WHO Drug Information

Contents

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Herbal Medicines

Herbal medicinal products in the European Union

European pharmaceutical law classifes herbal products as “regular” medicinal products if they claim to treat or prevent ilness or if they are to be administered with a view to restoring, correcting or modifying physiological functions (1). Several decisions of the European Court of Justice confirm this status. There are examples where a herbal preparation, such as peppermint tea, could be either food or medicine, depending on the claim made for the product. In other cases, such as for senna extract, a product has to be declared a medicine (notwithstanding the labelled claim) by virtue of its pharmacological action: in this case that of a laxative stimulant. The characteristics of herbal medicinal products make regulatory assessment difficult and present a challenge to health agencies and national authorities.

For centuries, herbal medicinal products have been part of cultural heritage. This may be one reason why herbal medicinal products continue to be widely used in Germany. In a recent study, more than 70% of the German population declared that they used natural medicines, and for most of them herbal medicinal products were the first choice in the treatment of minor diseases or disorders (2). With 39% of the total European market, the German market holds the biggest share by value, followed by France (29%), Italy (7%), Poland (6%) and the United Kingdom (6%). It is important to stress that in Germany and some other European Union countries, herbal medicines are fully integrated into conventional therapies, especially by general practitioners. The share in the prescribed herbal medicines market is 73% in France, 43% in the United Kingdom and 38% in Germany. Herbal medicinal products are found among the top 200 of the 2000 most prescribed medicines that were reimbursed by state-supported health insurances in the year 2000 (3). As an example, a product composed of saccharomyces yeast used for the symptomatic treatment of diarrhoea holds rank 51 with 1.5 million prescriptions, whereas the most popular brand antidarrhoeal, loperamide, is placed at 145 with 851 000 prescriptions. By value, the most important herbals are ginkgo leaves, hypericum, ivy (*Hedera helix*), mistletoe, hawthorn, saw palmetto and horse chestnut.

These data show that herbal medicines are rightly classified as medicinal products because they are used as such. Another reason involves the risks that may be associated with these products. Some herbal medicines may present risks even when properly used. Such risks are mostly mild and can be avoided by appropriate labelling. However, in some cases, the withdrawal of products from the market has been necessary because serious reactions were identified.

An increasing problem is the potential interaction of herbal medicinal products with conventional medicines: the most prominent example here is hypericum. Such risks have to be carefully assessed, balanced against potential benefits and clearly labelled for consumers and health professionals in order to protect public health. Such an approach can be enforced if herbal medicines are subject to pharmaceutical legislation.

An additional aspect that makes herbal products a very special group is the particular character of the quality requirements. Herbal products are, even if they contain only one herb, very complex biological mixtures and in most cases it will not be possible to identify a certain chemical constituent responsible for the efficacy of the product in question. Consistent production parameters and process validation become increasingly important to achieve reproducible efficacy. Because of this complexity, strict quality control is a prerequisite for safety. There are plenty of examples where insufficient quality control has led to toxic effects, such as by contamination with heavy metals or adulteration with toxic plants.

Since many herbal products rely on traditional use, only very few new clinical studies are available. Industry is not motivated to perform such studies, because the results cannot be patented and protec-

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Lecture presented at the 26th International Conference on Internal Medicine, Kyoto May 25-30, 2002, by Konstantin Keller, Federal Institute for Drugs and Medical Devices, Bonn, Germany, and Chair of the EMEA / CPMP Herbal Medicinal Products Working Party.

tion of intellectual property is practically absent. Clinical trials with herbal medicinal products pose specific difficulties. For essential oils, blinded studies are not feasible because of their strong smell and taste. Recent studies with hypericum in major depression demonstrate that in studies with an active comparator, sertraline in the case of hypericum, the comparator was unblinded due to side effects (6). This makes the interpretation of results very difficult. Finally, anyone who has been involved in the design of clinical trials will agree that trials that are particularly important for herbal medicines (i.e. symptomatic treatment of minor conditions in an over-the-counter (OTC) environment) are most difficult to plan and perform.

Regulatory action

These specific challenges were acknowledged at the Eighth International Conference of Drug Regulatory Authorities (ICDRA), in Bahrain in1996. WHO Member States were encouraged to establish groups of experts for herbal medicines in their own countries and regions and to update national legislation in order to allow registration of herbal medicinal products. This was reconfirmed at the Ninth ICDRA in Berlin in 1999.

In 1996, the European Parliament requested facilitated systems for marketing of herbal medicinal products; and in 1997 a specific Herbal Medicinal Products Working Party was created at the European Medicines Evaluation Agency (EMEA). A permanent working group is now composed of delegates from all member countries of the European Union, experts and observers from future new member countries, the European Commission, European Parliament and European Pharmacopoeia.

The main focus of the group is to facilitate mutual recognition of marketing authorizations within the European Union by preparing guidance for documentation and assessment of quality, safety and efficacy of herbal medicines. In addition to these tasks, the group may give advice on pharmacovigilance action and on future legislation. All documents prepared by the group are available from http://www.emea.eu.int. The work of the group is complemented by the European Pharmacopoeia that has established two working parties to prepare general and specific monographs on herbal drugs. These monographs are fully integrated into the official European Pharmacopoeia.

Quality assurance

Quality assurance and control of herbal medicinal products has to start at a very early stage, i.e. at collection or agricultural production of a medicinal herb. A specific guideline addressing this aspect was published recently. Two other documents defining criteria on how to test quality and how to set appropriate specifications are available as well. One important part of both guidelines is the glossary that explains how the term “herbal medicinal product” is defined in the European Union. It should be understood that isolated constituents such as digoxin, taxol, or menthol are not classified as herbal drug preparations.

Safety and efficacy

The most controversial topic relates to assessment of the safety and efficacy of herbal medicines. The European Union facilitates the registration of well-established and traditional herbal medicinal products by permitting different types of applications for marketing authorization.

Herbal medicines may be authorized on the basis of new pre-clinical tests and new clinical trials. This type of full dossier application is mandatory for any new product, including herbals. The same type of dossier is required if a completely new indication is requested for a product that has already been marketed for a different use. However, if the product has “well-established medicinal use with recognized efficacy and an acceptable level of safety” an applicant may substitute new tests and trials by reference to bibliographic data.

The concept is based on the idea that long-term use in humans will probably have resulted in sufficient and even more reliable experience than animal experiments could ever provide. Factors that have to be taken into account are the time and extent of use, the amount and quality of bibliographic information and the consistency of that information. A minimum time frame of ten years of medicinal use within the EU is requested.

The European Herbal Medicinal Products Working Party has clarified the extent of pre-clinical data that are required for a bibliographic application for a herbal medicinal product: new studies should concentrate on effects that are difficult — or even impossible — to detect clinically. This includes data on mutagenicity / genotoxicity, toxicity on reproduction and carcinogenicity. If sufficient experience in

humans can be extracted from the literature, tests such as single dose toxicity, repeated dose toxicity, immunotoxicity and local tolerance are not required. Due to the complex composition of herbal medicinal products, pharmacokinetic studies are not required unless there are safety concerns.

A specific guideline addresses the assessment of efficacy. The strategy is to follow the concept of evidence-based medicine and to require evidence that will relate to the type of claim, e.g. treatment of symptoms, cure or prophylaxis of disease, etc. and seriousness of diseases. For the treatment of symptoms in minor disorders, a lower level of evidence will be acceptable if experience with a particular herbal medicinal product is well documented and plausible on the basis of pharmacological data. However, such an approach can only be accepted if the product does not present any risk to the consumer / patient. For more serious conditions, or if the product may present any direct risk, a higher level of evidence must be provided and the therapeutic alternatives have to be carefully considered.

This concept is in line with WHO guidelines (5) published in 2001, and similar approaches in other countries, such as Australia. On the basis of this concept, agreement has been reached for a number of herbal drugs, and core data have been published. These core data give a summary of the herbal product characteristics, including indications, contra-indications, side effects, warnings, etc. An example would be isphagula husks, where different levels of evidence support three different indications.

Despite the fact that these two types of marketing authorization will be appropriate for a great number of herbal medicinal products, especially those covered by monographs published by the WHO (6) or the European Scientific Cooperative on Phytopharmaceuticals, ESCOP, (7) it is evident that there will be traditional herbal medicinal products that do not dispose of sufficient bibliographic evidence. As an example, the hop plant has been used as a mild sedative for centuries but experimental or clinical data are virtually absent. The question was raised whether such products should be classified as food or whether a third level should be introduced under pharmaceutical law.

The European Union has decided to introduce a new category of traditional medicines into pharmaceutical legislation and a proposed Directive is about to be discussed by the European Parliament (8). The benefit of this regulation will be that traditional medicines are classified, labelled and controlled as medicines. This will include strict quality control, compliance with good manufacturing practice (GMP), control of safety, and application of all rules and regulations related to pharmacovigilance.

Herbal medicinal products that have been used for at least 30 years, with a minimum of 15 years in the European Union, will be eligible for registration as a traditional medicinal product. In respect of quality-related data, such registration will be identical to full marketing authorization. The applicant has to submit bibliographic evidence that the product is safe. For the documentation of efficacy, the applicant must produce expert evidence of the traditional use that makes the claim of efficacy plausible — even though scientific evidence is not available. A new committee will be set up to publish European lists of traditional herbal substances and monographs on traditional and well-established herbal medicinal products. These lists and monographs will serve as the basis of any marketing authorization within the EU unless new evidence is submitted.

This threefold requirement for more complete evidence for new products and for treatment options in serious diseases, lesser evidence for minor claims, and allowing a "traditionally used" label for really traditional herbal medicinal products, will guarantee protection of consumers from fraudulent and unsafe herbal medicines while allowing access to well-founded and safe treatment options.

In summary, the European experience is that herbal medicines are rightly classified as medicinal products because they are used in the same way as any other medicine, they may have risks that must be identified, assessed and labelled as with any other medicine; they have clear pharmacological effects and need, probably more than many chemically defined pure substances, strict quality control and adherence to GMP.

To do this, specific experience and expertise is needed coupled with fair assessment of long-term experience; while marketing authorization procedures have to be adapted to this special group of medicines.

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Current Topics

Miltefosine registered for visceral leishmaniasis in India

Scientists have developed a new treatment for visceral leishmaniasis — a disease also known as "black fever" and "kala azar". The new drug, miltefosine (Impavido®) could potentially save most of the 60 000 people who die from the disease every year. Miltefosine is likely to cost less and is much easier to deliver than all current therapies. In clinical trials, it cured 95% of treated patients.

Miltefosine is the first oral drug against leishmaniasis. It moved from the laboratory bench through to registration in 6 years (most medicines take twice as long) thanks to collaboration between the Government of India, the drug's manufacturer, German biopharmaceutical company Zentaris, and TDR (Tropical Diseases Research), a programme co-sponsored by UNDP, the World Bank, and WHO. Miltefosine has now been approved for use in India, which has 50% of the global burden of visceral leishmaniasis. With this drug, the Government of India hopes to reach its goal of eliminating leishmaniasis by 2010.

Leishmaniasis is a parasitic disease transmitted through the bite of the sandfly. The disease is found in 88 countries. While the 350 million people living in these areas are the most vulnerable, others at risk are travellers, vacationers, missionaries, development workers and soldiers. The regions where leishmaniasis is endemic have expanded significantly since 1993. Mass population movements are fuelling the growing epidemic. Major outbreaks in Brazil, for example, were triggered by large migrations of rural populations to the suburbs of the country's largest cities. An outbreak in Sudan killed 100 000 in an area with a population of less than 1 million. More recently, co-infections of leishmaniasis and HIV are becoming more common. The interaction of the two diseases makes each more destructive, accelerating the onset of AIDS and shortening the life of HIV-infected people.

Until now, all treatments for the disease have had substantial drawbacks. Some are toxic and can cause permanent damage such as diabetes. Up to 60% of cases in India are now resistant to the first-line drug. Other drugs trigger dangerous reactions that can be lethal in about 9% of patients. Some treatments require injections while others need to be provided intravenously over a period of 15 to 30 days in hospital. And all are so expensive that the people infected are unable to afford them.

Asta Medica originally developed miltefosine to fight breast cancer, but TDR scientists discovered that it also had an effect on the leishmaniasis parasite. No drug is without some side effects. The drug can induce vomiting, but this is not strong and usually limited to a few days. Due to a potential danger to the foetus, care must be taken when administering the drug to women of child-bearing age. Studies are under way in India to assess how well the drug performs in a real life situations and its potential long term impact on the control of leishmaniasis.

Researchers hope the future will yield better methods of diagnosing visceral leishmaniasis. In many tropical settings, the high fever brought on by the disease is easily confused with malaria. An easy to use test would greatly facilitate visceral leishmaniasis control. Trials, supported by TDR, of such diagnostic kits are now under way in Ethiopia, Kenya and Sudan.

Reference: *Weekly Epidemiological Record*, **77**: 210–212 (2002) and http://www.who.int/tdr

Tetanus vaccine pre-filled injection device

UNICEF has announced concentrated efforts to deliver a vaccine against maternal and neonatal tetanus in an effort to potentially save the lives of thousands of women and their newborn children. The first campaign, begun in Mali, is being enhanced by the introduction of a pre-filled injection device that will make it easier to immunize women in remote areas. The new device is a single dose, pre-filled syringe with tetanus toxoid that can be administered by lay people.

Maternal and neonatal tetanus can be eliminated globally through immunization and hygienic birth practices. But it has often been difficult to reach

women and children in remote communities since the traditional vaccine can only be administered by trained health workers. As a result, last year alone, tetanus claimed the lives of 200 000 newborns and 30 000 women in 57 developing countries.

Since lay people can use the new device, traditional birth attendants, teachers and community workers are being trained to support health workers in immunizing women in communities without access to clinics or health centres.

The pre-filled device has additional advantages:

- It is a single-use needle and syringe, reducing the possibility of transmission of blood-borne diseases such as HIV and hepatitis.
- It has a very small needle, about an inch long, making it easier to dispel fears of needles and vaccinations.

UnijectT® is manufactured by Becton, Dickinson and Company and Bio Farma produces the vaccine and fills the syringe. The two companies have jointly donated 9 million units to UNICEF over the next three years for use in the collaborative effort to eliminate maternal and neonatal tetanus.

The global campaign to eliminate maternal and neonatal tetanus is being spearheaded by Ministries of Health, UNICEF, WHO, UNFPA, PATH, BASICS, Save the Children (US) and other partners. The Maternal and Neonatal Tetanus Elimination Initiative has received major donations from the Government of Japan, the US Fund for UNICEF, the UK National Committee for UNICEF, Ronald McDonald House Charities, The Bill and Melinda Gates Foundation, and Becton Dickinson.

About maternal and neonatal tetanus

Neonatal tetanus is a deadly disease, common in poor countries, mostly affecting populations with little or no access to basic health care services and education. The disease, which was eliminated in the industrialized world as far back as the 1950s, is still a major killer of infants in the developing world, responsible for no less than 200 000 infant deaths every year and accounting for 14% of all neonatal deaths.

Up to 70% of all babies that develop the disease die in their first month of life. Tetanus occurs as a result of unhygienic birth practices, leading to contamination of the umbilical cord with tetanus spores when it is being cut or dressed after delivery. The disease usually presents itself on the third day after birth, causing the baby to stop feeding due to stiffness of the jaw muscles. The baby then goes into painful convulsions, coma and eventually dies.

Maternal tetanus is also caused by contamination from tetanus spores through puncture wounds, and is linked to unsafe and unclean deliveries. Maternal tetanus is responsible for at least five per cent of all maternal deaths, and accounts for up to 30 000 deaths each year.

Unlike smallpox and polio, complete eradication of tetanus is not possible as the tetanus spores can survive outside the human body, in dirt and in the stools of infected people and animals. The disease can be transmitted without any human contact. Over the 2-year period since the Initiative began (in 1999/2000) the partnership has been able to prevent 15 000 additional newborn deaths.

Reference: UNICEF Press Centre, 26 July 2002 http://www.unicef.org/newsline/02pr46mali.htm

Nonoxinol 9 ineffective in preventing HIV infection

Spermicides containing nonoxynol-9 do not protect against HIV infection and, according to a WHO report, may even increase the risk of HIV infection in women using these products frequently (1). The report also advises women at high risk of HIV infection against using nonoxinol 9 spermicides for contraception.

The report contains the recommendations of a meeting of experts convened by WHO's Department of Reproductive Health and Research and the CONRAD Program based in the Eastern Virginia Medical School, USA. The experts also concluded that spermicides containing nonoxinol 9 do not protect against two other common sexually transmitted infections — cervical gonorrhoea and chlamydia.

Nonoxinol 9 is present in most spermicides on the market today. It has been used over the past half-century in a wide range of spermicidal products — vaginal gels, creams, foams, suppositories, sponges, and films, used alone or with other contraceptive devices, such the diaphragm. While it had been hoped that these products might reduce the

risk of sexually transmitted infections, including HIV infection, they have primarily been used as methods of contraception. Estimated numbers of women of reproductive age using spermicides vary from country to country, from less than 1 % in Asia to nearly 17% in some Latin American countries.

In the 1970s and 1980s, laboratory tests showed that nonoxinol 9 could inactivate the organisms that cause gonorrhoea, chlamydial infections, and other sexually transmitted infections, as well as HIV. These findings fuelled hopes that it could be used not only for contraceptive but also for microbicidal purposes. Clinical trials conducted to date do not support these hopes.

On the contrary, two studies mentioned in the report point to an increased risk of sexually transmitted infections, including HIV infection, in women using nonoxinol 9 products. A possible reason, suggested by the findings of other studies, is that nonoxinol 9 can disrupt the epithelium, or wall, of the vagina, thereby potentially facilitating invasion by an infective organism. The frequency of this epithelial disruption seems to depend on the intensity of use of the product — from 18% of women using the product every other day to 53% using it four times a day.

Regarding the use of spermicides for contraception, the report concluded that, when used alone, nonoxinol is only moderately effective for pregnancy prevention but better than no contraceptive method at all. Nonoxinol 9 is sometimes added to male condoms as a lubricant. The experts found no evidence that nonoxinol 9-lubricated condoms provided any more protection against pregnancy or sexually transmitted infections than condoms lubricated with silicone and nonoxinol 9 may cause adverse effects.

Reference: WHO/CONRAD Technical Consultation on Nonoxinol 9 Summary Report of the Meeting held on 9–10 October 2001. http://www.who.int/ reproductive-health/rtis/ index.htm

New formula oral rehydration salts

A new formula for oral rehydration salts (ORS), has been released by the World Health Organization. The new formula ORS, a sodium and glucose solution. is widely used to treat children with acute diarrhoea. Since WHO adopted ORS in 1978 as its primary tool to fight diarrhoea, the mortality rate for children suffering from acute diarrhoea has fallen from 5 million to 1.3 million deaths annually.

The new improved formula is the result of extensive research sponsored by WHO's Department of Child and Adolescent Health and Development and supported by the United States Agency for International Development (USAID). The latest study was conducted in five developing countries among children from one month to two years old with acute diarrhoea and dehydration.

The study's findings suggest that using the low-sodium, low-glucose ORS formulation reduces the need for intravenous fluids by 33 percent. The effect of this reduction could result in fewer children requiring hospitalization, fewer secondary infections, a diminished need to handle blood with its potentially dangerous consequences, and lower health care costs.

Reduced osmolarity

For more than 25 years, WHO and UNICEF have recommended a single formulation of glucose-based oral rehydration salts to prevent or treat dehydration from diarrhoea irrespective of the cause or age group affected. This product, which provides a solution containing 90 mEq/l of sodium with a total osmolarity of 311 mOsm/l, has proven effective and without apparent adverse effects in worldwide use. It has contributed substantially to the dramatic global reduction in mortality from diarrhoeal disease during the period.

For the past 20 years, numerous studies have been undertaken to develop an "improved" ORS. The goal was a product that would be at least as safe and effective as standard ORS for preventing or treating dehydration from all types of diarrhoea but which, in addition, would reduce stool output or have other important clinical benefits. One approach has consisted in reducing the osmolarity of ORS solution to avoid possible adverse effects of hypertonicity on net fluid absorption. This was done by reducing the solution's glucose and salt (NaCl) concentrations.

Studies to evaluate this approach were reviewed at a consultative technical meeting held in New York (USA) in July 2001, and technical recommendations were made to WHO and UNICEF on the efficacy and safety of reduced osmolarity ORS in children with acute non-cholera diarrhoea, and in adults and children with cholera.

These studies showed that the efficacy of ORS solution for treatment of children with acute non-cholera diarrhoea is improved by reducing its

Reduced osmolarity ORS	grams/litre
Sodium chloride	2.6
Glucose, anhydrous	13.5
Potassium chloride	1.5
Trisodium citrate dihydrate	2.9

Reduced osmolarity ORS	mmol/litre
Sodium	75
Chloride	65
Glucose, anhydrous	75
Potassium	20
Citrate	10
Total Osmolarity	**245**

sodium concentration to 75 mEq/l, its glucose concentration to 75 mmol/l, and its total osmolarity to 245 mOsm/l. The need for unscheduled supplemental IV therapy in children given this solution was reduced by 33%. In a combined analysis of this study and studies with other reduced osmolarity ORS solutions (osmolarity 210-268 mOsm/l, sodium 50-75 mEq/l) stool output was also reduced by about 20% and the incidence of vomiting by about 30%. The 245 mOsm/l solution also appeared to be as safe and at least as effective as standard ORS for use in children with cholera.

The reduced osmolarity ORS containing 75 mEq/l sodium, 75 mmol/l glucose (total osmolarity of 245 mOsm/l) is as effective as standard ORS in adults with cholera. However, it is associated with an increased incidence of transient, asymptomatic hyponatraemia. This reduced osmolarity ORS may be used in place of standard ORS for treating adults with cholera, but careful monitoring is advised to better assess the risk, if any, of symptomatic hyponatraemia.

Because of the improved effectiveness of reduced osmolarity ORS solution, especially for children with acute, non-cholera diarrhoea, WHO and UNICEF now recommend that countries use and manufacture the following formulation in place of the previously recommended ORS solution with a total osmolarity of 311 mOsm/l.

Although this single ORS formulation is recommended, WHO and UNICEF have previously published criteria, which remain unchanged, for acceptable ORS formulations. These criteria are listed below; they specify the desired characteristics of the solution after it has been prepared according to the instructions on the packet:

The total substance concentration (including that contributed by glucose) should be within the range of **200-310 mmol/l**.

The individual substance concentration:

Glucose should at least equal that of sodium but **should not exceed 111 mmol/l**

Sodium should be within the range of **60-90 mEq/l**

Potassium should be within the range of **15-25 mEq/l**

Citrate should be within the range of **8-12 mmol/l**

Chloride should be within the range of **50-80 mEq/l**

International AIDS Society recommendations for antiretroviral treatment: adult HIV infection

Because of increased awareness of the activity and toxicity of current drugs, the threshold for initiation of therapy has shifted to a later time in the course of HIV disease. However, the optimal time to initiate therapy remains imprecisely defined. Availability of new drugs has broadened options for therapy initiation and management of treatment failure. The present updated recommendations written by the International AIDS Society, USA panel, are intended to guide practising physicians in the care of HIV infection and AIDS.

Progress in antiretroviral therapy has resulted in achievements as well as new challenges. The partial restoration of CD4 and CD8 T cell number and function during suppression of HIV replication with potent antiretroviral therapy has resulted in dramatic reductions in morbidity, mortality, and health care utilization. However, the toxicity of many current regimens, suboptimal activity and tolerability, and the emergence of drug resistance all point to the need for effective treatment strategies.

The emerging threshold for initiating therapy is the result of recognition of limitations of currently available agents and is not necessarily a reflection of a major change in understanding of disease pathogenesis, nor an indication that more aggressive treatment approaches should not be pursued.

When to initiate antiretroviral therapy

Highly active antiretroviral therapy (HAART) is usually effective in reducing plasma HIV RNA levels (viral load) in antiretroviral-naive patients, accompanied by a gradual increase in CD4 cell counts. Because currently available antiretroviral regimens will not eradicate HIV, the goal of therapy is to durably inhibit viral replication so that the patient can attain and maintain an effective immune response to most potential microbial pathogens.

Recent cohort data have provided support for the CD4 cell count being the major determinant of initiating therapy. It is clear that antiretroviral therapy should not be delayed until the patient is at high risk for serious opportunistic diseases.

The CD4 cell level above 200/μL at which to initiate therapy remains unclear and the following considerations support use of a CD4 cell count threshold higher than 200/μL.

- Some serious illnesses, especially active tuberculosis and bacteraemic pneumonia, may occur when the CD4 cell count is above 200/μL (16).
- The immune reconstitution syndrome and its associated morbidity may be observed in some patients starting antiretroviral therapy at low CD4 cell counts.
- Some laboratory markers show lower rates of favourable responses when antiretroviral therapy is delayed until the 200 cells/μL threshold is reached.
- Finally, the genetic complexity of HIV in persons increases with time, and this may facilitate escape from host immune defences.

In persons with CD4 cell counts above 350/μL, risk of 3-year clinical progression is low. For persons who have already initiated therapy at higher CD4 cell count thresholds and have had durable HIV RNA suppression and no adverse effects over periods of months to years, it is not clear whether it is safe to discontinue therapy.

Physicians and patients must thoroughly weigh risks and benefits of starting antiretroviral therapy for CD4 cell counts in the 200/μL to 350/μL range and above, and make individualized informed decisions. The strength of the recommendation should depend on the immunologic status, as well as the patient's understanding of and commitment to an often complex regimen.

Therapy continues to be recommended in all patients with symptomatic established HIV infection. Immediate treatment, but not prophylaxis, of a serious opportunistic infection in patients with advanced HIV disease may take precedence over starting antiretroviral therapy. If potential for adverse drug-drug interactions exists, it is wise to choose drugs with minimal or no interactions, or to delay antiretroviral treatment for a few weeks until drugs causing the interactions can be discontinued.

Choice of initial therapy

No drug combination can be defined as the optimal initial regimen in all patients. Therapy should thus be individualized using a number of criteria, including efficacy and durability of antiretroviral activity, tolerability and adverse effects, convenience of the regimen, drug-drug interactions, and potential salvageability of initial regimen. Many patients will ultimately experience at least one treatment failure.

There are currently no data on preferred sequencing of NRTIs. Stavudine and didanosine in combination should be avoided or used with caution in pregnant women because of increased risks of lactic acidosis.

There are generally three types of initial combination regimens that should be considered:

- a protease inhibitor (with or without low-dose ritonavir) with two nucleoside reverse transcriptase inhibitors (NRTIs);
- a non-nucleoside reverse transcriptase inhibitor (NNRTI) with two NRTIs; or
- three NRTIs.

Other regimen combinations include a protease inhibitor (with or without low-dose ritonavir) with an NNRTI plus one or two NRTIs, which should be reserved for special circumstances; and a protease inhibitor (with low-dose ritonavir) with an NNRTI.

Adherence: assessment and reinforcement

Incomplete adherence to one or more prescribed medications is a key cause of virological failure of antiretroviral regimens. Factors that limit full adherence are complex and incompletely defined but may include high pill number and large pill size, medication schedule and dietary restrictions, toxic adverse effects, and ineffective education and support of patients regarding adherence. Progress in developing new drug formulations and fixed-dose combinations that can simplify regimens is encouraging.

Effective communication between patient and provider is essential both before and after treatment has begun. Some health care centres may use non-physicians (pharmacists, nurses, peer educators, and others) to effectively assess and support adherence, but the physician should also be actively involved. Once treatment has begun, weekly contact may be appropriate until the patient has established a consistent daily routine of medication use and has passed the time that any short-term adverse effects would be expected. Reinforcing the need for adherence at every health care provider contact is important.

Changing drugs or therapy

In the absence of virological or immunologic failure, a regimen may pose problems with adherence, intolerance, or cumulative (long-term) toxic effects. As long as the antiviral activity of the overall regimen is maintained, exchanging individual components of the regimen is acceptable.

Treatment failure

The definition of "treatment failure" (a term that subsumes virological, immunologic, or clinical failure) depends on the clinical setting and mirrors the objective of ongoing therapy at a given time in the patient's treatment course.

In the case of the first or second regimen, when virus is wild type or harbours few resistance mutations, maintaining an undetectable viral load is an achievable goal of therapy; in this setting, treatment failure is best defined as inability to achieve a viral load below assay detection limits (<50 copies/mL) or as any sustained return of the viral load to above the target value (>400 copies/mL). With increasing rounds of treatment failure, the level and spectrum of virus resistance may increase, and it may become more difficult to construct an active combination. In patients for whom several regimens have failed, the virus may become multiply resistant, with fewer than three active drugs being available, and the objective of achieving stable undetectable viral load with conventional regimens may be unrealistic. Problems with toxicity may further restrict the number of available drugs.

Treatment failure occurs within the first year of therapy in a substantial proportion of treatment-naive patients. Thus, failure should be anticipated as part of the long-term strategy of antiretroviral treatment.

Adjuvant therapy to antiretroviral drugs

The concept of manipulating the immune response for host benefit has received increased emphasis. Approaches include attempts to augment or dampen the immune response generally, and attempts designed to stimulate relevant HIV-specific immune effector responses. At this point, however, sufficient clinical data do not exist to recommend these approaches beyond the setting of a clinical trial.

Summary

The future of antiretroviral therapy rests with the development of new drugs that will result in simpler, more effective, and less toxic regimens along with development of an improved understanding of innate immune system responses and novel approaches to exploit these responses. Several new agents are currently in development, derived from current drug classes and new drug classes, including entry inhibitors and integrase inhibitors. Potential advantages of these drugs include once-daily dosing, smaller pill size, lower incidence of adverse effects, new viral targets, and activity against virus that is resistant to other drugs in the respective classes.

The benefits of current and future agents will continue to be felt by HIV-infected persons in the developed world. Extending these benefits to those living with HIV in the developing world is a challenge that needs to be met.

Reference: Yeni, P.G., Hammer, S.M., Carpenter, C.J. et al. Antiretrocvial treatment for adult HIV infection in 2002. *Journal of the American Medical Association*, **288**: 222–235 (2002).

Good Clinical Practices

Development of Chinese good clinical practices (GCP)

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State Drug Administration
Beijing, China

The State Drug Administration (SDA) was established in August 1998 to enhance government administration of drug regulation and took over responsibility for regulating pharmaceutical products and medical devices from the Ministry of Public Health. Through new regulations, the SDA is making efforts to upgrade pharmaceutical regulations and strengthen their implementation to meet international standards and thereby ensure the safety and efficacy of medicines. In line with China's adhesion to the World Trade Organization (WTO), the SDA will continue to improve pharmaceutical product legislation and will implement the “rule of law” in the pharmaceutical sector, including regulations covering clinical trial performance and protection of trial subjects, through good clinical practices (GCP).

On 28 February 2001, the newly revised Drug Administration Law of the People’s Republic of China was approved by the National People’s Congress and entered into force on 1 December, 2001. Detailed Rules of Drug Administration Law are about to be promulgated. The main objectives of the new regulations and law are:

1. To ensure protection of rights, safety and welfare of human subjects.

2. To conform with international, generally recognized principles on clinical trials, ethical standards and scientific principles.

3. To ensure that clinical trials of all drugs, including biotechnology products and traditional medicines (in whatever phase, including human bioavailability or bioequivalence studies) are performed according to Chinese GCP.

4. To ensure that the clinical trial process is standardized and the results scientific and credible.

5. To emphasize the importance of ethics committees and informed consent to ensuring the protection of trial subjects.

Drug Administration Law

The new law addresses implementation of clinical trials in China. This law has been enacted to:

- strengthen drug administration;
- ensure drug quality and safety; and
- protect people's health and their legitimate rights and interests in the use of drugs.

All institutions and individuals engaged in research, production, distribution, use, or administration of drugs in the People’s Republic of China shall abide by this law. The drug regulatory authority, the SDA, is responsible for drug administration nationwide. Practical, effective and new drug administrative procedures covering research and development of new drugs are included in the new law.

Before approval for conducting a clinical trial can be obtained, a dossier for new drug research and development should be submitted to the SDA specifying:

- the manufacturing process;
- quality specifications;
- results of pharmacological and toxicological studies;
- related data and samples.

Finally, this new law clearly indicates that the clinical research institution shall implement GCP. Therefore, Chinese GCP has become an important part of law which can be legally enforced.

Major regulations on new drug clinical evaluation

China has made significant progress in recent years to improve its medicinal product regulatory and evaluation procedures. Within the structure of

Table 1. Regulations concernig new drug evaluation and management in China

Key elements related to GCP and protection of trial subjects in the New Drug Approval provisions

1. The sponsor and clinical research institution shall comply with the requirements of "good clinical practice" (GCP) stipulated by the State Drug Administration when a clinical study for a new drug is carried out.

2. When submitting the application for a clinical trial, the sponsor should select the principal clinical research institution and the research sites from the clinical research bases designated by the SDA (except for Phase IV clinical trials). The selection should be approved by the SDA. If an additional research site is needed or the clinical study will be performed in hospitals other than clinical research bases for a particular reason, additional applications should be submitted for approval.

3. The designated clinical research institutions should be aware of the properties, action, efficacy and safety of the test drug. The institution should subscribe to the clinical trial protocol with the sponsor in accordance with the requirements of GCP and conduct the trial strictly in line with the protocol.

4. The sponsor should appoint a qualified person to monitor the clinical trial so as to ensure implementation of the protocol in compliance with the requirements of GCP. Drug administration bodies at provincial level are responsible for the supervision and inspection of the clinical study as requested by the SDA.

5. In case of the occurrence of serious adverse events during the clinical study, the research sites must immediately take all necessary measures to protect the subject from risk, and report the events to the local drug administration at provincial level and the SDA within 24 hours.

the SDA, two major departments deal with drug registration and drug safety and inspection. They are jointly responsible for the evaluation and inspection of conducting clinical trials and inspecting new drugs. Since April 1999, certain provisions have been introduced by SDA to replace and update regulations established in 1985. Table 1 above gives details of major regulations on new drug clinical evaluation and their interaction.

Development of Chinese GCP

In order to guarantee the safe and proper use of new drugs, and to participate in international competition and cooperate in the field of medical and pharmaceutical science, technology and trade, the drug regulatory department and scientists in China are fully aware that Chinese regulations and laws regarding the development of a new drug must be in line with international standards. SDA concluded that the existing regulations were inappropriate for the change from a planned to a market economy, in particular after China's entry into the WTO. Since 1992, China recognizes GCP as the international ethical and scientific standard for designing, conducting, recording, and reporting clinical trials that involve the participation of human subjects.

The *International Guidelines for Biomedical Research Involving Human Subjects*, prepared by the Council of International Organization for Medical Sciences (CIOMS) indicates how ethical principles set forth in the *Declaration of Helsinki* can be effectively applied, particularly in developing countries, with consideration of their socioeconomic circumstances, laws, regulations, executive and administrative arrangements.

Table 2 on page 127 summarizes activities undertaken in the preparation and development of Chinese GCP guidelines. These were adopted by the SDA on 23 July 1999 and entered into force from 1 September 1999

Ethical principles and trial subject protection

Chinese GCP contains 13 chapters and includes 66 articles. The *Declaration of Helsinki* is included as an appendix. Fundamental articles relating to ethics and protection of trial subjects are as follows:

Table 2. Development of GCP in China

1986–1992	Information/data collection
1993	Translation into Chinese of Code of Federal Regulations and FDA guidelines; WHO GCP; GCP from EC, Australia, Canada, France, Japan, Nordic countries, and Republic of Korea
1994	Preparation meeting and workshop on GCP
1995	Establishing a 5 member draft group for Chinese GCP
1996	Training course on GCP; A computer-based clinical research training and reference system was introduced into China
1998	Chinese GCP was promulgated by Ministry of Public Health
1999	Chinese GCP was revised and promulgated by SDA, and entered into effect
2000	GCP training and teaching material published by SDA
2001	Translation into Chinese of ICH GCP and revised Declaration of Helsinki
2002	SDA commences re-revision of Chinese GCP
1999–2001	Training and implementation on GCP by SDA's Training Centre

Table 3. Designation and Development of Drug Clinical Research Bases in China

Year	Number of bases	Disciplines	Designator
1990	46	30	MOPH
1998	113	70	MOPH
2000	132	66	SDA

1. All research involving human subjects shall be conducted in accordance with the ethical principles contained in the *Declaration of Helsinki*, namely justice, respect for persons, beneficence (maximize benefits and minimize harms and wrongs) and non-maleficence (do no harm) (Article 4).

2. Prior to planning a clinical trial in humans, specific aims, problems to be solved, anticipated efficacy and possible risks must be considered thoroughly. Anticipated benefits should prevail over possible risks. The chosen clinical trial solutions must conform to scientific and ethical standards (Article 5).

3. An ethics Committee should be established within the medical institution where the clinical trial is to be conducted to ensure the protection of the rights and welfare of human subjects taking part in the trial and to provide public reassurance (Article 9).

4. Prior to a clinical trial, the protocol must be approved by the Ethics Committee before implementation. During the trial, any subsequent protocol amendment must be approved by the Ethics Committee before its implementation. All serious adverse events occurring during the trial must be reported to the Ethics Committee (Article 10).

5. In order to protect the rights and welfare of trial subjects, the Ethics Committee should review the protocol strictly (Article 12).

6. Investigators, or their appointed representatives, should provide trial subjects with detailed information relating to the clinical trial (Article 14).

7. Informed consent is obtained after a sufficient and comprehensive explanation of the trial (Article 15).

8. The contents of a trial protocol should include the following (Article 17):

- Purpose and objectives of the trial, including the known potential risks and benefits to human subjects.

- Criteria for inclusion and exclusion of trial subjects and process of recruitment, methods of allocation of subjects, withdrawal criteria.

9. The investigator is required to conduct the clinical trial in an institution with sound medical facilities, laboratory equipment and staff. The institution should have all necessary emergency facilities to ensure safety of trial subjects (Article 21).

10. The investigator is responsible for medical decision-making in relation to the trial, and to ensure adequate medical treatment to be provided to the subject whenever any adverse event occurs (Article 24).

11. The investigator is obliged to take necessary measures to ensure the safety of subjects, and such measures should be documented. In case of serious adverse events, the investigator must take appropriate measures to protect subjects, and report to the drug regulatory authorities, the sponsor and the Ethics Committee immediately (Article 25).

12. As soon as a serious adverse event occurs, the sponsor must discuss this with the investigator(s), take necessary measures to safeguard trial subjects, report in a timely manner to drug regulatory authorities, and notify the other investigators involved in the same trial (Article 39).

13. The sponsor should provide insurance and treatment compensation to trial subjects to cover trial-related injuries or death, and provide indemnity (legal and financial coverage) for the investigator, except for claims resulting from medical malpractice (Article 42).

Requirements for foreign agencies conducting clinical studies in China (Interim)

1. A foreign agency can conduct a clinical study in China only after the SDA approves the application filed by the Chinese agent.

2. Foreign products intended to be studied within a clinical study in China must be registered abroad or have entered into Phase II clinical trials for drugs and Phase III for vaccines.

3. The application form for a *Clinical Trial of a Foreign Drug in China* should be completed and submitted with the relevant dossiers for approval.

4. The protocol of the clinical study must be formulated and implemented according to Chinese GCP.

5. If, at any time, the drug demonstrates serious or unexpected adverse reactions in any other countries, it must be reported in a timely way to the SDA according to regulations.

Globalization tends to ignore individual needs, especially those of developing countries. When clinical trials are planned in China, it is the ethical duty of investigators and pharmaceutical companies to consider the specific needs and benefits of the Chinese people. The newly Revised *Declaration of Helsinki* (5th Amendment at the 52 General Assembly, Edinburgh, October 2000) should be followed.

Shortcomings in GCP management

The following problems have been encountered during the application of GCP within China.

1. There is a wide range in the practice and implementation of clinical trials, of considerable variety, (although most leading investigators follow GCP and ICH).

2. In some cases, clinical trials have started without approval by SDA and an ethics committee. This practice also involved foreign vaccine trials.

3. Not all institutions have an ethics committee. In others, the ethics committee may not have the required membership, or correctly follow meeting schedules and record-keeping.

4. Use of a written informed consent containing inadequate information. The explanation given is that doctors worry that if all potential adverse effects are listed in the informed consent form, the subject will not wish to enrol.

6. Conduct of the clinical trial may not follow strictly the protocol.

7. The protocol may be changed or modified without informing the ethics committee and drug regulatory authority.

8. Domestic sponsors are less aware of the *Declaration of Helsinki* and GCP principles.

Conclusion

1. Basic requirements for conducting a clinical trial of medical products in China should meet internationally-recognized principles on ethics issues and protection of subject's rights, welfare and safety.

2. All clinical trials conducted in China should be performed according to the Drug Administration Law, Chinese GCP and related regulations.

3. Familiarity with and implementation of the principles of the Declaration of Helsinki, WHO or ICH GCP will enable data from clinical trials conducted in China to be accepted internationally.

4. It is important for investigators, sponsors and regulatory authorities to join in efforts to improve the current status of implementation of GCP in China thereby protecting subject's rights, welfare and safety.

5. Special guidelines for biotechnology products and vaccine clinical trials should be formulated on the basis of their specific characteristics. More attention should be paid to the safety of vaccines and recombinant products in relation to ethical considerations.

6. A general training programme for medical doctors, manufacturers and the public on the ethical principles and protection of subjects in drug clinical trial is strongly recommended in China in order to comply with international standards.

Safety Information

Statins: rhabdomyolysis and myopathy

Statins belong to a class of cholesterol-lowering agents that inhibit the liver enzyme 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. The use of HMG-CoA reductase inhibitors has been associated with severe myopathy, including rhabdomyolysis (1–6).

The statins approved for sale in Canada include atorvastatin (Lipitor®), cerivastatin (Baycol®), fluvastatin (Lescol®), lovastatin (Mevacor®, Apo-Lovastatin®, Gen-Lovastatin®), pravastatin (Pravachol®, Apo-Pravastatin®, Bio Pravastatin®, Lin-Pravastatin®) and simvastatin (Zocor®). In August 2001, Bayer voluntarily suspended the marketing and distribution of Baycol® in Canada (7, 8). The continued scrutiny of postmarketing reports of rhabdomyolysis, including related deaths, has revealed an increased reporting rate of rhabdomyolysis with Baycol compared to other statins, especially when gemfibrozil is prescribed concurrently (7).

The Canadian Adverse Drug Reaction Monitoring Program (CADRMP) has received reports of rhabdomyolysis or myopathy with all statins approved for sale in Canada (Table 1). In severe cases,

Table 1. Rhabdomyolysis, myopathy and increased CPK reactions associated with statins as reported to the CADRMP from date marketed in Canada to 24 August 2001*

	Drug and year marketed in Canada: no. of reports					
Reaction†	**Atorvastatin 1997**	**Cerivastatin 1998**	**Fluvastatin 1994**	**Lovastatin 1988**	**Pravastatin 1990**	**Simvastatin 1990**
Rhabdomyolysis	10	54	–	12	3	7
Myopathy‡	32	8	5	24	17	34
CPK increased with myopathy‡	16	11	1	6	4	6
CPK increased without myopathy‡	5	6	–	4	6	5
Total no. of reports received	231	121	43	182	123	170

CPK = creatine phosphokinase, CADRMP = Canadian Adverse Drug Reaction Monitoring Program.

** These data cannot be used to determine the incidence of adverse drug reactions because neither patient exposure nor the amount of time the drug was on the market has been taken into consideration.*

†Each report may contain more than one of these reactions; however, reports were only included in the most significant category.

‡ Myopathy may include muscle symptoms such as myositis, myalgia, muscle ache, muscle weakness, muscle cramp, muscle discomfort.

rhabdomyolysis can result in kidney failure (8). The statin cases of rhabdomyolysis outlined in Table 1 with which acute renal failure was also reported were: atorvastatin (2 cases), cerivastatin (15), lovastatin (5), pravastatin (1) and simvastatin (2). The reports of rhabdomyolysis with a fatal outcome were: atorvastatin (1), cerivastatin (2) and lovastatin (1).

Various factors may increase the risk of myopathy and rhabdomyolysis with statins. Rhabdomyolysis can occur with all statins when used alone and particularly when combined with other drugs or chemicals that are themselves myotoxic or that elevate the concentrations of the statin to the toxic range (9). Evidence suggests that myopathy is dose-dependent, (9) and it is usually recommended that statin therapy be initiated at lower therapeutic doses (1–6). Combined use with niacin in lipid-lowering doses, with fibric acid derivatives such as bezafibrate, fenofibrate and gemfibrozil, (1–6) or with drugs or foods that inhibit the cytochrome P450 (CYP450) system, particularly CYP3A4, (including but not limited to cyclosporins, macrolide antibiotics, antidepressants such as nefazodone, azole antifungals and grapefruit juice) can potentially increase the toxicity of statins (1,3,5,6,9)

Atorvastatin, cerivastatin, lovastatin and simvastatin are metabolized mainly by CYP3A4 (10). Lovastatin and simvastatin may particularly be affected by the inhibition of first-pass metabolism, which could result in 10- to 20-fold elevations (oral availability increasing from 5% to 100%) in steady-state concentrations with a marked potential for drug toxicity (9). Pravastatin is not metabolized by CYP3A4 to a clinically significant extent (2). Fluvastatin is metabolized mainly by CYP2C9 (4, 10) and would have a different spectrum of interactions than would statins metabolized by CYP3A4 (9). Further information concerning drug interactions may be obtained from the product monograph of each statin (1–6). In addition, caution should be exercised when using statins in patients with impaired renal function (1–6).

The product monograph of each statin has no clear recommendation for biochemical monitoring of muscle effect (creatine phosphokinase [CPK] measurement). In the absence of symptoms, there is no evidence to suggest that routine monitoring of plasma CPK activity is of benefit (10). However, further investigation is required to provide more definitive monitoring guidelines. It was suggested in a recent review article (10) that it is important to measure the baseline CPK level at least once before starting statin therapy.

Patients taking a statin or a fibrate should be made aware of rhabdomyolysis as a potential side effect. They should be advised to report promptly any signs of muscle problems (i.e., unexplained muscle weakness, tenderness or pain, either occurring at rest or exacerbated by exercise) and dark urine, particularly if these symptoms are accompanied by malaise or fever.

Duc Vu, Mano Murty, and Marielle McMorran, Bureau of Licensed Product Assessment, Canada

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Tamoxifen and risks of thromboembolic events

Tamoxifen is already a widely used hormonal treatment in women following treatment for early and advanced breast cancer. Now, in addition to its use as a treatment in cancer, preliminary results from the International Breast Cancer Intervention Study (IBIS) provide evidence for the use of tamoxifen to prevent breast cancer in healthy women at high risk. The results so far show that the incidence of breast cancer has been reduced by one-third in women at high risk, compared to women taking placebo. However, the study also indicated that tamoxifen can increase the risk of thromboembolism, particularly during and immediately after major surgery or periods of immobility. The Department of Health in the United Kingdom has communicated the following information.

1. The benefits for women being treated for breast cancer with tamoxifen outweigh the risks. It is important that women taking the drug as a treatment continue to do so.

2. There is evidence of some increase in risk from thromboembolism with tamoxifen especially during and immediately after major surgery or periods of immobility. Patients should be made aware of the symptoms of venous thromboembolism and if they have any sudden onset of breathlessness they should consult their doctor immediately.

2. The IBIS study gives evidence of the preventative action of tamoxifen in breast cancer. However this is not a use of tamoxifen that has yet been approved except in the context of clinical trials.

Reference: Urgent Communication from Chief Medical Officer, 27 March 2002. http://www.mca.gov.uk

Oral contraceptives and risk of cervical cancer

The Department of Health in the United Kingdom has issued an urgent communication informing health professionals of a recent study which, although not conclusive, strengthens the evidence that oral contraceptives may contribute to the development of cervical cancer in women with high risk type human papilloma (HPV) (1) .

The study reports an association between increasing risk of cervical cancer and duration of use of oral contraceptives (threefold increase in risk following 5–9 years of oral contraceptive use versus a fourfold increase after 10 or more years) in women with HPV. HPV is a sexually transmitted infection. There are more than 80 HPV viruses, but only a few are associated with an increased risk of cervical cancer. On current evidence it is difficult to state whether it is the use of oral contraceptives, sexual activity, the type of HPV or the duration of HPV infection which is /are the main precipitating factor(s) for cervical cancer.

Furthermore, the original studies were carried out in women from developing countries with no adequate cervical screening programme. While cervical screening is not perfect, between 80% and 90% of cervical abnormalities can be detected and treated in women who attend regular screening programmes. The communication therefore advises that all sexually active women, especially those on long-term oral contraceptives, be encouraged to have regular cervical smears. The benefits of using OCs outweigh the risks in the vast majority of women who use them.

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HIV-associated lipodystrophy syndrome overview

HIV-associated lipodystrophy syndrome (LDS) is a disorder in HIV-infected patients receiving highly active antiretroviral therapy (1–3). It presents as a range of *clinical* (morphologic) and *metabolic* changes. The following clinical changes have been described: body fat redistribution such as visceral adiposity (fat gain within the abdomen, breasts, over the dorsocervical spine and other lipomata) and peripheral lipoatrophy (fat loss in the face, limbs, buttocks). The metabolic changes have included hypertriglyceridemia, hypercholesterolemia, insulin resistance, type 2 diabetes mellitus, impaired glucose tolerance and lactic acidaemia (1, 2, 4). The term “lipodystrophy” has been used to describe fat loss, fat redistribution and, on a broader level, both clinical and metabolic features of HIV-associated LDS (2).

The pathogenesis of LDS is unknown (1). However, it has been associated with combination antiretroviral therapy including protease inhibitors and nucleoside reverse transcriptase inhibitors, the latter having been linked to mitochondrial toxicity (1–3). As well, it has been suggested that LDS features are the result of chronic HIV infection, chronic immunodeficiency or recovery from immune dysfunction (5).

No validated case definition of LDS has yet been formulated. However, a working case definition has been described as having at least one *clinical* feature and at least one *metabolic* abnormality, and no AIDS-defining event or other severe clinical illness or use of anabolic steroids, glucocorticoids or immune modulators within 3 months of assessment (4).

The CADRMP database was searched for LDS-related ADRs up to 31 August 2001. The search focused on metabolic and nutritional disorders and endocrine disorders associated with antiretroviral drugs containing abacavir, amprenavir, delavirdine, didanosine, efavirenz, indinavir, lamivudine, lopinavir, nelfinavir, nevirapine, ritonavir, saquinavir (base and mesylate), stavudine or zalcitabine. A total of 119 ADR reports were found, of which only 4 met the LDS working case definition (Table 1). In addition to the cases described in Table 1, other reports found in the database denoted potential LDS: lipodystrophy (3 cases) and fat disorder (13 cases). These additional cases did not clearly report the presence of combined clinical and metabolic features, possibly because of the available scientific knowledge at that time.

Retrospective studies have reported a prevalence of LDS of 17%–84% among HIV-infected cohorts receiving highly active antiretroviral therapy (6). It is clear that LDS is highly underreported to Health Canada. Reports of ADRs are an important source

Table 1. Cases of potential lipodystrophy syndrome* associated with antiretroviral drugs reported to the CADRMP (up to 31 August 2001)

Reported clinical reactions†	Reported metabolic reactions†	Concomitant drugs	Duration of treatment	Suspect drug reported	
				PI	NRTI
Lipodystrophy	Diabetes mellitus	lamivudine, nadolol, Prevacid®, Zoloft®	NA	–	stavudine
Fat disorder	Hyperglycaemia	lamivudine, stavudine	26 wks	indinavir	–
Fat disorder	Hyperglycaemia, hypertriglyceridaemia	nelfinavir	NA	saquinavir	–
Lipodystrophy, enlarged abdomen	Hypertriglyceridaemia	azithromycin lamivudine, saquinavir, stavudine	Continuing	ritonavir	–

CADRMP = Canadian Adverse Drug Reaction Monitoring Program,
PI = protease inhibitor, NRTI = nucleoside reverse transcriptase inhibitor, NA = not available.

** Met working case definition: at least one clinical feature and at least one metabolic abnormality, and no AIDS-defining event or other severe clinical illness or use of anabolic steroids, glucocorticoids or immune modulators within 3 months of assessment.*

† Based on the "preferred term" of the World Health Organization Adverse Reaction Dictionary (WHOART).

of potential new and undocumented signals. To this end, a pilot project under way within the Therapeutic Products Directorate is promoting increased reporting to Health Canada of ADRs in HIV-infected patients (7). Its purpose is to develop alternative methods and formats for clinicians and patients to report ADRs. One such method proposed for testing in the pilot project is the electronic entry of ADR data as part of the everyday practice of clinicians.

Susanne Reid, Bureau of Licensed Product Assessment, Canada

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**Spontaneous monitoring systems are useful in detecting signals of relatively rare, serious and unexpected adverse drug reactions. A signal is defined as "reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously. Usually, more than a single report is required to generate a signal, depending upon the seriousness of the event and the quality of the information". All signals must be validated before any regulatory decision can be made.*

Regulatory Action

Alosetron hydrochloride: restricted marketing

United States of America — The Food and Drug Administration (FDA) has approved a supplemental new drug application (sNDA) that permits marketing of alosetron hydrochloride (Lotronex®) with restrictions. The manufacturer of the drug will be implementing a risk management and prescribing programme for physicians who wish to prescribe alosetron. The drug's indication has been narrowed to treatment of women with severe, diarrhoea-predominant irritable bowel syndrome (IBS) who have failed to respond to conventional IBS therapy. Limiting the use of alosetron to this severely affected population is intended to maximize the benefit to risk ratio.

Serious and unpredictable gastrointestinal adverse events, including some that resulted in death, have been reported in association with alosetron use. Less than 5% of IBS is considered severe, and only a fraction of severe cases are diarrhoea-predominant IBS. Severe IBS is a chronic condition (in this case, generally lasting more than six months) with symptoms that disable or significantly curtail the daily activities of patients.

The risk management programme is designed to help ensure that patients and physicians are fully informed of the risks and benefits and that only appropriate patients are prescribed the drug. Action follows a recommendation by FDA's Gastrointestinal Drugs Advisory Committee and the Drug Safety and Risk Management Subcommittee of the Advisory Committee for Pharmaceutical Science.

FDA first approved alosetron in February 2000. The manufacturer voluntarily withdrew alosetron hydrochloride from the market in November 2000.

Reference: http://www.fda.gov/cder/drug/infopage/lotronex/lotronex.htm.

Baclofen: abrupt discontinuation dangerous

United states of America — The prescribing information for baclofen injection (Lioresal® Intrathecal) has been updated to include a warning about rare cases of withdrawal that can lead to life threatening sequelae and/or death in patients who abruptly discontinue therapy.

Baclofen injection is indicated for use in the management of severe spasticity of cerebral and spinal origin. A warning has been added to the prescribing information as follows.

Abrupt discontinuation of intrathecal baclofen, regardless of the cause, has resulted in sequelae that include high fever, altered mental status, exaggerated rebound spasticity, and muscle rigidity, that in rare cases has advanced to rhabdomyolysis, multiple organ-system failure and death.

Prevention of abrupt discontinuation of intrathecal baclofen requires careful attention to proper programming and monitoring of the infusion system, refill scheduling and procedures, and pump alarms. Special attention should be given to patients at apparent risk (e.g. spinal cord injuries at T-6 or above, communication difficulties, history of withdrawal symptoms from oral or intrathecal baclofen).

In the first 9 years of post-marketing experience, 27 cases of withdrawal temporally related to the cessation of baclofen therapy were reported; six patients died.

Reference: Novartis Pharmaceuticals Corporation letter posted on the FDA's MedWatch program at http://www.fda.gov/medwatch

Irinotecan: prescribing changes

United States of America — Changes in the prescribing information for irinotecan (Camptosar®), indicated as a component of therapy for first-line treatment of metastatic colorectal cancer in combination with 5-fluorouracil (5-FU) and leucovorin (LV) and for treatment of metastatic colorectal cancer that has recurred or progressed following initial 5-FU based treatment.

The following labelling changes arose following recommendations made at a meeting of the Food and Drug Administration's Oncologic Drugs Advisory Committee.

- Both the bolus and the infusional regimens of CAMPTOSAR plus 5-FU/LV® remain approved for the first-line treatment of patients with metastatic colorectal cancer.

- The starting dose and schedule for both regimens remain unchanged.

The prescribing information has been revised to identify patients at higher risk of severe toxicity, to clarify dose modification guidelines, and to augment the information about management of treatment-related toxicities.

Reference: Pharmacia Oncology Web site http://www.pharmaciaoncology.com

Sodium oxybate/GHB approved for cataplexy

United States of America — The Food and Drug Administration has approved sodium oxybate or gamma hydroxybutyrate (also known as GHB) (Xyrem ®) for treatment of patients with narcolepsy who experience episodes of cataplexy, a condition characterized by weak or paralysed muscles. Because of safety concerns associated with the use of the drug, distribution will be highly restricted.

In the early 1990s, GHB was marketed as a dietary supplement with claims for enhancing athletic performance, sexual activity and for inducing sleep. It was also abused as a recreational drug and is well-known for use in date rape. As a result of a number of serious adverse events, including death, FDA intervened to prohibit marketing of GHB.

Sodium oxybate has been designated as a Schedule III Controlled Substance for medical use, meaning it cannot be sold, distributed, or provided to anyone other than for its prescribed use. Illicit use will be subject to penalties under Schedule I, the most restrictive schedule of the Controlled Substances Act.

Narcolepsy affects about 120 000 people in the United States. This rare condition causes an irresistible tendency to fall asleep even in unlikely circumstances such as in the middle of a conversation or at a meal. Cataplexy, a symptom of this condition, is a sudden loss of muscular control and weakness usually triggered by emotions such as amusement, anger or excitement, and is estimated to affect about 20 000 to 50 000 individuals. The effects of cataplexy range from dropping of the jaw and slumping of the head, to buckling of the legs and even collapse of the whole body. These effects can last for a few seconds or up to many minutes.

Side effects associated with sodium oxybate include confusion, depression, nausea, vomiting, dizziness, headache, bedwetting, and sleepwalking. Abuse could also lead to dependence, i.e, craving for the medicine, and severe withdrawal symptoms. A medication guide further advises patients about proper use, administration and disposal of the drug.

Reference: http://www.fda.gov/medwatch

Rofecoxib: new indication and label changes

United States of America — The Food and Drug Administration has approved new labelling text and precautions for rofecoxib based on the results of the Vioxx Gastrointestinal Outcomes Research (VIGOR) study.

The VIGOR study, a prospective, randomized, double-blind, one year study, evaluated approximately 4000 patients on rofecoxib 50 mg a day (twice the highest approved dose for chronic use) and approximately 4000 patients on the standard dose of naproxen, 1000 mg a day, a nonsteroidal anti-inflammatory drug (NSAID). Patients who were under treatment with low dose aspirin for heart attack prevention were excluded from the study.

The study demonstrated that rofecoxib was associated with a lower incidence of serious upper gastrointestinal(GI) adverse events of major bleeding, perforation and obstruction compared to naproxen. The reduction in risk was over 50 percent in cumulative rates for rofecoxib (.52%) compared to naproxen (1.22%).

An additional finding in the study, however, was that there was a higher cumulative rate of serious cardiovascular thromboembolic adverse events (such as heart attacks, angina pectoris, and peripheral vascular events) in the rofecoxib group (1.8%) compared to the naproxen group (0.6%). Data from two smaller studies comparing placebo and rofecoxib 25 mg daily did not show a difference in the rate of serious cardiovascular thromboembolic adverse events. The relationship of the cardiovas-

cular findings in the VIGOR study to use of rofecoxib is not known.

After carefully reviewing the results of the VIGOR Study, FDA agreed with the Arthritis Advisory Committee recommendations of February 8, 2001 that the label for Vioxx® should include gastrointestinal and cardiovascular information. The committee advised that the NSAID-class warning regarding GI adverse events should be modified, but not removed, from the VIOXX® label. This warning advises patients and their doctors about the risks of GI ulcers, bleeding, and perforation.

The committee also advised that the CV findings should be included in the Vioxx® label to provide doctors and patients with the available data on the potential risks and benefits compared to naproxen. The new labelling information approved by FDA will advise doctors to use caution in prescribing rofecoxib for patients with ischemic heart disease and notes that rofecoxib 50 mg is not recommended for chronic use.

In addition, the geriatric section of the label will reinforce information in the existing standard warning section of all NSAIDs indicating that the elderly are at higher risk of serious GI and renal events such as GI bleeding and acute renal failure.

The Food and Drug Administration has approved a supplemental application for the use of rofecoxib (Vioxx ®) for rheumatoid arthritis in addition to the previously approved indications for osteoarthritis and pain. The new label also provides information from studies of patients with rheumatoid arthritis at the chronic dose of 25 mg rofecoxib compared to naproxen.

References

1. *FDA Talk Paper*, T02–18, 11 April 2002

2. Letter from Merck & Co. Inc. dated April 2002 http://www.fda.gov

Essential Medicines

New procedures for updating the Model List of Essential Medicines

At its previous meeting in 1999, the Expert Committee on Selection and Use of Essential Drugs proposed that methods for updating and disseminating the Model List of Essential Drugs be revised with regard to (i) advances in the science of evidence-based decision-making; (ii) the increasing link between essential medicines and guidelines for clinical health care; and (iii) the high cost of many new and effective medicines. The Expert Committee concluded that current procedures do not define the range of conditions covered with adequate specificity, nor are the reasons for inclusion recorded with sufficient clarity.

In May 2001, an information document containing a proposed timetable for developing revised procedures to update the Model List was presented to the WHO Executive Board and all Member States were invited to comment on a discussion paper "Updating and disseminating the WHO Model List of Essential Drugs: the way forward". Comment was also requested from WHO collaborating centres, members of expert advisory panels, organizations of the United Nations system, nongovernmental organizations, professional associations, national essential medicines programmes, universities, representatives of the pharmaceutical industry, and patients' organizations.

Key features of the new procedure

As a result of the consultation process, a new procedure for updating and disseminating the Model List has been developed. Major features include:

1. Use of the term "essential medicines" as an alternative to "essential drugs" with immediate effect, reflecting the common use of the term "medicines" to describe pharmaceutical preparations used in clinical health care practice.

2. A more systematic approach to encouraging and handling applications for medicines to be included in or deleted from the Model List.

3. A more transparent process for selecting medicines to be included in the list, including systematic analysis of medicines proposed for use in the care of different health conditions (comparing efficacy, safety and, where possible and appropriate, cost-effectiveness).

4. Opportunities for interested parties to comment on both an application and the draft recommendations of the Expert Committee.

5. The full involvement of different WHO departments in the application and selection process, linking the process to clinical guidelines disseminated by WHO.

6. Development of a new WHO essential medicines library which facilitates access to information about medicines on the Model List.

7. Steps to ensure that the Expert Committee operates with full scientific independence as it makes its final recommendations (in line with current practice for decisions on regulatory approval, procurement, and reimbursement within Member States).

At the WHO Executive Board in January 2002 the new procedures were presented in a Report by the Secretariat (1). The Board noted the report and its Annex with the new procedures and the Department of Essential Drugs and Medicines Policy was requested to organize the next meeting of the Expert Committee according to the new procedures while recognizing that due to the relatively short time these could not all be implemented immediately.

References

1. Annex to Document EB109/8 (WHO, 2002), also reproduced on the WHO/Medicines website as "Procedures to update and disseminate the WHO Model List of Essential Medicines". http://www.who.int/medicines

2. Guidelines for Scaling Up Antiretroviral Therapy. http://www.who.int/medicines

3. 2002 WHO Model List of Essential Drugs. http://www.who.int/medicines

WHO Model List of Essential Medicines

Core list (revised in April 2002)

1: Anaesthetics

1.1 GENERAL ANAESTHETICS AND OXYGEN

ether, anaesthetic (1c) (2)	inhalation
halothane (2)	inhalation
ketamine (2)	injection, 50 mg (as hydrochloride)/ml in 10-ml vial
nitrous oxide (2)	inhalation
oxygen	inhalation (medicinal gas)
▫ thiopental (2)	powder for injection, 0.5 g, 1.0 g (sodium salt) in ampoule

1.2 LOCAL ANAESTHETICS

▫ bupivacaine (2, 9)	injection, 0.25%, 0.5% (hydrochloride) in vial
	injection for spinal anaesthesia, 0.5% (hydrochloride) in 4-ml ampoule to be mixed with 7.5% glucose solution
▫ lidocaine	injection, 1%, 2% (hydrochloride) in vial
	injection for spinal anaesthesia, 5% (hydrochloride) in 2-ml ampoule to be mixed with 7.5% glucose solution
	topical forms, 2–4% (hydrochloride)
▫ lidocaine + epinephrine (adrenaline)	injection, 1%, 2% (hydrochloride) + epinephrine 1:200 000 in vial
	dental cartridge, 2% (hydrochloride) + epinephrine 1:80 000

1.3 PREOPERATIVE MEDICATION & SEDATION FOR SHORT-TERM PROCEDURES

atropine	injection, 1 mg (sulfate) in 1-ml ampoule
chloral hydrate	syrup, 200 mg/5 ml
▫ diazepam (1b)	injection, 5 mg/ml in 2-ml ampoule
	tablet, 5 mg

Explanatory Notes

The core list presents a list of minimum medicine needs for a basic health care system, listing the most efficacious, safe and cost-effective medicines for priority conditions. Priority conditions are selected on the basis of current and estimated future public health relevance, and potential for safe and cost-effective treatment.

When the strength of a drug is specified in terms of a selected salt or ester, this is mentioned in brackets; when it refers to the active moiety, the name of the salt or ester in brackets is preceded by the word "as". Many drugs included in the list are preceded by a box ▫ to indicate that they represent an example of a therapeutic group and that various drugs could serve as alternatives. It is imperative that this is understood when drugs are selected at national level, since choice is then influenced by the comparative cost and availability of equivalent products. Examples of acceptable substitutions include:

- ¤ Hydrochlorothiazide: any other thiazide-type diuretic currently in broad clinical use.
- ¤ Hydralazine: any other peripheral vasodilator having an antihypertensive effect.
- ¤ Senna: any stimulant laxative (either synthetic or of plant origin).

Numbers in parentheses following drug names indicate:
(1) Drugs subject to international control under: (a) the Single Convention on Narcotic Drugs (1961); (b) the Convention on Psychotropic Substances (1971); or (c) the United Nations Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances (1988).
(2) Specific expertise, diagnostic precision, individualization of dosage or special equipment required for proper use.
(3) Greater potency or efficacy.
(4) In renal insufficiency, contraindicated or dosage adjustments necessary.
(5) To improve compliance.
(6) Special pharmacokinetic properties.
(7) Adverse effects diminish benefit/risk ratio.
(8) Limited indications or narrow spectrum of activity.
(9) For epidural anaesthesia.
(10) Sustained-release preparations are available. A proposal to include such a product in a national list of essential drugs should be supported by adequate documentation.
(11) Monitoring of therapeutic concentrations in plasma can improve safety and efficacy.

Drugs are listed in alphabetical order.

▫morphine (1a)	injection, 10 mg (sulfate or hydrochloride) in 1-ml ampoule
▫promethazine	elixir or syrup, 5 mg (hydrochloride)/5 ml

2: Analgesics, Antipyretics, Nonsteroidal Anti-Inflammatory Medicines (NSAIMs), Medicines Used to Treat Gout and Disease-Modifying Agents used in Rheumatic Disorders (DMARDs)

2.1 NON-OPIOID ANALGESICS & NON-STEROIDAL ANTI-INFLAMMATORY MEDICINES (NSAIMs)

acetylsalicylic acid	tablet, 100–500 mg
	suppository, 50–150 mg
▫ibuprofen	tablet, 200 mg, 400 mg
paracetamol	tablet, 100–500 mg
	suppository, 100 mg
	syrup, 125 mg/5 ml

2.2 OPIOID ANALGESICS

▫codeine (1a)	tablet, 30 mg (phosphate)
▫morphine (1a)	injection, 10 mg (sulfate or hydrochloride) in 1-ml ampoule
	oral solution, 10 mg (hydrochloride or sulfate))/5 ml
	tablet, 10 mg (sulfate)

2.3 MEDICINES USED TO TREAT GOUT

allopurinol (4)	tablet, 100 mg
colchicine (7)	tablet, 500 micrograms

2.4 DISEASE-MODIFYING AGENTS USED IN RHEUMATIC DISORDERS

azathioprine (2)	tablet, 50 mg
chloroquine (2)	tablet, 100 mg, 150 mg (as phosphate or sulfate)
cyclophosphamide (2)	tablet, 25 mg
methotrexate (2)	tablet, 2.5 mg (as sodium salt)
penicillamine (2)	capsule or tablet, 250 mg
sulfasalazine (2)	tablet, 500 mg

3: Antiallergics and Medicines Used in Anaphylaxis

▫chlorphenamine	tablet, 4 mg (hydrogen maleate)
	injection, 10 mg (hydrogen maleate) in 1-ml ampoule
▫dexamethasone	tablet, 500 micrograms, 4 mg
	injection, 4 mg dexamethasone phosphate (as disodium salt) in 1-ml ampoule
epinephrine (adrenaline)	injection, 1 mg (as hydrochloride or hydrogen tartrate) in 1-ml ampoule
hydrocortisone	powder for injection, 100 mg (as sodium succinate) in vial
▫prednisolone	tablet, 5 mg

4: Antidotes and Other Substances Used in Poisoning

4.1 NON-SPECIFIC

▫charcoal, activated	powder
ipecacuanha	syrup, containing 0.14% ipecacuanha alkaloids calculated as emetine

4.2 SPECIFIC

acetylcysteine	injection, 200 mg/ml in 10-ml ampoule
atropine	injection, 1 mg (sulfate) in 1-ml ampoule
calcium gluconate (2, 8)	injection, 100 mg/ml in 10-ml ampoule
deferoxamine	powder for injection, 500 mg (mesilate) in vial
dimercaprol (2)	injection in oil, 50 mg/ml in 2-ml ampoule
▫DL-methionine	tablet, 250 mg
methylthioninium chloride (methylene blue)	injection, 10 mg/ml in 10-ml ampoule
naloxone	injection, 400 micrograms (hydrochloride) in 1-ml ampoule
penicillamine (2)	capsule or tablet, 250 mg
potassium ferric hexacyanoferrate(II) $\cdot 2H_2O$ (Prussian blue)	powder for oral administration
sodium calcium edetate (2)	injection, 200 mg/ml in 5-ml ampoule

sodium nitrite	injection, 30 mg/ml in 10-ml ampoule
sodium thiosulfate	injection, 250 mg/ml in 50-ml ampoule

5: Anticonvulsants/Antiepileptics

carbamazepine (10, 11)	scored tablet, 100 mg, 200 mg
▫ diazepam (1b)	injection, 5 mg/ml in 2-ml ampoule (intravenous or rectal)
ethosuximide	capsule, 250 mg
	syrup, 250 mg/5 ml
magnesium sulfate	injection, 500 mg/ml in 2-ml ampoule 500 mg/ml in 10-ml ampoule
phenobarbital (1b, 11)	tablet, 15–100 mg
	elixir, 15 mg/5 ml
phenytoin (7, 11)	capsule or tablet, 25 mg, 50 mg, 100 mg (sodium salt)
	injection, 50 mg (sodium salt)/ml in 5-ml vial
valproic acid (7, 11)	enteric coated tablet, 200 mg, 500 mg (sodium salt)

6: Anti-infective Medicines

6.1 ANTHELMINTHICS

6.1.1 INTESTINAL ANTHELMINTHICS

albendazole	chewable tablet, 400 mg
levamisole	tablet, 50 mg, 150 mg (as hydrochloride)
▫ mebendazole	chewable tablet, 100 mg, 500 mg
niclosamide	chewable tablet, 500 mg
praziquantel	tablet, 150 mg, 600 mg
pyrantel	chewable tablet, 250 mg (as embonate)
	oral suspension, 50 mg (as embonate)/ml

6.1.2 ANTIFILARIALS

diethylcarbamazine	tablet, 50 mg, 100 mg (dihydrogen citrate)
ivermectin	scored tablet, 3 mg, 6 mg

6.1.3 ANTISCHISTOSOMALS AND OTHER ANTITREMATODE MEDICINES

praziquantel	tablet, 600 mg
triclabendazole	tablet, 250 mg

6.2 ANTIBACTERIALS

6.2.1 BETA LACTAM MEDICINES

▫ amoxicillin	capsule or tablet, 250 mg, 500 mg (anhydrous)
	powder for oral suspension, 125 mg (anhydrous)/5 ml
ampicillin	powder for injection, 500 mg, 1 g (as sodium salt) in vial
benzathine benzylpenicillin	powder for injection, 1.44 g benzylpenicillin (= 2.4 million IU) in 5-ml vial
benzylpenicillin	powder for injection, 600 mg (= 1 million IU), 3 g (= 5 million IU) (sodium or potassium salt) in vial
▫ cloxacillin	capsule, 500 mg, 1 g (as sodium salt)
	powder for oral solution, 125 mg (as sodium salt)/5 ml
	powder for injection, 500 mg (as sodium salt) in vial
phenoxymethylpenicillin	tablet, 250 mg (as potassium salt)
	powder for oral suspension, 250 mg (as potassium salt)/5 ml
procaine benzylpenicillin	powder for injection, 1 g (= 1 million IU), 3 g (= 3 million IU) in vial

6.2.2 OTHER ANTIBACTERIALS

▫ chloramphenicol (7)	capsule, 250 mg
	oral suspension, 150 mg (as palmitate)/5 ml
	powder for injection, 1 g (sodium succinate) in vial
▫ ciprofloxacin	tablet, 250 mg (as hydrochloride)
▫ doxycycline (5, 6)	capsule or tablet, 100 mg (hydrochloride)
▫ erythromycin	capsule or tablet, 250 mg (as stearate or ethyl succinate)
	powder for oral suspension, 125 mg (as stearate or ethyl succinate)
	powder for injection, 500 mg (as lactobionate) in vial
▫ gentamicin (2, 4, 7, 11)	injection, 10 mg, 40 mg (as sulfate)/ml in 2-ml vial

▫metronidazole	tablet, 200–500 mg
	injection, 500 mg in 100-ml vial
	suppository, 500 mg, 1 g
	oral suspension, 200 mg (as benzoate)/5 ml
nalidixic acid (8)	tablet, 250 mg, 500 mg
nitrofurantoin (4, 8)	tablet, 100 mg
spectinomycin (8)	powder for injection, 2 g (as hydrochloride) in vial
▫sulfadiazine (4)	tablet, 500 mg
	injection, 250 mg (sodium salt) in 4-ml ampoule
▫sulfamethoxazole + trimethoprim (4)	tablet, 100 mg + 20 mg, 400 mg + 80 mg
	oral suspension, 200 mg + 40 mg/5 ml
	injection, 80 mg + 16 mg/ml in 5-ml and 10-ml ampoule
trimethoprim (8)	tablet, 100 mg, 200 mg
	injection, 20 mg/ml in 5-ml ampoule

6.2.3 ANTILEPROSY MEDICINES

clofazimine	capsule, 50 mg, 100 mg
dapsone	tablet, 25 mg, 50 mg, 100 mg
rifampicin	capsule or tablet, 150 mg, 300 mg

6.2.4 ANTITUBERCULOSIS MEDICINES

ethambutol (4)	tablet, 100–400 mg (hydrochloride)
isoniazid	tablet, 100–300 mg
isoniazid + ethambutol (5)	tablet, 150 mg + 400 mg
pyrazinamide	tablet, 400 mg
rifampicin	capsule or tablet, 150 mg, 300 mg
rifampicin + isoniazid (5)	tablet, 60 mg + 30 mg, 150 mg + 75 mg, 300 mg + 150 mg
	tablet, 60 mg + 60 mg *(for intermittent use 3 times weekly)*
	tablet, 150 mg + 150 mg *(for intermittent use 3 times weekly)*
rifampicin + isoniazid + pyrazinamide (5)	tablet, 60 mg + 30 mg + 150 mg, 150 mg + 75 mg + 400 mg
	tablet, 150 mg + 150 mg + 500 mg *(for intermittent use 3 times weekly)*
rifampicin + isoniazid + pyrazinamide + ethambutol	tablet, 150 mg + 75 mg + 400 mg + 275 mg
streptomycin (4)	powder for injection, 1 g (as sulfate) in vial

6.3 ANTIFUNGAL MEDICINES

amphotericin B (4)	powder for injection, 50 mg in vial
▫fluconazole	capsule, 50 mg
	injection, 2 mg/ml in vial
	oral suspension, 50 mg/5-ml
griseofulvin (7)	capsule or tablet, 125 mg, 250 mg
nystatin	tablet, 100 000, 500 000 IU
	lozenge, 100 000 IU
	pessary, 100 000 IU

6.4 ANTIVIRAL MEDICINES

6.4.1 ANTIHERPES MEDICINES

aciclovir (8)	tablet, 200 mg
	powder for injection, 250 mg (as sodium salt) in vial

6.4.2 ANTIRETROVIRALS

Antiretrovirals do not cure HIV infection, they only temporarily suppress viral replication and improve symptoms. They have various adverse effects and patients receiving thisetherapy require careful monitoring by adequately trained health professionals. For these reasons, continuous rigorous promotion of measures to prevent new infections is essential and the need for this has not been diminished in any way by the addition of antiretrovials to the Model List. Adequate resources and trained health professionals are a prerequisite for the introduction of this class of drugs. Effective therapy requires commencement of three or four antiretrovirals simultaneously, and alternative regimens are necessary to meet specific requirements at start-up, to substitute for first-line regimens in the case of toxicity, or to replace failing regimens. The Committee strongly recommends the use of three- or four-combinations as specifically recommended in the WHO treatment guidelines. The use of fixed dose preparations for these combinations is also recommended, with assured pharmaceutical quality and interchangeability with the single products as approved by the relevant drug regulatory authority.

6.4.2.1 NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS*

abacavir (ABC)	tablet, 300 mg (as sulfate)
	oral solution, 100 mg (as sulfate)/5 ml

** Refer to WHO Model Formulary 2002 for full details of dosage form and use (http://www.who.int/medicines/organization/par/formulary)*

didanosine (ddI)	(chewable) tablet, 25 mg, 50 mg, 100 mg, 150 mg, 200 mg
	capsule, 125 mg, 200 mg, 250 mg, 400 mg
	powder for oral solution, 100 mg, 167 mg, 250 mg (sachet)
lamivudine (3TC)	tablet, 150 mg,
	oral solution, 50 mg/5 ml
stavudine (d4T)	capsule, 15 mg, 20 mg 30 mg, 40 mg
	powder for oral solution, 5 mg/5 ml
zidovudine (ZDV or AZT)	tablet, 300 mg
	capsule, 100 mg, 250 mg
	oral solution or syrup, 50 mg/5 ml
	solution for infusion, 10 mg/ml in 20-ml vial

6.4.2.2 NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS*

efavirenz (EFV or EFZ)	capsule, 50 mg, 100 mg, 200 mg
	oral solution, 150 mg/5ml
nevirapine (NVP)	tablet, 200 mg
	oral suspension, 50 mg/5 ml

6.4.2.3 PROTEASE INHIBITORS*

Selection of two or three protease inhibitors from the Model List will need to be determined by each country after consideration of local treatment guidelines and experience, as well as the comparative costs of available products. Ritonavir is recommended for use in combination with indinavi, lopinavir and saquinavir as a booster, and not as a therapy in its own right.

indinavir (IDV)	capsule, 100 mg, 200 mg, 333 mg, 400 mg (as sulfate)
ritonavir (RTV/r)	capsule, 100 mg
	oral solution, 400 mg/5 ml
lopinavir (LPV/r) + ritonavir	capsule, 133.3 mg + 33.3 mg
	oral solution, 400 mg/5 ml + 100 mg/5 ml
nelfinavir (NFV)	tablet, 250 mg (as mesilate)
	powder, 50 mg (as mesilate)/g
saquinavir (SQV)	capsule, 200 mg

6.5 ANTIPROTOZOAL MEDICINES

6.5.1 ANTIAMOEBIC AND ANTIGIARDIASIS MEDICINES

▫ diloxanide	tablet, 500 mg (furoate)
▫ metronidazole	tablet, 200–500 mg
	injection, 500 mg in 100-ml vial
	oral suspension, 200 mg (as benzoate)/5 ml

6.5.2 ANTILEISHMANIASIS MEDICINES

▫ meglumine antimoniate	injection, 30%, equivalent to approx. 8.1% antimony, in 5-ml ampoule
pentamidine (5)	powder for injection, 200 mg, 300 mg (isetionate) in vial

6.5.3 ANTIMALARIAL MEDICINES

6.5.3.1 FOR CURATIVE TREATMENT

artemether + lumefantrine	tablet, 20 mg + 120 mg
▫ chloroquine	tablet, 100 mg, 150 mg (as phosphate or sulfate)
	syrup, 50 mg (as phosphate or sulfate)/5 ml
	injection, 40 mg (as hydrochloride, phosphate or sulfate)/ml in 5-ml ampoule
primaquine	tablet, 7.5 mg, 15 mg (as diphosphate)
▫ quinine	tablet, 300 mg (as bisulfate or sulfate)
	injection, 300 mg (as dihydrochloride)/ml in 2-ml ampoule

6.5.3.2 FOR PROPHYLAXIS

chloroquine	tablet, 150 mg (as phosphate or sulfate)
	syrup, 50 mg (as phosphate or sulfate)/5 ml
doxycycline	capsule or tablet, 100 mg (hydrochloride)
mefloquine	tablet, 250 mg (as hydrochloride)
proguanil *(for use only in combination with chloroquine)*	tablet, 100 mg (hydrochloride)

** Refer to WHO Model Formulary 2002 for full details of dosage form and use (http://www.who.int/medicines/organization/par/formulary)*

6.5.4 ANTIPNEUMOCYSTOSIS AND ANTITOXOPLASMOSIS MEDICINES

pentamidine (2)	tablet, 200 mg, 300 mg
pyrimethamine	tablet, 25 mg
sulfamethoxazole + trimethoprim	injection, 80 mg + 16 mg/ml in 5-ml ampoule, 80 mg + 16 mg/ml in 10-ml ampoule

6.5.5 ANTITRYPANOSOMAL MEDICINES

6.5.5.1 AFRICAN TRYPANOSOMIASIS

melarsoprol (2)	injection, 3.6% solution
pentamidine (2)	powder for injection, 200 mg, 300 mg (isetionate) in vial
suramin sodium	powder for injection, 1 g in vial

6.5.5.2 AMERICAN TRYPANOSOMIASIS

benznidazole (7)	tablet, 100 mg
nifurtimox (2, 8)	tablet, 30 mg, 120 mg, 250 mg

6.6 INSECT REPELLENTS

diethyltoluamide	topical solution, 50%, 75%

7: Antimigraine Medicines

7.1 FOR TREATMENT OF ACUTE ATTACK

acetylsalicylic acid	tablet, 300–500 mg
ergotamine (1c) (7)	tablet, 1 mg (tartrate)
paracetamol	tablet, 300–500 mg

7.2 FOR PROPHYLAXIS

▫propranolol	tablet, 20 mg, 40 mg (hydrochloride)

8: Antineoplastic and Immunosuppressive Medicines, and Medicines Used in Palliative Care

8.1 IMMUNOSUPPRESSIVE MEDICINES
Please see complementary list.

8.2 CYTOTOXIC MEDICINES
Please see complementary list.

8.3 HORMONES AND ANTIHORMONES
Please see complementary list.

8.4 DRUGS USED IN PALLIATIVE CARE

The WHO Expert Committee on the Selection and Use of Essential Medicines recommended that all the drugs mentioned in the WHO publication *Cancer Pain Relief: with a Guide to Opioid Availability, Second edition,* be considered essential. The drugs are included in the relevant sections of the Model List according to their therapeutic use, e.g. analgesics.

9: Antiparkinsonism Medicines

▫biperiden	tablet, 2 mg (hydrochloride)
	injection, 5 mg (lactate) in 1-ml ampoule
levodopa + ▫carbidopa (5, 6)	tablet, 100 mg + 10 mg, 250 mg + 25 mg

10: Medicines affecting the Blood

10.1 ANTIANAEMIA MEDICINES

ferrous salt	tablet, equivalent to 60 mg iron
	oral solution, equivalent to 25 mg iron (as sulfate)/ml
ferrous salt + folic acid *(nutritional supplement for use during pregnancy)*	tablet, equivalent to 60 mg iron + 400 microgram folic acid
folic acid (2)	tablet, 1 mg, 5 mg
	injection, 1 mg (as sodium salt) in 1-ml ampoule
hydroxocobalamin (2)	injection, 1 mg in 1-ml ampoule

10.2 MEDICINES AFFECTING COAGULATION

desmopressin (8)	injection, 4 micrograms (acetate)/ml in 1-ml ampoule
	nasal spray, 10 micrograms (acetate)/metered dose
heparin sodium	injection, 1000 IU/ml, 5000 IU/ml, 20 000 IU/ml in 1-ml ampoule
phytomenadione	injection, 10 mg/ml in 5-ml ampoule
	tablet, 10 mg
protamine sulfate	injection, 10 mg/ml in 5-ml ampoule
▫warfarin (2, 6)	tablet, 1 mg, 2 mg and 5 mg (sodium salt)

11: Blood Products and Plasma Substitutes

11.1 PLASMA SUBSTITUTES

▫ dextran 70	injectable solution, 6%
▫ polygeline	injectable solution, 3.5%

11.2 PLASMA FRACTIONS FOR SPECIFIC USE

All plasma fractions should comply with the WHO Requirements for the Collection, Processing and Quality Control of Blood, Blood Components, and Plasma Derivitives (Revised 1992). WHO Technical Report Series, No. 840, 1994, Annex 2.

12: Cardiovascular Medicines

12.1 ANTIANGINAL MEDICINES

▫ atenolol	tablet, 50 mg, 100 mg
glyceryl trinitrate	tablet (sublingual), 500 micrograms
▫ isosorbide dinitrate	tablet (sublingual), 5 mg
▫ verapamil (10)	tablet, 40 mg, 80 mg (hydrochloride)

12.2 ANTIARRHYTHMIC MEDICINES

▫ atenolol	tablet, 50 mg, 100 mg
digoxin (4, 11)	tablet, 62.5 micrograms, 250 micrograms
	oral solution, 50 micrograms/ml
	injection, 250 micrograms/ml in 2-ml ampoule
lidocaine	injection, 20 mg (hydrochloride)/ml in 5-ml ampoule
verapamil (8, 10)	tablet, 40 mg, 80 mg (hydrochloride)
	injection, 2.5 mg (hydrochloride)/ml in 2-ml ampoule

12.3 ANTIHYPERTENSIVE MEDICINES

▫ atenolol	tablet, 50 mg, 100 mg
▫ captopril	scored tablet, 25 mg
▫ hydralazine	tablet, 25 mg, 50 mg (hydrochloride)
	powder for injection, 20 mg (hydrochloride) in ampoule
▫ hydrochlorothiazide	scored tablet, 25 mg
methyldopa (7)	tablet, 250 mg
▫ nifedipine (10)	sustained-release formulations tablet, 10 mg
▫ reserpine	tablet, 100 micrograms, 250 micrograms
	injection, 1 mg in 1-ml ampoule

12.4 MEDICINES USED IN HEART FAILURE

▫ captopril	scored tablet, 25 mg
digoxin (4, 11)	tablet, 62.5 micrograms, 250 micrograms
	oral solution, 50 micrograms/ml
	injection, 250 micrograms/ml in 2-ml ampoule
dopamine	injection, 40 mg (hydrochloride) in 5-ml vial
▫ hydrochlorothiazide	tablet, 25 mg, 50 mg

12.5 ANTITHROMBOTIC MEDICINES

acetylsalicylic acid	tablet, 100 mg

12.6 LIPID-LOWERING AGENTS

The WHO Expert Committee on Selection and Use of Essential Medicines recognizes the value of lipid-lowering drugs in treating patients with hyperlipidaemia. HMG CoA reductase inhibitors, often referred to as "statins", are a family of potent and effective lipid-lowering drugs with a good tolerability profile. Several of these drugs have been shown to reduce the incidence of fatal and non-fatal myocardial infarction, stroke and mortality (all causes), as well as the need for coronary by-pass surgery. All remain very costly but may be cost-effective for secondary prevention of cardiovascular disease as well as for primary prevention in some very high-risk patients. Since no single drug has been shown to be significantly more effective or less expensive than others in the group, none is included in the Model List; the choice of drug for use in patients at highest risk should be decided at national level.

13: Dermatological Medicines (topical)

13.1 ANTIFUNGAL MEDICINES

benzoic acid + salicylic acid	ointment or cream, 6% + 3%
▫ miconazole	ointment or cream, 2% (nitrate)
sodium thiosulfate	solution, 15%

13.2 ANTI-INFECTIVE MEDICINES

▫ methylrosanilinium chloride (gentian violet)	aqueous solution, 0.5% tincture, 0.5%
neomycin sulfate + ▫ bacitracin (7)	ointment, 5 mg neomycin sulfate + 500 IU bacitracin zinc/g
potassium permanganate	aqueous solution, 1:10 000
silver sulfadiazine	cream, 1%, in 500-g container

13.3 ANTI-INFLAMMATORY AND ANTIPRURITIC MEDICINES

▫ betamethasone (3)	ointment or cream, 0.1% (as valerate)
▫ calamine lotion	lotion
▫ hydrocortisone	ointment or cream, 1% (acetate)

13.4 ASTRINGENT MEDICINES

aluminium diacetate	solution, 13% for dilution

13.5 MEDICINES AFFECTING SKIN DIFFERENTIATION AND PROLIFERATION

benzoyl peroxide	lotion or cream, 5%
coal tar	solution, 5%
dithranol	ointment, 0.1–2%
fluorouracil	ointment, 5%
▫ podophyllum resin (7)	solution, 10–25%
salicylic acid	solution 5%
urea	ointment or cream, 10%

13.6 SCABICIDES AND PEDICULICIDES

▫ benzyl benzoate	lotion, 25%
permethrin	cream, 5% lotion, 1%

13.7 ULTRAVIOLET-BLOCKING AGENTS

Please see complementary list

14: Diagnostic Agents

14.1 OPHTHALMIC MEDICINES

fluorescein	eye drops, 1% (sodium salt)
▫ tropicamide	eye drops, 0.5%

14.2 RADIOCONTRAST MEDIA

▫ amidotrizoate	injection, 140–420 mg iodine (as sodium or meglumine salt)/ml in 20-ml ampoule
barium sulfate	aqueous suspension
▫ iohexol	injection, 140–350 mg iodine/ml in 5-ml, 10-ml and 20-ml ampoule
▫ iopanoic acid	tablet, 500 mg
▫ propyliodone *(For administration only into the bronchial tree).*	oily suspension, 500–600 mg/ml in 20-ml ampoule

15: Disinfectants and Antiseptics

15.1 ANTISEPTICS

▫ chlorhexidine	solution, 5% (digluconate) for dilution
▫ ethanol	solution, 70% (denatured)
▫ polyvidone iodine	solution, 10%

15.2 DISINFECTANTS

▫ chlorine base compound	powder (0.1% available chlorine) for solution
▫ chloroxylenol	solution, 4.8%
glutaral	solution, 2%

16: Diuretics

▫ amiloride (4, 7, 8)	tablet, 5 mg (hydrochloride)
▫ furosemide	tablet, 40 mg injection, 10 mg/ml in 2-ml ampoule
▫ hydrochlorothiazide	tablet, 25 mg, 50 mg
spironolactone (8)	tablet, 25 mg

17: Gastrointestinal Medicines

17.1 ANTACIDS AND OTHER ANTIULCER MEDICINES

aluminium hydroxide	tablet, 500 mg oral suspension, 320 mg/5 ml
▫ cimetidine	tablet, 200 mg injection, 200 mg in 2-ml ampoule
magnesium hydroxide	oral suspension, equivalent to 550 mg magnesium oxide/10 ml

17.2 ANTIEMETIC MEDICINES

metoclopramide	tablet, 10 mg (hydrochloride)

	injection, 5 mg (hydrochloride)/ml in 2-ml ampoule
▫promethazine	tablet, 10 mg, 25 mg (hydrochloride)
	elixir or syrup, 5 mg (hydrochloride)/5 ml
	injection, 25 mg (hydrochloride)/ml in 2-ml ampoule

17.3 ANTIHAEMORRHOIDAL MEDICINES

▫local anaesthetic, astringent and anti-inflammatory drug	ointment or suppository

17.4 ANTI-INFLAMMATORY MEDICINES

hydrocortisone	suppository, 25 mg (acetate)
	▫retention enema
▫sulfasalazine (2)	tablet, 500 mg
	suppository, 500 mg
	retention enema

17.5 ANTISPASMODIC MEDICINES

▫atropine	tablet, 1 mg (sulfate)
	injection, 1 mg (sulfate) in 1-ml ampoule

17.6 LAXATIVES

▫senna	tablet, 7.5 mg (sennosides) (or traditional dosage forms)

17.7 MEDICINESUSED IN DIARRHOEA

17.7.1 ORAL REHYDRATION

oral rehydration salts (for glucose–electrolyte solution) — powder, 27.9 g/l

Components to reconstitute one litre of glucose electrolyte solution	*g/l*
sodium chloride	3.5
trisodium citrate dihydrate*	2.9
potassium chloride	1.5
glucose	20.0

*Trisodium citrate dihydrate may be replaced by sodium bicarbonate (sodium hydrogen carbonate).

17.7.2 ANTIDIARRHOEAL (SYMPTOMATIC) MEDICINES

▫codeine (1a)	tablet, 30 mg (phosphate)

18: Hormones, other Endocrine Medicines and Contraceptives

18.1 ADRENAL HORMONES AND SYNTHETIC SUBSTITUTES

▫dexamethasone	tablet, 500 micrograms, 4 mg
	injection, 4 mg dexamethasone phosphate (as disodium salt) in 1-ml ampoule
hydrocortisone	powder for injection, 100 mg (as sodium succinate) in vial
▫prednisolone	tablet, 1 mg, 5 mg

18.2 ANDROGENS

18.3 CONTRACEPTIVES

18.3.1 HORMONAL CONTRACEPTIVES

▫ethinylestradiol + ▫levonorgestrel	tablet, 30 micrograms + 150 micrograms,
▫ethinylestradiol + ▫levonorgestrel	tablet, 50 micrograms + 250 micrograms (pack of four)
▫ethinylestradiol + ▫norethisterone	tablet, 35 micrograms + 1.0 mg
levonorgestrel	tablet, 0.75 mg (pack of two)

18.3.2 INTRAUTERINE DEVICES

copper-containing device

18.3.3 BARRIER METHODS

condoms with or without spermicide (nonoxinol[+])

diaphragms with spermicide (nonoxinol[+])

18.4 ESTROGENS

▫ethinylestradiol	tablet, 10 micrograms, 50 micrograms

18.5 INSULINS AND OTHER ANTIDIABETIC AGENTS

▫glibenclamide	tablet, 2.5 mg, 5 mg
insulin injection (soluble)	injection, 40 IU/ml in 10-ml vial, 100 IU/ml in 10-ml vial
intermediate-acting insulin (as compound	injection, 40 IU/ml in 10-ml vial, 100 IU/ml in 10-ml vial insulin zinc suspension or isophane insulin)

[+] *See also page 120 for further information.*

metformin	tablet, 500 mg (hydrochloride)

18.6 OVULATION INDUCERS

▫clomifene (2, 8)	tablet, 50 mg (citrate)

18.7 PROGESTOGENS

norethisterone	tablet, 5 mg

18.8 THYROID HORMONES AND ANTITHYROID DRUGS

levothyroxine	tablet, 50 micrograms, 100 micrograms (sodium salt)
potassium iodide	tablet, 60 mg
▫propylthiouracil	tablet, 50 mg

19: Immunologicals

19.1 DIAGNOSTIC AGENTS

All tuberculins should comply with the WHO Requirements for Tuberculins (Revised 1985). WHO Expert Committee on Biological Standardization Thirty-sixth report (WHO Technical Report Series, No. 745, 1987, Annex 1).

tuberculin, purified protein derivative (PPD)	injection

19.2 SERA AND IMMUNOGLOBULINS

All plasma fractions should comply with the WHO Requirements for the Collection, Processing and Quality Control of Blood, Blood Components and Plasma Derivatives (Revised 1992). WHO Expert Committee on Biological Standardization Forty-third report (WHO Technical Report Series, No. 840, 1994, Annex 2).

anti-D immunoglobulin (human)	injection, 250 micrograms in single-dose vial
▫antitetanus immunoglobulin (human)	injection, 500 IU in vial
antivenom serum	injection
diphtheria antitoxin	injection, 10 000 IU, 20 000 IU in vial
immunoglobulin, human normal (2)	injection (intramuscular)
immunoglobulin, human normal (2, 8)	injection (intravenous)
▫rabies immunoglobulin	injection, 150 IU/ml

19.3 VACCINES

All vaccines should comply with the WHO Requirements for Biological Substances.

19.3.1 FOR UNIVERSAL IMMUNIZATION

BCG vaccine

diphtheria vaccine

hepatitis B vaccine

measles vaccine

pertussis vaccine

poliomyelitis vaccine

tetanus vaccine

19.3.2 FOR SPECIFIC GROUPS OF INDIVIDUALS

influenza vaccine

meningococcal meningitis vaccine

mumps vaccine

rabies vaccine (inactivated: prepared in cell culture)

rubella vaccine

typhoid vaccine

yellow fever vaccine

20: Muscle Relaxants (peripherally acting) and Cholinesterase Inhibitors

▫alcuronium chloride (2)	injection, 5 mg/ml in 2-ml ampoule
▫neostigmine	tablet, 15 mg (bromide)
	injection, 500 micrograms, 2.5 mg (metilsulfate) in 1-ml ampoule
pyridostigmine (2, 8)	tablet, 60 mg (bromide)
	injection, 1 mg in 1-ml ampoule
suxamethonium (2)	injection, 50 mg (chloride)/ml in 2-ml ampoule
	powder for injection

21: Ophthalmological Preparations

21.1 ANTI-INFECTIVE AGENTS

▫gentamicin	solution (eye drops), 0.3% (sulfate)
▫idoxuridine	solution (eye drops), 0.1%
	eye ointment, 0.2%
silver nitrate	solution (eye drops), 1%
▫tetracycline	eye ointment, 1% (hydrochloride)

21.2 ANTI-INFLAMMATORY AGENTS

▫ prednisolone	solution (eye drops), 0.5% (sodium phosphate)

21.3 LOCAL ANAESTHETICS

▫ tetracaine	solution (eye drops), 0.5% (hydrochloride)

21.4 MIOTICS AND ANTIGLAUCOMA DRUGS

acetazolamide	tablet, 250 mg
▫ pilocarpine	solution (eye drops), 2%, 4% (hydrochloride or nitrate)
▫ timolol	solution (eye drops), 0.25%, 0.5% (as maleate)

21.5 MYDRIATICS

atropine	solution (eye drops), 0.1%, 0.5%, 1% (sulfate)

22: Oxytocics and Antioxytocics

22.1 OXYTOCICS

ergometrine	tablet, 200 micrograms (hydrogen maleate)
	injection, 200 micrograms (hydrogen maleate) in 1-ml ampoule
oxytocin	injection, 10 IU in 1-ml ampoule

22.2 ANTIOXYTOCICS

▫ salbutamol (2)	tablet, 4 mg (as sulfate)
	injection, 50 micrograms (as sulfate)/ml in 5-ml ampoule

23: Peritoneal Dialysis Solution

intraperitoneal dialysis solution (of appropriate composition)	parenteral solution

24: Psychotherapeutic Medicines

24.1 MEDICINES USED IN PSYCHOTIC DISORDERS

▫ chlorpromazine	tablet, 100 mg (hydrochloride)
	syrup, 25 mg (hydrochloride)/5 ml
	injection, 25 mg (hydrochloride)/ml in 2-ml ampoule
▫ fluphenazine (5)	injection, 25 mg (decanoate or enantate) in 1-ml ampoule
▫ haloperidol	tablet, 2 mg, 5 mg
	injection, 5 mg in 1-ml ampoule

24.2 MEDICINES USED IN MOOD DISORDERS

24.2.1 MEDICINES USED IN DEPRESSIVE DISORDERS

▫ amitriptyline	tablet, 25 mg (hydrochloride)

24.2.2 MEDICINES USED IN BIPOLAR DISORDERS

carbamazepine (10, 11)	scored tablet, 100 mg, 200 mg
lithium carbonate (2, 4)	capsule or tablet, 300 mg
valproic acid (7, 11)	enteric coated tablet, 200 mg, 500 mg (sodium salt)

24.3 MEDICINES USED IN GENERALIZED ANXIETY AND SLEEP DISORDERS

▫ diazepam (1b)	scored tablet, 2 mg, 5 mg

24.4 MEDICINES USED IN OBSESSIVE COMPULSIVE DISORDERS AND PANIC ATTACKS

clomipramine	capsules, 10 mg, 25 mg (hydrochloride)

25: Medicines Acting on the Respiratory Tract

25.1 ANTIASTHMATIC MEDICINES

▫ aminophylline (2)	injection, 25 mg/ml in 10-ml ampoule
▫ beclometasone	inhalation (aerosol), 50 micrograms, 250 micrograms, (dipropionate) per dose
▫ epinephrine (adrenaline)	injection, 1 mg (as hydrochloride or hydrogen tartrate) in 1-ml ampoule
ipratropium bromide	inhalation (aerosol), 20 micrograms/metered dose
▫ salbutamol	tablet, 2 mg, 4 mg (as sulfate)
	inhalation (aerosol), 100 micrograms (as sulfate) per dose
	syrup, 2 mg (as sulfate)/5 ml

	injection, 50 micrograms (as sulfate)/ml in 5-ml ampoule
	respiratory solution for use in nebulizers, 5 mg (as sulfate)/ml
theophylline (10, 11)	tablet, 100 mg, 200 mg, 300 mg

25.2 ANTITUSSIVES

▫ dextromethorphan	oral solution, 3.5 mg (bromide)/5 ml

26: Solutions correcting Water, Electrolyte and Acid–base Disturbances

26.1 ORAL

oral rehydration salts (for glucose–electrolyte solution)	for composition see section 17.7.1
potassium chloride	powder for solution

26.2 PARENTERAL

glucose	injectable solution, 5% isotonic, 10% isotonic, 50% hypertonic
glucose with sodium chloride	injectable solution, 4% glucose, 0.18% sodium chloride (equivalent to Na^+ 30 mmol/l Cl^- 30 mmol/l)
potassium chloride (2)	11.2% solution in 20-ml ampoule, (equivalent to K^+ 1.5 mmol/ml, Cl^- 1.5 mmol/ml)
sodium chloride	injectable solution, 0.9% isotonic (equivalent to Na^+ 154 mmol/l, Cl^- 154 mmol/l)
sodium hydrogen carbonate	injectable solution, 1.4% isotonic (equivalent to Na^+ 167 mmol/l, HCO_3^- 167 mmol/l)
	solution, 8.4% in 10-ml ampoule (equivalent to Na^+ 1000 mmol/l, HCO_3^- 1000 mmol/l)
▫ sodium lactate, compound solution	injectable solution

26.3 MISCELLANEOUS

water for injection	2-ml, 5-ml, 10-ml ampoules

27: Vitamins and Minerals

ascorbic acid	tablet, 50 mg
▫ ergocalciferol	capsule or tablet, 1.25 mg (50 000 IU)
	oral solution, 250 micrograms/ml (10 000 IU/ml)
iodine (8)	iodized oil, 1 ml (480 mg iodine), 0.5 ml (240 mg iodine) in ampoule (oral or injectable)
	solution, 0.57 ml, (308 mg iodine) in dispenser bottle
	capsule, 200 mg
▫ nicotinamide	tablet, 50 mg
pyridoxine	tablet, 25 mg (hydrochloride)
▫ retinol	sugar-coated tablet, 10 000 IU (as palmitate) (5.5 mg)
	capsule, 200 000 IU (as palmitate) (110 mg)
	oral oily solution, 100 000 IU/ml in multidose dispenser (as palmitate)
	water-miscible injection, 100 000 IU (as palmitate) (55 mg) in 2-ml ampoule
riboflavin	tablet, 5 mg
▫ sodium fluoride	in any appropriate formulation
thiamine	tablet, 50 mg (hydrochloride)

The following additions to the WHO Model List (both core and complementary lists) have been approved by the WHO Expert Committee on the Selection and Use of Essential Medicines. The report of the meeting will be published in the WHO Technical Report Series.

abacavir, didanosine, lamivudine, stavudine, efavirenz, indinavir, ritonavir, lopinavir, nelfinavir, saquinavir, artemether + lumefantrine, amikacin, *p*-aminosalicylic acid, capreomycin, cycloserine, ethionamide, kanamycin, levofloxacin, ofloxacin.

WHO Model List of Essential Medicines: Complementary List

1: Anaesthetics

1.2 LOCAL ANAESTHETICS

ephedrine (C)	injection, 30 mg (hydrochloride)/ml in 1-ml ampoule
(For use in spinal anaesthesia during delivery to prevent hypotension)	

2: Analgesics, Antipyretics, Nonsteroidal Anti-Inflammatory Medicines (NSAIDs), Medicines Used to Treat Gout and Disease-Modifying Agents used in Rheumatic Disorders (DMARDs)

2.2 OPIOID ANALGESICS

▫pethidine (A) (1a, 4)	injection, 50 mg (hydrochloride) in 1-ml ampoule
	tablet, 50 mg, 100 mg (hydrochloride)

5: Anticonvulsants/Antiepileptics

▫clonazepam (B) (1b)	scored tablet, 500 micrograms

6: Anti-infective Medicines

6.1 ANTHELMINTHICS

6.1.2 ANTIFILARIALS

suramin sodium (B) (2, 7)	powder for injection, 1 g in vial

6.1.3 ANTISCHISTOSOMALS AND OTHER ANTITREMATODE MEDICINES

oxamniquine (C) (8)	capsule, 250 mg
	syrup, 250 mg/5 ml

6.2 ANTIBACTERIALS

6.2.1 BETA LACTAM MEDICINES

Restricted indications

▫amoxicillin + ▫clavulanic acid (D)	tablet, 500 mg + 125 mg

Explanatory Notes

The **complementary list** presents essential medicines for priority diseases which are efficacious, safe and cost-effective but not necessarily affordable, or for which specialised health care facilities or services may be needed.

When the strength of a drug is specified in terms of a selected salt or ester, this is mentioned in brackets; when it refers to the active moiety, the name of the salt or ester in brackets is preceded by the word “as”. Many drugs included in the list are preceded by a box (¤) to indicate that they represent an example of a therapeutic group and that various drugs could serve as alternatives. It is imperative that this is understood when drugs are selected at national level, since choice is then influenced by the comparative cost and availability of equivalent products. Examples of acceptable substitutions include:

¤ Hydrochlorothiazide: any other thiazide-type diuretic currently in broad clinical use.
¤ Hydralazine: any other peripheral vasodilator having an antihypertensive effect.
¤ Senna: any stimulant laxative (either synthetic or of plant origin).

Numbers in parentheses following drug names indicate:
(1) Drugs subject to international control under: (a) the Single Convention on Narcotic Drugs (1961); (b) the Convention on Psychotropic Substances (1971); or (c) the United Nations Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances (1988).
(2) Specific expertise, diagnostic precision, individualization of dosage or special equipment required for proper use.
(3) Greater potency or efficacy.
(4) In renal insufficiency, contraindicated or dosage adjustments necessary.
(5) To improve compliance.
(6) Special pharmacokinetic properties.
(7) Adverse effects diminish benefit/risk ratio.
(8) Limited indications or narrow spectrum of activity.
(9) For epidural anaesthesia.
(10) Sustained-release preparations are available. A proposal to include such a product in a national list of essential drugs should be supported by adequate documentation.
(11) Monitoring of therapeutic concentrations in plasma can improve safety and efficacy.

Letters in parentheses following the drug names indicate the reasons for the inclusion:
(A) When drugs in the main list cannot be made available.
(B) When drugs in the main list are known to be ineffective or inappropriate for a given individual.
(C) For use in rare disorders or in exceptional circumstances.
(D) Reserve antimicrobials to be used only when there is significant resistance to other drugs on the list.

Drugs are listed in alphabetical order

ceftazidime (D)	powder for injection, 250 mg (as pentahydrate) in vial
▫ ceftriaxone (D)	powder for injection, 250 mg (as sodium salt) in vial
imipenem + cilastatin (D)	powder for injection, 250 mg (as monohydrate) + 250 mg, (as sodium salt) 500 mg (as monohydrate) + 500 mg (as sodium salt) in vial

6.2.2 OTHER ANTIBACTERIALS

chloramphenicol (C)	oily suspension for injection, 0.5 g (as sodium succinate)/ml in 2-ml ampoule
clindamycin (B) (8)	capsule 150 mg,
	injection, 150 mg (as phosphate)/ml
Restricted indication	
vancomycin (D)	powder for injection 250 mg (as hydrochloride) in vial

6.2.4 ANTITUBERCULOSIS MEDICINES

thioacetazone + isoniazid (A) (5, 7)	tablet, 50 mg + 100 mg, 150 mg + 300 mg

Reserve second-line medicines for the treatment of multidrug-resistant tuberculosis (MDR-TB) should be used in specialized centres adhering to WHO standards for TB control.

amikacin (D)	powder for injection. 1000 mg in vial
p-aminosalicylic acid (D)	tablet 500 mg
	granules, 4 g in sachet
capreomycin (D)	powder for injection, 1000 mg in vial
ciprofloxacin (D)	tablet, 250 mg, 500 mg
▫ cycloserine (D)	capsule or tablet, 250 mg
▫ ethionamide (D)	tablet, 125 mg, 250 mg
kanamycin (D)	powder for injection, 1000 mg in vial
levofloxacin (D)	tablet, 250 mg, 500 mg
ofloxacin (D)	tablet, 200 mg 400 mg

6.3 ANTIFUNGAL MEDICINES

flucytosine (B) (4, 8)	capsule, 250 mg
	infusion, 2.5 g in 250 ml
potassium iodide (A)	saturated solution

6.5 ANTIPROTOZOAL MEDICINES

6.5.2 ANTILEISHMANIASIS MEDICINES

amphotericin B (B) (4)	powder for injection, 50 mg in vial

6.5.3 ANTIMALARIAL MEDICINES

6.5.3.1 FOR CURATIVE TREATMENT

▫ doxycycline (B) *(for use only in combination with quinine)*	capsule or tablet, 100 mg (hydrochloride)
mefloquine (B)	tablet, 250 mg (as hydrochloride)
▫ sulfadoxine + pyrimethamine (B)	tablet, 500 mg + 25 mg
Restricted indications	
artemether (D)	injection, 80 mg/ml in 1-ml ampoule
artesunate (D)	tablet, 50 mg

6.5.5 ANTITRYPANOSOMAL MEDICINES

eflornithine (C)	injection, 200 mg (hydrochloride)/ml in 100-ml bottles

8: Antineoplastic and Immunosuppressive Medicines and Medicines Used in Palliative Care

8.1 IMMUNOSUPPRESSIVE MEDICINES

Adequate resources and specialist oversight are a prerequisite for the introduction of this class of drugs.

▫ azathioprine (2)	tablet, 50 mg
	powder for injection, 100 mg (as sodium salt) in vial
▫ ciclosporin (2) *(for organ transplantation)*	capsule, 25 mg
	concentrate for injection, 50 mg/ml in 1-ml ampoule

8.2 CYTOTOXIC MEDICINES

Adequate resources and specialist oversight are a prerequisite for the introduction of this class of drugs.

asparaginase (2)	powder for injection, 10 000 IU in vial
bleomycin (2)	powder for injection, 15 mg (as sulfate) in vial
calcium folinate (2)	tablet, 15 mg
	injection, 3 mg/ml in 10-ml ampoule
chlorambucil (2)	tablet, 2 mg
chlormethine (2)	powder for injection, 10 mg (hydrochloride) in vial

cisplatin (2)	powder for injection, 10 mg, 50 mg in vial
cyclophosphamide (2)	tablet, 25 mg
	powder for injection, 500 mg in vial
cytarabine (2)	powder for injection, 100 mg in vial
dacarbazine (2)	powder for injection, 100 mg in vial
dactinomycin (2)	powder for injection 500 µg in vial
daunorubicin (2)	powder for injection, 50 mg (as hydrochloride) in vial
▫ doxorubicin (2)	powder for injection, 10 mg, 50 mg (hydrochloride) in vial
etoposide (2)	capsule, 100 mg
	injection, 20 mg/ml in 5-ml ampoule
fluorouracil (2)	injection, 50 mg/ml in 5-ml ampoule
levamisole (2)	tablet, 50 mg (as hydrochloride)
mercaptopurine (2)	tablet, 50 mg
methotrexate (2)	tablet, 2.5 mg (as sodium salt)
	powder for injection, 50 mg (as sodium salt) in vial
procarbazine	capsule, 50 mg (as hydrochloride)
vinblastine (2)	powder for injection, 10 mg (sulfate) in vial
vincristine (2)	powder for injection, 1 mg, 5 mg (sulfate) in vial

8.3 HORMONES AND ANTIHORMONES

▫ prednisolone	tablet, 5 mg
	powder for injection, 20 mg, 25 mg (as sodium phosphate or sodium succinate) in vial
tamoxifen	tablet, 10 mg, 20 mg (as citrate)

8.4 MEDICINES USED IN PALLIATIVE CARE

The WHO Expert Committee on Selection and Use of Essential Medicines recommended that all the drugs mentioned in the WHO publication *Cancer Pain Relief: with a Guide to Opioid Availability, 2nd edition,* be considered essential. The drugs are included in the relevant sections of the model list according to their therapeutic use, e.g. analgesics.

10: Medicines affecting the Blood

10.1 ANTIANAEMIA DRUGS

▫ iron dextran (B) (5)	injection, equivalent to 50 mg iron/ ml in 2-ml ampoule

11: Blood Products and Plasma Substitutes

11.2 PLASMA FRACTIONS FOR SPECIFIC USE

All plasma fractions should comply with the WHO Requirements for the Collection, Processing and Quality Control of Blood, Blood Components, and Plasma Derivitives (Revised 1992). WHO Technical Report Series, No. 840, 1994, Annex 2.

▫ factor VIII concentrate (C) (2, 8)	dried
▫ factor IX complex (coagulation factors II, VII, IX, X) concentrate (C) (2, 8)	dried

12: Cardiovascular Medicines

12.2 ANTIARRHYTHMIC MEDICINES

epinephrine (adrenaline) (C)	injection, 1 mg (as hydrochloride)/ml in ampoule
isoprenaline (C)	injection, 20 micrograms (hydrochloride)/ml
▫ procainamide (B)	injection, 100 mg (hydrochloride)/ml in 10-ml ampoule
▫ quinidine (A) (7)	tablet, 200 mg (sulfate)

12.3 ANTIHYPERTENSIVE MEDICINES

▫ prazosin (B)	tablet, 500 micrograms, 1 mg
▫ sodium nitroprusside (C) (2, 8)	powder for infusion, 50 mg in ampoule

12.5 ANTITHROMBOTIC MEDICINES

streptokinase (C)	powder for injection, 100 000 IU, 750 000 IU in vial

13: Dermatological Medicines (topical)

13.1 ANTIFUNGAL MEDICINES

selenium sulfide (C)	detergent-based suspension, 2%

13.7 ULTRAVIOLET-BLOCKING AGENTS

topical sun protection agent with activity against ultraviolet A and ultraviolet B (C) — cream, lotion or gel

14: Diagnostic Agents

14.2 RADIOCONTRAST MEDIA

▫ meglumine iotroxate (C) — solution, 5 – 8 g iodine in 100–250 ml

16: Diuretics

▫ mannitol (C) — injectable solution, 10%, 20%

18: Hormones, other Endocrine Medicines and Contraceptives

18.1 ADRENAL HORMONES AND SYNTHETIC SUBSTITUTES

fludrocortisone (C) — tablet, 100 micrograms (acetate)

18.2 ANDROGENS

testosterone (C) (2) — injection, 200 mg (enantate) in 1-ml ampoule

18.3 CONTRACEPTIVES

18.3.1 HORMONAL CONTRACEPTIVES

levonorgestrel — tablet, 30 micrograms

medroxyprogesterone acetate (B) (7, 8) — depot injection, 150 mg in 1-ml vial

norethisterone enantate (B) (7, 8) — oily solution, 200 mg/ml in 1-ml ampoule

18.7 PROGESTOGENS

medroxyprogesterone acetate (B) — tablet, 5 mg

20: Muscle Relaxants (peripherally acting) and Cholinesterase Inhibitors

vecuronium bromide (C) — powder for injection, 10 mg in vial

21: Ophthalmological Preparations

21.5 MYDRIATICS

epinephrine (A) — solution (eye drops), 2% (as hydrochloride)

25: Medicines acting on the Respiratory Tract

25.1 ANTIASTHMATIC MEDICINES

▫ cromoglicic acid (B) — inhalation (aerosol), 20 mg (sodium salt) per dose

27: Vitamins and Minerals

calcium gluconate (C) (2, 8) — injection,100 mg/ml in 10-ml ampoule

Recent Publications and Sources of Information

Genomics and world health

The report of the Advisory Committee on Health Research "Genomics and World Health" concludes that information generated by genomics will, in the long term have major benefits for the prevention, diagnosis and management of many diseases which have been difficult or impossible to control. However, if public education in genomics is not achieved, it will be impossible for society to enter into informed debate on the ethical issues involved and there is a danger that those who administer health services will be unable to distinguish between hyperbole and reality in a new and rapidly expanding research field.

Societies need to be better prepared for the era of genomics. Genomics research is complex and an understanding of its medical potential and the ethical issues involved requires a basic understanding of the principles of genetics. The report warns that the planned development of large-scale genetic data bases offers a series of hazards and ethical issues which have not been previously encountered. There is still considerable controversy about the desirability of establishing data bases of this type and there are many ambiguities regarding access and control. Another ethical problem deals with the decisions families may make regarding children as a result of DNA research.

This publication serves as a state-of-the-art guide to this field of science.

Genomics and World Health is available from: Distribution and Sales, World Health Organization, 1211 Geneva 27, Switzerland. ISBN 92 4 154554 2 Price: US$ 31.50 publications@who.int

Legal status of traditional and complementary medicine

National policies are the basis for defining the role of traditional and complementary/alternative medicine in national health care programmes ensuring that the necessary regulatory and legal mechanisms are created for promoting and maintaining good practice: assuring authenticity, safety and efficacy of traditional and complementary therapies: and providing equitable access to health care resources and information about those resources.

National recognition and regulation of traditional and complementary medicine varies considerably from one country to another. The present worldwide review of the legal status of traditional and complementary medicine covers data from 123 countries and is intended to facilitate the development of legal frameworks and sharing of experience between countries. This information will be beneficial to policy makers, researchers, universities, the public, insurance companies and the pharmaceutical industry.

Legal status of traditional and complementary/alternative medicine. WHO/EDM/TRM/2001.2. Available from Essential Drugs and Medicines Policy, World Health Organization, 1211 Geneva 27, Switzerland.

Kinetoplastid research source launched

Kinetoplastid Biology and Disease (KBD) is an electronic publication which aims to strengthen ties between research and clinical/field applications, increasing dialogue between bench scientists, theoreticians and planners, and the professionals in the field. KBD accepts basic science, epidemiologic, public health, clinical, veterinary and agricultural papers on trypanosomiasis, leishmaniasis and related disease which meet the criteria of peer review.

The advent of KBD enables the free dissemination of scientific information about kinetoplastid diseases and their control. This is critical, since most scientific journals are not free and even the ones with cheaper subscription rates may not be accessible to researchers, clinicians, and field researchers in the poorest and affected developing countries. Moreover, the journal will serve as a focus in which the whole kinetoplastid community can participate: to educate, notify and debate about progress and direction. We hope our new journal will serve as a vehicle to promote pragmatic research and as a

practical first step in tackling some of the communication difficulties that face those concerned with the eradication of these diseases.

KBD is created as peer-review journal, freely available to anyone in the world with a networked computer. KBD is published by BiomedCentral (www.biomedcentral.com), and has a world class editorial board (http://www.kinetoplastids.com/edboard/). It will be indexed by most of the major scientific indexing services such as PubMed. Articles will be available in html and .pdf formats. KBD is supported by the Vice-Presidencia de Desenvolvimento Institucional, Informacao e Comunicacao" and the "Instituto Oswaldo Cruz" of the Oswaldo Cruz Foundation. The journal is recipient of a Soros Foundation award for promoting open publishing.

In its first issue, *Kinetoplastid Biology and Disease* presents:

- Combating Kinetoplastid diseases, http://www.kinetoplastids.com/content/pdf/1475-9292-1-6.pdf
- Salivaria or Stercoraria? The Trypanosoma rangeli dilemma, http://www.kinetoplastids.com/content/pdf/1475-9292-1-5.pdf
- What can we hope to gain for trypanosomiasis control from molecular studies on tsetse biology ? http://www.kinetoplastids.com/content/1/1/4
- From the cell biology to the development of new chemotherapeutic approaches against trypanosomatids: dreams and reality. http://www.kinetoplastids.com/content/pdf/1475-9292-1-3.pdf
- PCR identification of Trypanosoma lewisi, a common parasite of laboratory rats, http://www.kinetoplastids.com/content/1/1/2
- Molecular determinants and regulation of Leishmania virulence, http://www.kinetoplastids.com/content/1/1/1

Papers and feedback may be sent to kbd@trypanosome.com

Kinetoplastid Biology and Disease is available from: http://www.kinetoplastids.com .

Endocrine disrupting chemicals

Are chemicals that have the potential to interfere with the normal functioning of the endocrine system threatening future generations of humans and certain wildlife species? An IPCS report concludes that further research and information is needed on endocrine disrupting chemicals or EDCs.

The report, entitled *Global Assessment of the State-of-the-Science of Endocrine Disruptors*, is the result of a global comprehensive review of the publicly available scientific literature on EDCs organized by the International Programme on Chemical Safety (IPCS). The IPCS is sponsored by the World Health Organization (WHO), the United Nations Environment Programme (UNEP) and the International Labour Organization.

The report states that there is sufficient evidence that adverse effects have occurred as a result of exposure to EDCs in some wildlife species. Therefore, because of continuing concerns and scientific uncertainties, studies on the potential effects posed by these chemicals should remain a high global priority requiring coordinated and strengthened international research strategies. There is, in particular, an urgent need for studies in vulnerable populations, and especially in infants and children, since exposure during critical developmental periods may have irreversible effects.

This assessment was requested in 1997 by the Intergovernmental Forum on Chemical Safety, the 1997 Declaration of the Environment Leaders of the Eight on Children's Environmental Health, and endorsed by the 50th World Health Assembly in 1997. The assessment is unique in providing a global perspective on the endocrine disruptor issue, and in providing a framework by which strength-of-the-evidence analysis can be performed to determine whether there is a causal association between an adverse biological effect and exposure to an endocrine disrupting chemical.

Global Assessment of the State-of-the-Science of Endocrine Disruptors is available at http://www.who.int/pcs/pcs_new.html . Printed copies of the report are available from: prout@niehs.nih.gov