarction, the agency considers that the risk of first infarction is unlikely to be reduced, except in the case of patients with unstable angina pectoris.

The agency is also concerned that the public perception of the safety of acetylsalicylic acid results from experience of short-term use only. It is particularly concerned about the increased risk of haemorrhagic stroke that has been associated with prolonged use. For this reason, information on the cardiovascular indications for acetylsalicylic acid is directed only to doctors. Safe use in these indications is considered to be dependent on both professional supervision and judgement as to whether the patient is likely to benefit.

**Source:** *Federal Register*, 58: 54224 (1993).

## Cell line management: revised guidelines

**United States of America** — The Food and Drug Administration has updated its guidance on the characterization of cell lines used in the manufacture of biological products with a view to assisting manufacturers to comply with regulations that require final products derived from these sources to be uniform, consistent lot-to-lot, and free from adventitious infectious agents. Revised advice concerning the manufacture and testing of monoclonal antibody products will be issued shortly.

The guidelines relate to three sets of operations:

- production, identification and characterization of the cell substrate;
- validation of the manufacturing process for removal and/or inactivation of adventitious agents; and
- testing of the bulk and final product to assure safety.

Given current concerns about the potential for transmission of pathogenic organisms through the administration of biological preparations, the purpose of this summary is to provide a general overview of the safeguards that manufacturers are required to observe to exclude adventitious organisms, particularly from the new generation of products now being developed. The source document must be consulted for details of the tests required.

Since the scientific basis for this technology is fast developing, and because each product must be evaluated with regard to its own particular characteristics, the adequacy of testing must always be reviewed on a case-by-case basis. The selection of tests depends upon many variables, including the nature of the cell line, the processing of the product and the indications for its use.

### Obsolete testing procedures

Some tests previously recommended have been eliminated. Others are now used on a selective basis. In particular:

- karyology control is no longer recommended as a routine procedure. Pre-existing characterization and monitoring procedures are still applied to diploid cell lines used for production of live virus vaccines, but their value in the characterization of continuous cell lines is now regarded as minimal.
- tumorigenicity testing continues to hold relevance to human epithelial cells, all cells used for live virus vaccine production, and some cells used in the production of somatic cell or gene therapies. Rodent cells need no longer be tested, however, since it is now recognized that virtually all cell lines of rodent origin are tumorigenic.

- oncogene testing is no longer required since it is now evident that these genes are involved in normal cell growth.

#### Characterization of the cell line

The history of the cell line should include information on the species, age and sex of the human or animal donor; the methods used for the isolation of the original tissue; its passage history, including a description of the media used; details of previous testing both to confirm the identity and to screen for adventitious agents.

The morphology and growth pattern of the cell line should be described and shown to be stable throughout processing. The stability of specific marker chromosomes and surface markers should be described and, for cells with a finite life expectancy, the total number of cell divisions through to senescence should be determined.

#### The cell bank system

A two-tier cell bank system — consisting of a master bank and a working cell bank — should be generated, to assure an adequate supply of equivalent cells throughout the life-span of the product.

The master cell bank, which is derived from a single tissue or cell, is cryopreserved in ampoules and stored in the liquid or vapour phase of liquid nitrogen.

The manufacturer's working cell bank is created by expanding cells from the master bank by serial subculture up to an approved passage number. The cells are then pooled, dispensed into ampoules and cryopreserved. One or more of these ampoules is used to produce one lot of the final product. The population doubling level of the cells used for production should not exceed an upper limit based upon criteria established by the manufacturer.

The identity and inventory of all ampoules in each cell bank should be fully documented. To avoid loss of the cell line, each bank should be stored in two or more separate areas both within the production facility and also at a distant site.

#### Qualification of cell banks

Master cell banks should be tested to demonstrate freedom from adventitious agents including bacteria, fungi, mycoplasmas, viruses (using *in vivo* and cell culture inoculation tests) and, in most circumstances, retroviruses. Identity testing should include morphology (as determined by light and electron microscopy); species of origin; split ratio;

and evidence that the cells are appropriate for their intended purpose. If the cells contain an expression system to produce a recombinant DNA-derived protein, the copy number and physical state of the expression system should be demonstrated together with the quality and quantity of the protein that is produced.

Working cell banks need only to be spot checked for contaminants that may have been introduced from the culture medium. Recommended tests include sterility, mycoplasma, and routine virus tests. A routine check should also be made on authenticity to exclude cross contamination of cell-lines.

#### Production cultures and product testing

Accurate records should be kept of cell culture media. Serum or other additives of animal origin should be certified free from contaminants and adventitious agents, including the agent responsible for bovine spongiform encephalopathy. (See also p. 29). Porcine trypsin should additionally be certified free of porcine parvovirus. Penicillin or other beta-lactam antibiotics should not be present in production cell cultures and the presence of any other antibiotic or inducing agent is discouraged. Full information on the sources of supply and the testing procedures used for certification should be supplied. The manufacturer assumes responsibility for determining whether the testing programme on which these supplies are certified is sufficient, and for ensuring that the residual amount of serum or other additive in the final product does not exceed 1:1 000 000.

The approach to quality control of cell substrates depends upon the nature of the propagation system. When short-term cultures are used, quality control testing may need to be performed on each harvest before pooling into the bulk lot. If the product is an infectious virus, it will usually replicate in one or more of the cell cultures used for routine testing for adventitious agents. Nonreplicating viruses, used as vectors for gene therapy, are also tested in this way for the presence of adventitious agents. When long-term cultures are used, testing should be performed on each bulk lot and, if possible, on cells separated from the pooled production harvest. Criteria for termination of long-term cultures should be established.

Testing for bacterial and fungal sterility is generally performed on the unprocessed bulk lot, the final bulk lot and the final product. The final product should be tested for sterility and presence of endotoxin.

Routine testing for mycoplasmas and *in vitro/in vivo* testing for adventitious viruses should be performed on every lot using production cells and unprocessed bulk fluids. If a cell line is known to produce an adventitious virus, testing on a lot-to-lot basis to demonstrate its absence from the product after purification may be required.

It is considered that presence in the final product of nucleic acid derived from cell lines in amounts less than 100 pg cellular DNA/dose does not constitute a tangible risk. Lot-to-lot testing should be undertaken to ensure that established lot-release limits are not exceeded.

Manufacturers are responsible for establishing lot release procedures that provide assurance of all significant aspects of product quality.

**Source:** Food and Drug Administration, Center for Biologics Evaluation and Research. *Points to consider in the characterization of cell lines used to produce biologics* (1993).

## A new approach to the treatment of cystic fibrosis

**United States of America** — The Food and Drug Administration has announced that it has approved the marketing of dornase alfa (Pulmozyme®, aerosolized recombinant human DNase, Genentech) as a treatment for cystic fibrosis.

This inherited disorder, which affects some 30 000 patients in the USA, is characterized by accumulation of thick mucous secretions in the lungs, repeated lung infections, reduced pulmonary function and a life expectancy of less than 30 years. An important factor raising the viscosity of the abnormal mucous is the accumulation within the lungs of DNA released from disintegrating white blood cells.

*In vitro* — and, it now seems, *in vivo* — dornase alfa administered by aerosol catabolizes DNA in lung secretions. A phase III clinical trial conducted in centres across North America and which involved almost 1000 patients has indicated that this treatment reduces the incidence of respiratory infections requiring treatment with parenteral antibiotics by more than 25% and maintains or improves lung function. A majority of treated patients reported a reduction in cough and congestion and a generally improved quality of life.

The only adverse effects of note associated with treatment were sporadic cases of rash, hoarseness and sore throat.

No patients have yet been treated for more than 12 months, and patients aged less than 5 years and those with severe degrees of pulmonary dysfunction were excluded from the initial study. Further studies are ongoing to define optimal dosing schedules, to investigate the effects of long-term treatment, and the response of very young children.

**Source:** US Department of Health and Human Services. *HHS News*, P93-47, 30 December 1993.

## Good practices in drug distribution

**European Communities** — The European Commission has issued guidelines intended to assure the quality of pharmaceutical products throughout the distribution chain. The guidelines proposed are established upon the following principles:

- all products within the distribution chain shall be authorized in accordance with Community legislation;
- correct storage conditions shall be observed at all times, including during transportation;
- contamination of or from other products shall be avoided;
- adequate turnover of stored products shall be maintained;
- products shall be stored in appropriate safe and secure areas;
- a tracing system shall be maintained to enable any product suspected of being faulty to be found; and
- an effective recall procedure shall be in operation.

Particular emphasis is laid upon the need to locate a manager in each distribution point who should have defined responsibility for ensuring that a quality system is implemented and maintained, and to keep records at the time each operation is undertaken in such a way that all significant activities and events are traceable.

When counterfeit products are identified, it is advised that they should be kept apart from other products, clearly labelled as not for sale, and that both the competent authorities and the holder of the licence for the genuine product be informed immediately.

**Source:** Guidelines on good distribution practice of medicinal products for human use. *Official Journal of the European Communities*, No. C 63: pp. 4-7, 1. 3. 1994.

### Metformin hydrochloride: a reassessment

**United States of America** — The biguanide oral hypoglycaemic agents, phenformin hydrochloride and metformin hydrochloride, act distinctively by increasing the metabolic response to endogenous insulin. The sulfonylureas, in contrast, stimulate the secretion of insulin. Phenformin is now generally regarded as obsolete because of an unacceptable risk of lactic acidosis. In some countries metformin has also been removed from the market on the same grounds, although several epidemiological studies suggest that the associated risk is substantially smaller.

However, there are no satisfactory alternative hypoglycaemic agents for patients with non-insulin-dependent diabetes mellitus who are either unresponsive to or intolerant of sulfonylureas, or who have severe insulin resistance. The Food and Drug Administration has consequently decided to make metformin hydrochloride available to clinical investigators for treating patients who meet stringent protocol criteria for non-insulin-dependent diabetes mellitus and, at the same time, it is studying all available information accumulated outside the United States on the use of both metformin and phenformin.

Two placebo-controlled, randomized studies recently undertaken in North America have demonstrated that metformin significantly lowers both glycosylated haemoglobin levels and fasting blood sugar, and that this effect is augmented when metformin is administered concurrently with glibenclamide. No cases of lactic acidosis or other serious adverse events were described during these studies, and small favourable effects were also reported on total cholesterol, low density lipoprotein, and triglyceride serum levels. The FDA aims to extend these studies to define both the benefits and the risks associated with metformin more precisely.

**Source:** Nightingale, S. From the Food and Drug Administration. *Journal of the American Medical Association*, 270: 2669 (1993).

### Royal jelly: life-threatening allergic reactions

**Australia** — Severe allergic reactions, including one death and four life-threatening cases, have been associated with use of royal jelly in recent years within Australia. Royal jelly, a secretion from the salivary glands of honey bees, is widely used in alternative medicine in Australia as a health tonic. It consists mainly of proteins and moisture, and studies are now in hand to identify the allergenic components.

Warning labels will be carried on every product containing royal jelly to advise patients with asthma and other allergic conditions that they are at particular risk and should avoid taking the product.

Contact has been made with relevant professional societies, the Australian Association of Asthma Foundations, industry groups and consumer organizations to ensure that information about the hazard is widely circulated.

**Source:** Open letter from the Therapeutic Goods Administration to WHO dated 22 February 1994.

### Fixed-dose combinations with rifampicin: promise and reality

The Tuberculosis Programme of the World Health Organization and the International Union against Tuberculosis and Lung Diseases have jointly issued the following statement:

"The resurgence of tuberculosis on a global scale has been widely and accurately reported and is of major concern. The fact that there has been a concurrent rise of *M. tuberculosis* resistant to isoniazid and rifampicin, and often to other drugs as well, has been cited as a global public health emergency. Resistance to medications in tuberculosis is almost always caused by inappropriate prescribing or taking of medications, effectively resulting in monotherapy. The consequences may appear in the patient being treated or in a person who has been infected by another patient who had monotherapy for whatever reason.

"It is obvious that one of the most important ways to reduce the possibility of monotherapy is to give the antituberculosis medications in combination tablets or capsules (1). Such therapy is not new, has been well studied (2, 3), and has been recommended by the IUATLD in its Statement on the Treatment of Tuberculosis in 1989 (4) and by the WHO in a more detailed statement in 1993 (5). These statements, however, make the caveat that **any** fixed-dose combination that contains rifampicin (in combination with isoniazid or with isoniazid and pyrazinamide) **must** be of demonstrated bioavailability.

"It has long been recognized that there are fixed-dose combinations of assured bioavailability. However, studies of several fixed-dose combinations containing rifampicin have shown that in some of the preparations the rifampicin was poorly absorbed or not absorbed at all (6). Unfortunately, the message that derives from these studies went largely unheeded, and fixed-dose combinations of questionable quality have continued to be marketed and used (7). Moreover, continued analysis has revealed ongoing problems with bioavailability of rifampicin in these products. Since an important component of the strategy to solve the increasing problem of multidrug-resistant tuberculosis is prescription of fixed-dose combinations, it is likely that their use will increase.

"Therefore, the IUATLD and the WHO Tuberculosis Programme, being extremely concerned that any fixed dosage combination of rifampicin must be **demonstrably bioavailable** is not being followed, recommend that the following measures be accorded extremely high priority:

- All organizations or persons, including National Tuberculosis Control Programmes and Ministries of Health, when purchasing medicaments for the treatment of tuberculosis, should ensure that fixed dose combination tablets or capsules containing rifampicin are of assured bioavailability.
- This assurance should be provided by the manufacturer in a product data sheet, as approved by the responsible national drug regulatory authority, which should describe the tests undertaken to establish bioavailability as well as the results obtained. Assurances for imported products should be obtained through the WHO Certification Scheme in the Quality of Pharmaceutical Products moving in International Commerce (8).
- An independent laboratory should be established where the bioavailability of rifampicin-containing products can be evaluated on contract using standardized methods (3), at the request of national drug regulatory authorities, or other bodies purchasing medications, including Ministries of Health and National Tuberculosis Programmes. This is important to ensure proper screening of products that have not been tested for bioavailability."

The IUATLD and the WHO Tuberculosis Programme will provide information on request to interested parties about manufacturing facilities and the results of independent assessment of products.

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## Varicella vaccine: promising performance but clinical implications still to be resolved

**United States of America** — A varicella zoster virus vaccine (Merck, Sharp and Dohme) that has been administered over the past 10 years to more than 10 000 healthy adults and children over 1 year of age has been judged to be safe and effective by an advisory committee to the US Food and Drug Administration. However, the committee considered that further information is needed on which to base dosage regimens, and to determine, in particular:

- whether vaccination provides long-term immunity;
- if extensive vaccination of children will shift the disease to adults in whom the disease may be more severe; and
- how it will affect the occurrence of shingles.

It is estimated that within the United States varicella (chicken pox) affects nearly 4 million individuals each year, three quarters of whom are under 9 years of age. Generally, the disease is mild, but adults and immunosuppressed individuals are at higher risk of serious illness. The number of persons hospitalized as a result of infection approaches 10 million annually, of whom 50 to 100 die.

**Source:** US Food and Drug Administration. *Talk Paper T94-9*, 28 January 1994.

## Bovine spongiform encephalitis

**United States of America** — The Food and Drug Administration has advised manufacturers that bovine materials derived from cattle that have originated or resided in countries where bovine spongiform encephalitis has been diagnosed should not be used in the manufacture of any products regulated by the agency that are intended for administration to human beings. Formal restriction of the use of these materials is under consideration.

Bovine spongiform encephalitis, the agency explains, is a transmissible neurological disease similar to scrapie in sheep and Creutzfeldt-Jacob disease in human beings. The latter disease has been transmitted iatrogenically in pituitary-derived human growth hormone (somatotropin) and grafted dura mater. Each of the diseases is transmitted by

a subviral agent that is highly resistant to inactivation by normal disinfection or sterilization procedures. Infection is uniformly fatal, and no rapid antemortem diagnostic test for infection is currently available. Research remains ongoing to determine the exact nature of the causative agents, their host range, and their pattern of pathogenicity.

Whereas the transmission of the causative agent of bovine spongiform encephalitis to human beings has not as yet been reported, the agency considers it prudent in the current state of knowledge to reduce as far as is possible any risk of exposure through use of FDA-regulated products.

The highest incidence of bovine spongiform encephalitis has been reported from the United Kingdom, where the most recent official quarterly report indicates that more than 109 000 cattle have been infected. A list of countries where the disease is known to exist is maintained by the United States Department of Agriculture. Currently included, in addition to the United Kingdom, are the Falkland Islands, France, the Republic of Ireland, Switzerland and Oman.

Manufacturers of products that contain bovine-derived material are asked:

- to obtain from suppliers information on all countries in which the animals were reared, and relevant inspection certificates of slaughter; and
- to maintain within batch records retained at the site of manufacture, details of each lot of bovine material used, and each lot of any regulated product — whether or not it is approved at the time of manufacture — in which the material has been incorporated.

**Source:** Food and Drug Administration. Open letter to all manufacturers of FDA-regulated products. 17 December 1993.

## Placental-derived albumin preparations withdrawn

**France** — In the light of a review recently undertaken by the national Medicines Agency, Pasteur-Mérieux has decided voluntarily to withdraw from the market all products containing albumin derived from placental blood as from 1 December 1993 (1). These products, which have been estimated to account for some 8% of the global market and 14%

of the European market in albumin, were manufactured from the same source material for over 20 years. The company was recently collecting more than 8 million placentas annually from maternity units in some 45 countries, and it will continue to collect a smaller number needed to manufacture glucocerebrosidase which is used as a specific treatment of Gaucher's disease.

Switzerland withdrew authorization for sale of albumin manufactured from placentas in 1991 while, in the United Kingdom, export of placentas from maternity hospitals has been banned.

It has been reported that some of these collections were made in countries where AIDS is common, without requiring information regarding the health of the women concerned, and without serological screening (2). It is emphasized that placental blood is used only for production of purified proteins, and that albumin — whether extracted from placentas or plasma — has in no instance ever been implicated in the transmission of an infectious condition. However, the Agency is understood to be concerned about the potential of transmission of viral and subviral particles and, in particular, the possibility that prions associated with Creutzfeldt-Jakob disease might be contained in placentas from women who have been treated with growth hormone derived from cadaver pituitaries.

In commenting on this concern (3), the company submits that:

- its fractionation process has been shown to be capable of inactivating and eliminating viral contaminants, notably parvovirus;
- reported detection of transmissible prions in sheep placentas (4) in the blood of patients with Creutzfeldt-Jakob disease (5), the placenta of an infected woman (6), and even in healthy volunteers (7) lack adequate confirmation (8);
- long-term administration of intramuscular gammaglobulin to numerous French children and adults since the 1960s has, thus far, never been associated with a case of Creutzfeldt-Jakob disease.

It claims that 1 million litres of plasma will be required annually to provide the albumin previously obtained from placentas, and that this use has avoided the waste of a "precious resource".

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### Captopril: indications extended to diabetic renal disease

**United States of America** — The Food and Drug Administration has additionally approved the antihypertensive agent, captopril (Capoten®, Bristol-Myers), for treating nephropathy and preventing renal failure in juvenile-onset (type 1), insulin-dependent diabetics with retinopathy (1), (see also page 4). Previously, diabetic nephropathy could be treated only by haemodialysis or renal transplantation.

Captopril is approved, at present, only for long-term treatment of patients with proteinuria in excess of 500 mg/day. It has not been shown to be effective in adult-onset diabetes or in non-insulin-dependent diabetes.

Labelled adverse effects, which are infrequent, include angioedema of the face, tongue or larynx, hypotension and neutropenia. A warning is also required in labelling to remind doctors that, because of its embryopathic potential, captopril should not be taken during pregnancy.

The manufacturer has claimed that the wholesale cost of treating a patient with captopril for one year

will be about US\$ 700. Dialysis is estimated to cost US\$ 32 000 per year and transplantation US\$56 000 per year (2).

#### Sources

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2. *Scrip*, No. 1896, 11 February 1994, p 21.

## Gangliosides

**Italy** — Following their temporary suspension some months earlier, all preparations containing bovine gangliosides were formally withdrawn by the Italian Ministry of Health in December 1993 (1, 2). Despite earlier restriction of the approved indications to the treatment of diabetic neuropathies and spinal cord lesions, nonspecific use of gangliosides as "neurotrophic" agents secured their continued inclusion among the most widely prescribed products in Italy (3, 4).

Concern about the safety of ganglioside therapy was first raised when it was reported that 8 cases of Guillain-Barré syndrome in treated patients had been reported spontaneously by Italian doctors to the health authorities between 1989 and 1991 (5). Shortly afterwards, gangliosides were withdrawn in Germany where their use was associated with a further 6 cases of the same syndrome (6). The possibility of a causal association was strengthened when another such patient was discovered to have a high titre of antibodies to monosialoganglioside (7).

The implication was that, when gangliosides form complexes with serum or tissue proteins, they become potentially immunogenic. However, it was subsequently shown that these antibodies can be demonstrated in some 30% of patients with Guillain-Barré syndrome who have not received gangliosides (8). Moreover, the possibility of a causal relationship between drug exposure and disease was brought into question when an epidemiological study failed to associate use of gangliosides with the syndrome (9).

The credibility of the latter study was immediately challenged on the grounds that it could not reliably exclude even a 200-fold increase in risk among patients treated with gangliosides (4). Its conclusions have been further undermined by two recently published series of cases reported from Spain (10) and Italy (11), respectively, that describe a total of

43 patients with Guillain-Barré syndrome who had been treated either with a mixture of gangliosides or with purified monosialoganglioside. The indications for ganglioside treatment in these patients as well as the interval between start of treatment and onset of the syndrome render unlikely the possibility that gangliosides were prescribed in any of these cases for unrecognized presentations of the Guillain-Barré syndrome. Moreover, 11 of 15 patients in one of the studies was demonstrated to have high antibody titres to monosialoganglioside. The authors conclude that "until larger epidemiological surveys allow better definition of this risk, health authorities in countries where these drugs are marketed should consider that a large number of patients may remain exposed to a rare but severe adverse effect."

Gangliosides were marketed in Italy by several companies including: Fidia (Cronassial, Sinassial, Sincronal, Sygen®); Medici (Megan®); and Rhone-Poulenc (Biosinax®).

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## Influenza vaccine formulations for 1994

WHO has advised national health authorities and pharmaceutical companies that the following virus strains should be used to produce vaccines against seasonal influenza outbreaks in 1994:

- an A/Shangdong/9/93 (H<sub>3</sub>N<sub>2</sub>)-like strain;
- an A/Singapore/6/86 (H<sub>1</sub>N<sub>1</sub>)-like strain;
- a B/Panama/45/90-like strain.

This differs from the formulation recommended in 1993 in that the Shangdong strain replaces an A/Beijing/32/92 (H<sub>3</sub>N<sub>2</sub>)-like strain.

The recommendation is based on data gathered from 118 laboratories in 81 countries and from three WHO Collaborating Centres for reference and research on influenza. WHO emphasizes that the specific viruses used in each country should be approved by the responsible national control authority.

**Source:** WHO Press Release WHO/16, 17 February 1994.

## Post-marketing company-sponsored trials: revised guidelines

**United Kingdom** — New guidelines, summarized below, have recently been issued on the conduct of company-sponsored studies undertaken either in general practice or in a hospital setting to evaluate the safety of a marketed medicinal product.

Such studies, it is emphasized, should not be conducted for promotional purposes, nor should the sponsoring company be engaged in a way that might create a perception of a promotional exercise. No inducement for a doctor to participate in a study should be offered, requested or given, but payment in accordance with published scales of fees may be offered in recompense for the work involved and expenses incurred.

The highest standards of professional conduct and confidentiality must be maintained. Personal

medical records should be accessible only to the patient's doctor who, alone, should hold the key to codes used to protect the identity of patients. Whenever personal information is to be requested from patients, when they are to be allocated systematically to alternative treatments, or when additional investigations are to be performed, the protocol should be referred for clearance to a Research Ethics Committee. A procedure should also be instituted for hearing and investigating complaints concerning scientific, ethical or promotional matters, including possible scientific fraud, and, when appropriate, transgressions should be referred to the professional disciplinary body.

At issue are all "formal investigations conducted for the purpose of assessing the clinical safety of marketed medicines in clinical practice." The emphasis is on clinical practice, not merely on surveillance, and the aim may be either to investigate possible hazards, or to identify previously unrecognized safety issues.

Four types of study design are considered:

In *observational cohort studies*, collaborating doctors should be provided with the approved data sheet for each drug to be used within the study. The patients selected should be as representative as possible of the general population of users, unless a particular subgroup is specifically targeted by the objectives of the study. The decision to prescribe a drug and the decision to include the patient in the cohort should be independent one from the other. Under no circumstances should a patient be prescribed a particular medicine with a view to involvement in a study: a drug must be prescribed solely on the basis of a normal clinical evaluation, and a justification for the prescription should be included in the study records for each patient. The study plan should stipulate the maximum number of patients to be entered by a single doctor, and no patient should be entered into more than one study simultaneously.

*Case-control studies*, in which comparison is made between the history of drug exposure of patients with the presumptive adverse effect and appropriate controls without this condition, are usually conducted retrospectively. The design of the study should attempt to account for known sources of bias and confounding.

*Case surveillance*, which seeks to establish or exclude drug exposure among patients with diseases that are likely to be drug-related and

appropriate controls, raise particular problems of design. Sponsoring companies are requested to liaise particularly closely with the regulatory authority when determining the most appropriate arrangements for reporting cases.

*Large clinical trials* can sometimes be useful in the investigation of postmarketing safety issues. They may involve random allocation to alternative treatments, but in other respects patients should be studied under conditions that are as normal as possible. The design and conduct of studies should conform to prevailing guidelines for phase IV clinical trials. Exclusion criteria should be limited to contraindications cited in the approved data sheet unless they are closely related to the particular objectives of the study.

In all instances, the responsibility for the conduct and quality of a company-sponsored study should be assumed either by a named registered medical practitioner within the medical department of the company, or a named medically-qualified agent engaged by the company to supervise the trial and liaise with the medical department. Consideration should be given to the appointment of an independent advisory group to oversee the study and to monitor aspects of the trial relevant to the safety of patients.

**Source:** *Guidelines for company-sponsored safety assessment of marketed medicines.* Medicines Control Agency; Committee on Safety of Medicines; Royal College of General Practitioners; British Medical Association; Association of the British Pharmaceutical Industry, November 1993.

### **The WHO Certification Scheme revisited: bilateral collaboration between the USA and the Russian Federation**

A bilateral agreement recently concluded between the United States and the Russian Federation provides for any pharmaceutical or biological product (with the exclusion of homoeopathic products) authorized for marketing in the US by the Food and Drug Administration to qualify for expedited registration within the Russian Federation. Registration of controlled substances will require the additional approval of the Federation's State Committee on Controlled Substances.

In essence, the Russian Federation has agreed to accept the FDA's regulations and decisions on

premarketing approval, licensing, monographs and related matters, as well as FDA's product quality standards and enforcement of manufacturing controls and other requirements.

US companies seeking to take advantage of these provisions to export a product will need to provide the following elements of information:

- a letter establishing the trading name of the company, the identity and signature of its authorized responsible representative, and a declaration that the drug has been produced in the USA;
- a copy of the letter from the FDA indicating that the product has been authorized for marketing within the USA;
- a copy and Russian translation of the FDA-approved product package insert, and a sample of the product in the proposed packaging;
- a copy of the official monograph as published in the US Pharmacopeia;
- a signed statement that the company is in compliance with FDA's current Good Manufacturing Practice Regulations;
- a copy of the most recent inspection report relevant to the manufacture of the product.

The company is also required to provide an attestation that all information provided is truthful, accurate and complete, and that any change relating to the information supplied will be communicated within a period of 30 days.

The Federation reserves the right to request additional documentation for the registration of vaccines and sera. For other products — and provided the agreed documentation is supplied — it has undertaken not to require any additional clinical or analytical review or testing of the product as a condition of importation.

Each country will supply the other with copies of laws, regulations, guidelines, and procedures concerning the registration of these products. Confidentiality of information will be respected on both sides, consultations will be arranged — and a coordinating committee may be established in which nationals of both countries will be represented — to promote cooperation and to facilitate implementation of the agreement.

Both in general concept and in the elements of information provided to support the product licensing process, the scheme corresponds closely with the WHO Certification Scheme. The most striking difference resides in the extent to which the bilateral scheme places the exporting manufacturer on trust to provide valid information directly to the competent authority in the importing country. The Certification Scheme, in contrast, invests the authority of the exporting country with the responsibility to transmit attested information. Within the limited field of application of a bilateral agreement involving exports from one of the world's most highly regulated drug markets, less rigorous precautions to assure the authenticity of information are doubtless acceptable. Within the multilateral context of the Certification Scheme, however, the active involvement of the national authority in the exporting country as a guarantor of standards remains a vital safeguard.

**Source:** Memorandum of Understanding between the Food and Drug Administration of the US Department of Health and Human Services and the Ministry of Health and Medical Industry and the State Committee for Sanitary and Epidemiological Surveillance of the Russian Federation, 28 January/15 February 1994.

## Corticosteroids and chickenpox

**United Kingdom** — The Committee on Safety of Medicines has advised doctors that a diagnosis of chickenpox (varicella) should not be overlooked in any patient receiving systemic corticosteroids who presents with fever and systemic illness (1). In these circumstances, the illness requires specialist care and urgent treatment, perhaps with aciclovir. Corticosteroids should not be stopped and the dose may need to be increased.

Varicella, which is normally a mild illness, results in about 30 deaths annually in the UK, and a recent case control study indicates that the risk of severe disease — whether it presents clinically as chickenpox or herpes zoster — is substantially increased among patients receiving systemic corticosteroids (2). Immunosuppression resulting from leukaemia or other underlying illness, or from cytotoxic drugs is also a risk factor.

The Committee emphasizes that severe chickenpox is rare and should not deter doctors from prescribing systemic corticosteroids. However, they are urged to take the following precautions to identify and minimize the risk:

- patients (or parents of children) at risk who use systemic corticosteroids should be advised to take reasonable steps to avoid close personal contact with cases of chickenpox or herpes zoster.
- patients at risk should be advised to seek urgent medical attention if exposed to chickenpox. Passive immunization with varicella-zoster immunoglobulin is needed by non-immune exposed patients who are receiving systemic corticosteroids or who have used them within the previous three months. Preferably this should be given within 3 days and not later than 10 days after exposure to chickenpox.

## References

1. Committee on Safety of Medicines. Severe chickenpox associated with systemic corticosteroids. *Current Problems in Pharmacovigilance*, Vol. 20, February 1994.
2. Dowell, S., Bresee, J. Severe varicella associated with steroid use. *Pediatrics*, **92**: 223-228 (1993).

## Rifabutin and uveitis

**United Kingdom** — The Committee on Safety of Medicines is aware of 48 cases of uveitis reported worldwide among patients receiving rifabutin (1). This is a relatively new rifamycin antibiotic that has both antibacterial and antiviral properties and which has previously been associated with a dose-related and reversible polyarthralgia-arthritis syndrome at doses exceeding 1 g daily (2). Its activity against *Mycobacterium avium* complex infections in patients with HIV infection is of particular interest, and it is in such patients that the majority of these reactions have been reported.

These patients were receiving combination antibiotic therapy which, in most instances, also included clarithromycin and fluconazole. Pending full results of interaction studies, which at present suggest that concomitant treatment with the latter drugs may substantially increase serum levels of rifabutin, the Committee has advised doctors that they should consider reducing the daily dose of rifabutin to 300 mg in patients also receiving macrolide antibiotics or triazole antifungals. Any patient who develops uveitis while receiving rifabutin should immediately be withdrawn from treatment and be referred to an ophthalmologist.

## Source

1. Committee on Safety of Medicines. Rifabutin (Mycobutin): uveitis. *Current Problems in Pharmacovigilance*, Volume 20, February 1994.

2. Siegal, F. Dose-limiting toxicity of rifabutin in AIDS-related complex: syndrome of arthralgia/arthritis. *AIDS*, 4: 433-441 (1990).

### Oral L-tryptophan: limited reinstatement for depression

**United Kingdom** — Preparations of oral L-tryptophan, which were indicated in the treatment of depressive illness, were withdrawn in the UK in April 1990 following reports of their association with eosinophilia-myalgia syndrome (EMS). This is a potentially fatal multisystem disorder characterized by eosinophilia (usually in excess of 2000/mm<sup>3</sup>), severe myalgia, arthralgia, oedema and rash. The lungs and central nervous system may also be involved.

Although the outbreak has never been fully explained, it was subsequently suggested that at least some of these cases were attributable to an impurity. In the current state of knowledge, use of L-tryptophan can no longer be justified in most cases of depression. However, with the introduction of stricter manufacturing controls, one brand (Optimax®, E. Merck Pharmaceuticals) will shortly be reintroduced in the UK specifically for resistant depression.

The Committee has requested that any suspected adverse effects of the preparation be reported immediately and, in view of the continuing uncertainties, the labelling will indicate that it has been reinstated subject to the following restrictions and conditions:

- it should be prescribed only by hospital specialists; for patients who have had severe depressive illness continuously for more than 2 years; after an adequate trial of standard drug therapy; and as an adjunct to other medication;
- patients will remain under close and regular surveillance for as long as they receive L-tryptophan with particular attention to eosinophil counts and symptoms or signs suggestive of EMS.

To assure such attention, Optimax will be supplied only if both the doctor and the patient are registered with a monitoring scheme operated by the product licence holder, that will provide information to the Committee on the patient's progress at 3 months and subsequently at 6-month intervals.

**Source:** Committee on Safety of Medicines. L-tryptophan (Optimax): limited availability for resistant depression. *Current Problems in Pharmacovigilance*, Vol. 20, February 1994.