

WHO Drug Information

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Aspects of Quality Assurance

Stability testing for hot and humid climates

In 1996, the WHO Expert Committee on Specifications for Pharmaceutical Preparations adopted the WHO Guidelines on Stability Testing (1). In 2000, the International Conference on Harmonization (ICH) Expert Working Group proposed a modification to the WHO guidelines concerning long-term conditions for climatic zone IV (hot and humid) from 30 °C and 70% relative humidity (RH) to 30 °C and 60% relative humidity. After broad consultation, conditions for real-time stability studies for climatic zone IV were agreed as 30 °C (± 2 °C) and 65% (± 5 %) RH (2). Where special transportation and storage conditions did not comply with these criteria, additional study data supporting these conditions might be needed (3).

The Association of South East Asian Nations (ASEAN) comprises Brunei Darussalam, Cambodia, Indonesia, Lao PDR, Malaysia, Myanmar, Philippines, Singapore, Thailand and Vietnam. These countries are all situated in climatic zone IV and ASEAN regulatory authorities are in the process of defining harmonized requirements for marketing authorization for pharmaceuticals with

a view to establishing a common market for pharmaceutical products. Such a process would include harmonization of requirements for stability testing. Regulators and experts from ASEAN countries have met regularly with WHO and IFPMA experts to discuss whether the conditions outlined in current WHO and ICH (4) guidelines are appropriate for countries which have vast areas with climatic conditions that are above the average relative humidity (RH) and temperature used to characterize zone IV. None the less, the most recent of such meetings, held in Jakarta on 12–13 January 2004, concluded that the conditions described in WHO and ICH guidelines do not adequately address the climatic conditions prevalent in the majority of ASEAN countries and has proposed that the conditions shown in Table 1 below should be adopted for stability studies in ASEAN countries. Arguments supporting this conclusion are set out as follows.

Average conditions versus more stressful conditions

Both WHO and ICH guidelines base their calculations on values of temperature and humidity that are the mean of the values calculated for 23 cities situated in Zone IV. These conditions are less stressful than those measured in half of the 23

Table 1 – Proposed conditions for stability testing in ASEAN countries

TYPE	CONDITIONS
Products in primary containers permeable to water vapour	30 °C \pm 2 °C/75% \pm 5% RH
Products in primary containers impermeable to water vapour	30 °C \pm 2 °C/RH not specified
Accelerated studies	40 °C \pm 2 °C/75% \pm 5% RH
Stress studies	Unnecessary if accelerated studies at above conditions are available

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cities. It should be noted that climatic data of cities are not necessarily representative of conditions of large areas of the countries sampled, which may experience higher humidity and/or temperature extremes. In addition, as pointed out in WHO guidelines (5), badly conditioned storage facilities may mitigate the lower extremes of temperature but not the higher ones. Finally, storage facilities are likely to be less protective in developing countries, and especially outside of cities.

On the basis of these considerations, as a matter of principle, testing should be biased towards more stressful rather than less stressful conditions so as to provide a margin of error in favour of the patients and to increase the likelihood of identifying substances or formulations that pose particular stability problems.

Activation energy and mean kinetic temperature

Activation energy (E_a) is a determining factor in the calculation of mean kinetic temperature (MKT) as drawn from climatic data. WHO and ICH guidelines refer to published data (6) which indicate the average value of 19.8 kcal/mole (or 82.8 kJ/mole) for E_a to be used for calculating MKT. These published data show that E_a for 38 active ingredients and excipients (many no longer in use) ranged from 9 to 47 kcal/mole.

Consequently, for many drugs, MKT is either overestimated or underestimated when the average of 19.8 kcal/mole is used. This in turn leads to underestimating or overestimating shelf-life values. Sample calculations have shown that shelf life values can be divided by four when E_a values are increased from 10 to 100 kcal/mole. It can be assumed that most degradation reactions have very low E_a and therefore long shelf-life values, but this needs to be demonstrated. What is relevant is that the use of an average value based on a limited sample of substances may be inappropriate to help identify substances or formulations that pose particular stability problems.

Calculations based on climatic data from ASEAN countries

ASEAN average values for temperature and RH are, respectively, 27.76 °C and 78.79% RH. Most ASEAN member countries have average RH values that are above the mean RH of the 23 cities used as a basis for the ICH Q1F guideline, which are 26.7 °C and 76% RH. ICH and WHO guidelines assume that, at a given temperature,

the amount of water in the air, or absolute humidity (AH), is the most relevant factor to consider when setting conditions for stability testing. Based on this assumption, AH values for ASEAN climatic conditions were calculated as follows:

- data on dew point and temperature were obtained from tables published by the World Meteorological Organization (WMO) and the European Centre for Medium-Range Weather Forecasts;
- from these data, calculations were performed to obtain:

partial vapour pressure, using Wexler's equation:

$$P_D = 6.112 \cdot e^{(17.67 \cdot T / (243.5 + T))}$$

(where T is the dew point obtained from meteorological data).

absolute humidity (or mix ratio), expressed as mass of water per kilogram of dry air using the following equation:

$$AH = \frac{0.018 \cdot P_D}{0.029 \cdot (P - P_D)}$$

where:

- 0.018 = molar mass of water [kg]
- 0.029 = molar mass of dry air [kg]
- P = total atmospheric pressure [mbar]
- P_D = partial vapour pressure of water [mbar]

saturation vapour pressure (P_s) from Wexler's equation at the corresponding measured temperature instead of dew point.

- the relationship between RH, P_s and P_D is based on:

$$RH = P_D \cdot 100 / P_s$$

The data obtained are reproduced in Table 2 overleaf:

The table shows that the ASEAN average AH is 0.0186 Kg_{water}/Kg_{dry air} and that the pair temperature/RH closest to that is 30 °C/70% RH. In line with the need for setting test conditions that better reflect extremes rather than mere average, and in order to provide a safety margin, the meeting agreed that the pair 30 °C/75% RH be recommended for long term stability studies.

Table 2.

Temperature/Relative Humidity	Absolute Humidity Kg _{water} /Kg _{dry air}
30 °C /60% RH	0.0161
25 °C /80% RH	0.0160
30 °C /65% RH	0.0174
30 °C /70% RH	0.0188
30 °C /75% RH	0.0202
40 °C /75% RH	0.0361
27.76 °C /78.79% RH	0.0186 (*)

(*) ASEAN average

It was also noted that the pair 40 °C/75% RH used in accelerated studies represents a better stress than the 25 °C/80% RH proposed for stress testing in the ICH Q1F Guideline. On this basis, the meeting agreed to eliminate the requirement for stress testing if data on accelerated studies conducted at 40°C /75% RH are made available.

Stability and packaging materials

Stability is obviously affected to a large extent by the permeability of primary packaging materials. Products packed in primary containers demonstrated to be impermeable to water vapour do not require testing at any specific RH, storage at constant temperature of 30 °C throughout real time testing being sufficient. However, guidelines will be needed to specify parameters, such as a thickness and permeability coefficient, which indicates demonstrated impermeability of packaging materials.

Cost implications for setup of new test conditions

It was noted that no significant costs are imposed on manufacturers to set up testing conditions at different RHs. The most practical approach would be to fill a container up to a certain level with an appropriate saturated salt solution that can keep the air in container at the required RH when the container is hermetically closed. The test samples would then be enclosed in the container kept in a room of constant temperature of 30 °C for the entire duration of the study.

Implementation strategies

Implementation of the above decision will be preceded by a transition period during which existing national guidelines will still be applicable. In addition, a science-based approach will be taken to ensure correct evaluation when submitted data is based on conditions that are less

stressful than those required (e.g. 30 °C/65% RH). Factors to be taken into consideration include:

- complementary data provided to enable proper scientific evaluation;
- detected instability
- data obtained under accelerated conditions
- when more protective packaging is provided
- commitment to generate data under the new guideline conditions (30 °C/75% RH, or 40 °C/75% RH, or both) within a specified period.

A suitable label recommendation such as “Store below 30 °C and protect from moisture” may also be applied.

Additional inputs from member countries will be considered during finalization and throughout the implementation of this new ASEAN guideline. In the light of the above there may be a need to review the WHO and ICH guidelines.

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WHO action plan for stability testing

In view of the decisions taken by ASEAN as described in the article above, WHO has responded with the following action plan:

1. Development of a WHO restricted working document, which has been circulated to interested parties for consultation. The document requests comments by 30 June 2004 on whether the WHO guidance on stability testing should be modified for long-term stability testing conditions (hot and humid climatic zone) and seeks suggestions on how modifications should be implemented.
2. Organization of an informal consultation to discuss comments received, and presentation of conclusions in an advisory report to be prepared for the WHO Expert Committee on Specifications for Pharmaceutical Preparations which will meet in October 2004.
3. In the event that ASEAN guidance is confirmed and adopted, WHO will organize a meeting including ASEAN, WHO, and International conference on Harmonization (ICH) experts and other interested parties in November/December 2004.
4. Depending on the outcome of action taken, revise and/or prepare WHO guidelines for implementation and compatibility of the different conditions with all parties involved in this process.

Safety and Efficacy Issues

Efficacy of artesunate for emergency malaria treatment

Plasmodium falciparum malaria causes hundreds of thousands of deaths annually, especially in children in sub-Saharan Africa. Many of those living in malaria-endemic areas do not have ready access to health facilities and for patients too ill to take oral medication, delay in access to prompt injectable therapy can be fatal. Rural health workers and even parents can be taught to identify the symptoms and signs of severe, life-threatening malaria (1) and rectal artesunate makes for a rapidly acting and effective drug for patients with acute malaria.

The UNDP, World Bank, and WHO Special Programme for Tropical Diseases Research (TDR) selected artesunate on the basis of its rapid antimalarial activity (2, 3), favourable bioavailability (4), and reassuring safety (5) and efficacy profiles (6) compared with other available

treatments. Despite isolated case reports of failed supervised treatment (7, 8), no evidence exists of stable parasite resistance developing during lengthy clinical use with artemisinin (9). A thermostable suppository formulation of artesunate was developed for reasons of easy storage and administration in difficult settings.

A study recently reported in the *Lancet* (10) has assessed the reliability, absorption and initial therapeutic efficacy of rectal artesunate. The Trial involved 109 children in Malawi and a smaller number of 35 adults in KwaZulu Natal, South Africa. Patients with moderately severe malaria were randomly assigned to a single dose of 10 mg/kg rectal artesunate or parenteral quinine. Since artemisinin derivatives are the most rapidly acting antimalarials known (4), the study aimed to determine whether early administration of rectal artesunate would provide beneficial initial antimalarial cover, indicated by a rapid fall in the density of parasitaemia (less than 60% of baseline after

Table 1: Selected baseline clinical and laboratory parameters

	Children Rectal artesunate (n=87)	Quinine IM/IV (n=22)	Adults Rectal artesunate (n=27)	Quinine IM (n=8)
Male	54	13	16	2
Female	33	9	11	6
Median (range) age	48.2 months (16-120)	45.7 months (18-121)	29.0 years (16-58)	24.5 years (17-45)
Mean (SD) weight (kg)	14.2 (3.7)	13.4 (3.6)	62 (10.4)	62 (20.5)
Mean (SD) respiratory rate (breaths/minute)	45 (14.3)	46 (13.0)	24 (5.2)	24 (7.1)
Mean (SD) temperature (°C)*	38.7 (1.0)	39.1 (1.1)	38.7 (1.3)	38.5 (1.5)
Median (range) parasitaemia (ring forms per µL)	185 977 (10 995- 848 732)	230 738 (4 293- 701 784)	54 800 (520- 246 000)	101 173 (7 000- 190 000)
Mean (SD) plasma lactate (mmol/L)	2.77 (2.1)	3.02 (0.9)	2.5 (0.7)	2.2 (1.0)
Mean (SD) packed cell volume (%)	30.4 (5.8)	28.9 (3.6)	39.1 (7.4)	33.9 (5.2)

IM=intramuscular. IV=intravenous. *Rectal in children, oral in adults.

12 hours), and clinical improvement without serious adverse reactions. In both study groups, treatment was completed with the administration of sulfadoxine-pyrimethamine according to prevailing national policy.

Clinical outcome

Rectal artesunate, given as a single dose of 10 mg/kg, showed rapid antimalarial efficacy within 24 hours of administration in moderately severe falciparum malaria in children and adults (Table 1). All patients had either pharmacodynamic or pharmacokinetic evidence of absorption of the drug. Clearance of asexual parasites from the peripheral blood was consistently faster with rectal artesunate than parenteral quinine, as is expected when an artemisinin is absorbed adequately (Table 2). The results were highly

significant not only in the large study of children, but also in the smaller study in adults, which was powered to detect only large effects. The clinical and parasitological responses show that rectal artesunate provides effective initial management of acute malaria in patients who cannot take medication by mouth, particularly when parenteral treatment is not available.

A faster decrease in peripheral parasitaemia does not necessarily ensure improved clinical outcome. In this study, the clinical success rate for rectal artesunate was similar to that for parenteral quinine. This is consistent with other studies comparing intramuscular artemether with intravenous quinine in severe malaria, where artemether showed more rapid decrease in parasitaemia but equivalent clinical outcomes (11).

Table 2: Parasite density over time by allotted treatment group

	Children		p	Adults		p
	Rectal artesunate (n=87)	Quinine IM/IV (n=22)		Rectal artesunate (n=27)	Quinine IM (n=8)	
Parasitaemia (ring forms per μL blood)						
Baseline	185977 (112 411-336 000)	230738 (170 078-325 029)	0.69	56480 (26 536-126 000)	58340 (45 110-118 230)	0.666
12 h	50596 (18 771-107 698)	210335 (170 078-325 029)	<0.0001	5560 (1 295-25 840)	35160 (22 720-80 400)	0.025
% baseline	26.7% (13.8-42.7%)	82.0% (62.5-102%)	<0.0001	12.8% (3.2-33.8%)	64.7% (35.5-85.5%)	0.002
24 h	222 (37-625)	111223 (24 590-168 143)	<0.0001	400 (120-1 000)	17320 (4 980-37 403)	0.004
% baseline	0.1% (0.02-0.5%)	59.2% (15-75%)	<0.0001	1% (0-3%)	27.5% (5-58.5%)	0.0004
PCT (h)						
Mean (95% CI)	36 (30-42)	45 (42-48)	0.0003*	49 (43-55.7)	63 (45.4-80.6)	0.10*
Censored observations	1	1		1	0	

*Data are median (IQR) unless specified otherwise.
IM=intramuscular. IV=intravenous. PCT=parasite clearance time. *Unpaired t test.*

Fever clearance times are shorter in artemisinin-treated patients than in quinine-treated patients (12). Rapid fever clearance is an important clinical benefit, but it does not reflect cure and might create a false sense of security since combination with a second effective antimalarial agent, or a prolonged treatment regimen for 5–7 days, is required to achieve cure (13). Health-care providers need to ensure that patients or caregivers understand the need for further curative treatment at a referral centre. Thus, single administration of rectal artesunate alone is not intended to cure malaria although repeated administration of parenteral quinine and artemisinin derivatives are proven effective treatments for severe *P. falciparum* malaria once a patient is admitted to hospital (14–17).

Earlier reappearance of parasites in artesunate-treated patients might reflect the fact that they received a single dose of medication (at the time of admission), whereas patients on quinine received a total of three to seven doses (over 24–72 hours). Late parasitaemia could be due either to failed treatment or to reinfection. Our study in children was not designed to distinguish between recrudescence and reinfection, but rather to establish the benefit of a single dose of rectal artesunate over the initial 24 hours. Careful clinical neurological examination in our studies detected no signs of neurotoxicity, which is consistent with other human studies of the artemisinins (5, 18–20) although few data are available in young children, and neurological examinations are less reliable in patients under 5 years of age (18, 21).

The study was confined to patients with moderately severe malaria, presenting to well-equipped units where close observations could be made. Many patients with potentially life-threatening malaria have more severe disease than those in this study, with deeper levels of coma, severe acidosis, severe anaemia, and impairment of pulmonary and renal function. Studies are being conducted to investigate the early administration of rectal artesunate in the planned context of remote rural communities in Africa and Asia.

Although artemisinin derivatives have been widely used in southeast Asia, this is not yet the case in Africa where they have a potentially important role, both in combination therapies and as prompt treatment of potentially life threatening malaria. Our results provide evidence that in children and adults with malaria of moderate severity, artesunate given by suppository is effective in

most individuals and is well tolerated. Artesunate suppositories can be given safely by personnel with little training, even in the home. Staff, patients, and parents should be informed of the need to watch for the expulsion of suppositories, and of the need to ensure follow-up with an effective curative treatment. Patients and their relatives readily accepted the use of rectal treatment in this study. Provided early administration of rectal artesunate does not deter patients from reaching a health-care facility that can provide further effective antimalarial treatment and appropriate supportive management, prereferral rectal artesunate has the potential to reduce malaria-related morbidity and mortality. This treatment is of greatest relevance to communities in rural areas of malaria-endemic countries, which commonly bear the heaviest malaria burden and for whom parenteral treatment is often not immediately available.

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Natural health products and drug interactions

Canadian Natural Health Products Regulations came into force in January 2004, and will be implemented in stages over 6 years. As with other product lines, reporting of adverse reactions (AR) to natural health products is now mandatory for industry. Also, because of their role in reporting ARs, health care professionals and consumers need to be aware of the reporting system for natural health products.

Health Canada has chosen three popular herbal medicines (echinacea, ginkgo biloba and St. John's wort) to illustrate some current safety concerns associated with the use of natural health products. Health Canada's database of spontaneous ARs was consulted for the period 1 January 1998 to 30 June 2003.

Echinacea species belong to the same family as ragweed and daisies (Asteraceae). Allergic reactions, including anaphylaxis, following the use of echinacea have been reported. The Health Canada database had 23 reports of suspected ARs associated with echinacea; 4 cases were allergic reactions, 3 of which involved single ingredient products. Symptoms ranged from rash to swelling of the tongue and lips, to anaphylactic reaction.

There were 21 reports of suspected ARs associated with **ginkgo biloba**. Most involved platelet, bleeding and clotting disorders, which is in line with its ability to inhibit platelet activating factor. One report was of a fatal gastrointestinal hemorrhage in which the suspect products included ticlopidine and ginkgo, both taken over two years, along with multiple concomitant

medications. There was also a report of stroke in a patient taking multiple drugs, including clopidogrel and ASA, as well as a herbal product containing ginkgo. Caution should be exercised when ginkgo is used concomitantly with anti-coagulants and drugs that affect platelet aggregation (e.g., warfarin, ASA, NSAIDs, ticlopidine and clopidogrel).

Patients also need to heed medical instructions regarding pre- and postoperative use of herbal products; for example, it has been recommended that patients stop taking ginkgo at least 36 hours before surgery.

Because **St. John's wort** (*Hypericum perforatum*) is a potent inducer of cytochrome P450, its concomitant use with CYP3A4 substrates may result in subtherapeutic levels of these drugs and may necessitate increased dosage requirements. St. John's wort may trigger serotonin syndrome, a result of potentiated serotonin (5-HT) reuptake inhibition when St. John's wort is taken concomitantly with 5-HT reuptake inhibitors or other drugs that enhance serotonergic activity (e.g., triptans).

There were 45 reports of suspected ARs associated with St. John's wort. The most common reactions involved central and peripheral nervous system disorders and psychiatric disorders. Of the psychiatric reactions, two cases involved suspected serotonin syndrome as a result of an interaction with sertraline, and one case included symptoms suggestive of serotonin syndrome as a result of an interaction with venlafaxine. There were two cases in which St. John's wort was suspected of inducing mania (one involved concomitant lithium and the other concomitant bupropion treatment).

*Jenna Griffiths, Scott Jordan, Karen Pilon.
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Valdecoxib: severe cutaneous reactions

Valdecoxib (Bextra™), a selective inhibitor of cyclo-oxygenase 2 (COX-2), is indicated for the treatment of acute and chronic signs and symptoms of adult rheumatoid arthritis and osteoarthritis as well as for the relief of pain associated with primary dysmenorrhea (1). Severe cutaneous adverse reactions (ARs) associated with valdecoxib, including erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis, have been reported internationally (2, 3). The Canadian product monograph (1) contains the following information:

- a recommendation to discontinue valdecoxib therapy at the first appearance of a rash or other sign of hypersensitivity;
- a contraindication for use in patients who have had allergic-type reactions to sulfonamides;
- a contraindication for use in patients who have experienced asthma, urticaria or an allergic-type reaction after taking ASA or other NSAIDs.

In a published case report, a patient with a previous allergy to an antimicrobial sulfonamide was diagnosed with toxic epidermal necrolysis after treatment with valdecoxib (5). Controversy

exists regarding the potential for cross-reactivity between sulfonamide antimicrobials and other sulfonamide-containing compounds (6). A recent study suggests that a predisposition to allergic reactions, rather than a crossreactivity with sulfonamide-based drugs, is possible (4). Health Canada has received reports of serious cutaneous reactions associated with celecoxib and rofecoxib in patients with and without a history of sulfa allergy. Valdecoxib and celecoxib have similar structures: both contain a benzene-sulfonamide moiety (5). The structure of rofecoxib contains a methylsulfonyl moiety (5).

At least 50% of patients with Stevens-Johnson syndrome and toxic epidermal necrolysis experience a one to 14-day prodrome of flu-like symptoms, including fever, malaise, rhinitis, chest pain, vomiting, sore throat, cough, diarrhea, headache, myalgia and arthralgia (7). The progression from rash to desquamation can occur within a few days, or hours, and may result in fatal complications, such as infection and renal or respiratory failure (8, 9). It has previously been shown that early discontinuation of drugs with half-lives of less than 24 hours may decrease the rate of death from Stevens-Johnson syndrome and toxic epidermal necrolysis (8). Because valdecoxib has a half-life of about 8 hours (1), withdrawal of this drug when flu-like symptoms develop may decrease the risk of Stevens-Johnson syndrome and toxic epidermal necrolysis in certain patients. Therefore, health care professionals should encourage patients taking valdecoxib to seek medical attention if any cutaneous or flu-like symptoms occur (1).

Violetta Skalski Extracted from: Canadian Adverse Reaction Newsletter, Volume 14, Issue 1, January 2004

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International Nonproprietary Names (INN)

An international role for nomenclature through INNs

The global pharmaceuticals market is characterized by the huge choice of medicinal preparations available to satisfy the demands of many diseases and conditions. As the range of preparations has expanded internationally, it has become increasingly important to have a centralized system for specialists to find their way through different pharmaceutical nomenclatures and simplify the choice and naming of drugs.

A vital reference for pharmaceutical preparations is the system of International Nonproprietary Names (INN) for Pharmaceutical Substances (1). The existence of an international nomenclature for pharmaceutical substances in the form of an INN is important for the precise and unambiguous identification, safe prescribing and delivery of drugs to patients as well as to promote communication and exchange of information between health specialists and scientists throughout the world.

By the same token, in order to ensure the unimpeded use of INNs in international practice the nomenclature must be free from any legal constraints. Consequently, in contrast to a proprietary (brand) name, which is given to a preparation containing one or several active ingredients, produced in a particular pharmaceutical form and dose and which belongs to the manufacturer (or trademark owner), an INN identifies the actual active pharmaceutical substance under a single internationally recognized nonproprietary (generic) name.

The INN system has been developed by WHO and is regulated with the aim of protecting the generic name of a pharmaceutical substance from infringement of property rights to guarantee international availability. It is thus possible to systematize the nomenclature of pharmaceutical preparations registered under numerous propri-

etary (brand) names and produced by different pharmaceutical firms in various countries of the world using a single criterion – the presence in the preparation of a specific active substance(s).

The INN process

The INN selection process is the responsibility of members of the INN Expert Panel and is coordinated by the WHO INN Programme Secretariat based in the Department of Essential Drugs and Medicines Policy at the World Health Organization. The composition of the INN Expert Panel follows a selection process and the following countries are currently represented: France, Japan, Nigeria, Poland, Russia, Singapore, Spain, United Kingdom, United States of America, and Tunisia. WHO also collaborates closely with national nomenclature committees and national regulatory agencies in the selection of a name which is unique, distinctive in sound and spelling and informative and that may be adopted throughout the world for each individual active pharmaceutical substance.

Nomenclature agencies exist in many countries and exercise different levels of authority. Together with the pharmaceutical industry, they are concerned with the selection of a suitable nonproprietary name for pharmaceuticals entering national markets. Because manufacturers supply their products to markets in other countries besides their own, and medical and pharmaceutical literature is widely translated throughout the world, the need for harmonized nomenclature between the main pharmaceutical-producing countries is vital.

As a whole, the INN Programme, the national committees and nomenclature bodies undertake the task of standardizing and unifying nomenclature and associated rules at the international level in order to guarantee precise and accurate information on product summary characteristics and thus avoid any confusion that could arise if different nonproprietary names were used for a medicine in one or several countries. The INN Expert Panel establishes rules and formulates the basic principles for selecting INNs.

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Brief history of the INN programme

The need to identify pharmaceutical substances by means of a single and freely available nonproprietary name was officially recognized for the first time in 1915 by the International Pharmaceutical Federation which set up a committee on international nomenclature of medicines. In 1924, the committee drew up the first such list of names which was used in the pharmacopoeia of several countries.

The concept of International Nonproprietary Names for pharmaceutical substances (INNs) was established during a meeting of the Committee on the Unification of Pharmacopoeias in 1949. At the time, when WHO was asked to take the lead in INN activities, a number of countries already had national nomenclature programmes to unify the names of pharmaceutical substances defined by each national pharmacopoeia committee. The first task facing WHO was to organize coordination of activities among national programmes. In 1949, an Expert Panel was constituted and set about drawing up general rules and a programme of work for determining and selecting international nonproprietary names.

The INN Programme in its present form was promulgated by World Health Assembly resolution WHA3.11 in 1951 and became effective in 1953 with the publication of the first INN list. The current procedure for selecting recommended INNs was adopted by the Executive Board in 1955, as endorsed in resolution EB15.R7. Subsequently, only one change has been made to the initial text – replacement of the term “pharmaceutical preparation” by the term “pharmaceutical substance”. Currently, there is a proposal to update the procedure. This has been circulated for comment to all interested parties, including national drug regulatory authorities, pharmacopoeia committees, and the International Federation of Pharmaceutical Manufacturers Associations (IFPMA).

National and international nonproprietary names

In some countries, official lists of national nonproprietary names are regularly published; for example, British Approved Names (BAN), United States Pharmacopoeia USP Dictionary of USAN and International Drug Names, and Japanese Accepted Names for Pharmaceuticals (JAN). Through long and permanent collaboration, national nonproprietary names of pharmaceutical substances (NNN) adopted by the pharmacopoeia committees or ad-hoc committees on

nomenclature are nowadays, with few exceptions, identical to the INNs (2).

However, there are some countries where national nonproprietary names different from INNs are also used to designate pharmaceutical substances. Many of these differences are frequently insignificant, the INN spelling is different only on account of the requirements of the language or pronunciation or on account of the replacement of certain letters (“t” for “th”, “f” for “ph”, “i” for “y” and so on). Moreover, pharmaceutical regulations in the European Union require the use of recommended INNs as common names to describe the composition of medicinal products (3, 4).

In Russia, the adoption of an INN is particularly necessary for the registration of pharmaceuticals. At present, the nomenclature of drugs authorized for medicinal use contains a list of Russian preparations whose names present the designation of the pharmacopoeial item corresponding to the pharmaceutical substance, for example: amiridin, arbidol, etaden, etacidin, fenazepam, proksodolol etc. There is therefore a need for a thorough review of the list of Russian substances and pharmaceutical preparations based on the concept of international and national nonproprietary names. Where newly developed substances are concerned, they should be composed in accordance with procedures followed by WHO.

Procedure and criteria for selecting an INN

Under the current procedure, a request for an INN is made on the relevant form and submitted to WHO. In countries where there is a national committee on nomenclature, the application is made through the appropriate national body. Should a nomenclature body not be active in a specific country, an application can be filed directly with the INN Programme at WHO. Nowadays, the number of direct requests is increasing and corresponding efforts have been made to streamline the INN selection process.

Data on the chemical structure, molecular formula (5), Chemical Abstract Service (CAS) registry number, company code designation, mechanism of action, and information on therapeutic use of the active substance, must be provided by the originator of the request, as well as suggested INNs (from 1 to 6 proposals) in English. The INN is selected, in principle, for a single, well-defined substance and designated for the active part of the molecule only. To avoid the multiplication of entries in cases where several salts and esters

are used, the user has to create a modified INN (INN_m). For example oxacillin and ibufenac are INNs and their salts are named oxacillin sodium and ibufenac sodium. The latter are referred to as modified INNs. The texts of the procedure and of General Principles are regularly published in *WHO Drug information* as annexes to lists of proposed INNs.

The name proposed by a manufacturer for consideration is examined, and the corresponding INN adopted by consensus among all members of the Expert Panel. The name is then published as a proposed INN. For a period of four months, the INN Secretariat receives comments or objections to the proposed name, for example, objections based on similarity with a brand name. If no objections are made to the proposed INN, it is then published as a recommended international nonproprietary name.

When INNs are selected for pharmaceutical substances, the following basic principles are to be followed:

- An INN must be distinctive in sound and spelling; should not be too long or liable to confusion with other names in common use.
- INNs for substances belonging to a pharmacologically related group of substances should as far as possible demonstrate this relationship. Care should be taken to avoid names that might convey to patients an anatomical, physiological, pathological or therapeutic suggestion.

In addition to the basic principles, when choosing an INN there are a number of other rules that should be followed in order for them to be suitable for international use. First of all, there are a number of linguistic and phonetic requirements. For example, use of the letters "h" and "k" is to be avoided; it is recommended that "e" should be used instead of "ae" and "oe", "i" instead of "y", "f" and "t" instead of "ph" and "th", etc.

When choosing INNs for pharmaceutical substances, specialists should be guided by the following WHO documents:

- Procedure for selection of recommended International Nonproprietary Names (INN) for Pharmaceutical Substances;
- General Principles for guidance in devising International Nonproprietary Names (INN) for Pharmaceutical Substances.

INN stem system

Of particular interest is the INN stem system. Many INNs consist of a common stem, mainly a series of letters — a suffix, prefix, infix or a combination of these — which shows the relationship between the pharmacologically related substance and use in combination with the distinctive part of the name. Table 1 presents examples of widely used stems. Among these are two examples of stems that are placed as prefixises (def- and grado-) whereas others are used mainly as suffixes, or in some cases as infixes. WHO regularly publishes a document on the use of common stems (6).

These stems and their definitions have been selected by INN experts and must be used when choosing new INNs for pharmaceutical substances related to an established group (series) of related compounds. For example, the stem "-caine" includes 64 INNs classified as local anaesthetics: benzocaine, procaine, lidocaine, tetracaine, etc. In Russia, different preparations based on 12 pharmaceutical substances are registered in this category of compounds; their international nonproprietary names contain the stem "-caine".

Conclusion

The process of selecting INNs becomes increasingly complicated each year. This is due to the constant development of innovative pharmaceutical preparations and biological products, new classes of compounds, and discovery of new mechanisms of action. Specific nomenclature systems are being established for these areas in collaboration with drug regulatory authorities and biological experts.

In accordance with World Health Assembly resolution WHA46.19, it is necessary to determine that brand names derived from international nonproprietary names or INN stems are not used as trade marks. The practice of unjustified use of stems in trade marks or brand names for pharmaceutical products undermines the principle whereby INNs are public domain property. Non respect of the INN system may impede future rational selection of INNs and ultimately jeopardize the safety of patients by creating confusion in drug nomenclature.

The INN system owes its success in great part to the international suitability, flexibility and application of the names. INNs are accessible to specialists dependent on drug nomenclature when

Table 1. Examples of widely used common stems (7)

Stem	Name of pharmacological group
ac	anti-inflammatory agents, ibufenac derivatives
adol	analgesics
ast	anti-asthmatic, anti-allergic substances not acting primarily as antihistaminics
astine	antihistaminics
azepam	diazepam derivatives
bol	steroids, anabolic
cain	class I antiarrhythmics, procainamide and lidocaine derivatives
caine	local anaesthetics
cef-	antibiotics, cephalosporanic acid derivatives
cillin	antibiotics, 6-aminopenicillanic acid derivatives
conazole	systemic antifungal agents, miconazole derivatives
cort	corticosteroids, except prednisolone derivatives
coxib	selective cyclo-oxygenase inhibitors
entan	endothelin receptor antagonists
gab	gabamimetic agents
gado-	diagnostic agents, gadolinium derivatives
gatran	thrombin inhibitors, antithrombotic agents
gest	steroids, progestogens
gli	antihyperglycaemics
io	iodine-containing contrast media
metacin	anti-inflammatory, indometacin derivatives
mycin	antibiotics, produced by <i>Streptomyces</i> strains
nidazole	antiprotozoal substances, metronidazole derivatives
olol	α -adrenoreceptor antagonists
oxacin	antibacterial agents, nalidixic acid derivatives
platin	antineoplastic agents, platinum derivatives
poetin	erythropoietin type blood factors
pril(at)	angiotensin-converting enzyme inhibitors
profen	anti-inflammatory substances, ibuprofen derivatives
prost	prostaglandins
relin	pituitary hormone release-stimulating peptides
sartan	angiotensin II receptor antagonists, antihypertensive (non-peptidic)
vaptan	vasopressin receptor antagonists
vin	vinca-type alkaloids

providing information on the pharmacological and therapeutic action of preparations. INN classification is also used by WHO, particularly for drug evaluation and safety monitoring.

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Regulatory and Safety Action

SSRIs: behavioural and emotional changes and risk of self-harm

Canada — Health Canada is advising that selective serotonin re-uptake inhibitors (SSRIs) and other new antidepressants now carry stronger warnings. These warnings indicate that patients of all ages taking these drugs may experience behavioural and/or emotional changes that may put them at increased risk of self-harm or harm to others. Health Canada has not authorized these drugs for use in patients under 18 years of age. The prescribing of drugs is a physician's responsibility although off-label use of these drugs in children is acknowledged to be an important tool for doctors.

In February 2004, a scientific advisory panel set up by Health Canada provided a clinical practice perspective on paediatric clinical trial safety data and spontaneous post-marketing reports for SSRIs and other newer antidepressants. The panel agreed that a contraindication was not warranted for these medications, and supported Health Canada's recommendation for warnings.

Consequently, the manufacturers of citalopram hydrobromide (Celexa®), venlafaxine (Effexor®), fluoxetine (Prozac®), mirtazapine (Remeron®), sertraline (Zoloft®), paroxetine (Paxol®), fluvoxamine (Luvox®) and bupropion (Wellbutrin®) (Zyban® for smoking cessation) have issued a class warning regarding the possibility that SSRIs (selective serotonin reuptake inhibitors) and other newer antidepressants may be associated with behavioural and emotional changes, including risk of self-harm.

Potential association with the occurrence of behavioural and emotional changes, including self harm

Patients under 18 years of age (paediatric): placebo-controlled clinical trial data

- Recent analyses of placebo-controlled clinical trial safety databases from SSRIs and other newer antidepressants suggests that use of these drugs in patients under the age of 18 may be

associated with behavioural and emotional changes, including an increased risk of suicidal ideation and behaviour over that of placebo.

- The small denominators in the clinical trial database, as well as the variability in placebo rates, preclude reliable conclusions on the relative safety profiles among these drugs.

Adult and paediatric patients: additional data

- There are clinical trial and post-marketing reports with SSRIs and other newer antidepressants, in both paediatrics and adults, of severe agitation-type adverse events coupled with self-harm or harm to others. The agitation-type events include: akathisia, agitation, disinhibition, emotional lability, hostility, aggression, depersonalization. In some cases, the events occurred within several weeks of starting treatment. Given that bupropion may be prescribed as either an antidepressant or a smoking cessation product, these conditions affect the conditions of use of both products.

Rigorous clinical monitoring for suicidal ideation or other indicators of potential for suicidal behaviour is advised in patients of all ages. This includes monitoring for agitation-type emotional and behavioural changes.

Patients currently taking SSRIs should NOT discontinue treatment abruptly, due to risk of discontinuation symptoms. At the time that a medical decision is made to discontinue an SSRI or other newer antidepressant drug, a gradual reduction in the dose rather than an abrupt cessation is recommended.

It should be noted that a causal role for SSRIs and other newer antidepressants in inducing self-harm or harm to others has not been established. The possibility of a suicide attempt is inherent in depression and other psychiatric disorders, and may persist until remission occurs. Therefore, patients should be closely supervised throughout therapy with appropriate consideration to the possible need for hospitalization. The warning informs practitioners that all patients being treated with SSRIs and other newer antidepressants

should be rigorously monitored for clinical worsening, or onset/worsening of agitation-type adverse events, or other indicators of potential for suicidal behaviour.

Reference: Health Canada advisories 26 May 2004, 3 June 2004 and 10 June 2004, on <http://www.hc-sc.gc.ca>

Proposed rule on combination products

United States of America — The Food and Drug Administration (FDA) has announced a proposed rule to assign a lead centre with responsibility for premarket review and regulation of a combination product.

Combination products are considered as a combination of a drug, a device, or a biological product. They represent a growing category of products incorporating cutting edge, novel technologies that hold great promise for advancing patient care. Products, such as drug-eluting stents (which combine a drug with a medical device), orthopedic implants with genetically engineered human protein, and antibiotic bone cement, often do not fit neatly into traditional categories of FDA-regulated items. But such innovative combination products have the potential to make treatments safer, more effective, more convenient or more comfortable for patients.

The purpose of the proposed rule is twofold: to codify the definition of “primary mode of action” (PMOA), the criterion the agency has used for more than a decade when assigning combination products for review; and to simplify the assignment process by providing a defined framework that sponsors may use when recommending and/or considering the PMOA and assignment of a combination product to an FDA Center.

Under the proposal, the “primary mode of action” would be defined as “the single mode of action (e.g., drug, device, biological product) of a combination product that provides the most important therapeutic action of the combination product.” This would be the mode of action that is expected to make the greatest contribution to the overall therapeutic effects of the combination product.

In certain cases, it is not possible for either FDA or the product sponsor to determine, at the time a request for assignment is submitted, which mode of action of a combination product provides the

most important therapeutic action. In those cases, the agency would assign the combination product to the FDA Center that regulates other combination products presenting similar questions of safety and effectiveness with regard to the combination product as a whole.

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2. *Primary Mode of Action Assignment Flowchart*. <http://www.fda.gov/OHRMS/DOCKETS/98fr/oc03366.pdf>.

European Medicines Agency : new name and advisory role

European Union — The European Agency for the Evaluation of Medicinal products (EMEA) has recently undergone a review based on experience gained during the six years since its establishment. EMEA will now be renamed The European Medicines Agency and the Committee on Proprietary Medicinal Products (CPMP) is renamed the Committee for Human Medicinal Products (CHMP), both with effect from 1 May 2004.

Among improvements to operations, an amendment concerning the scope of the Agency’s mandate to increase cooperation with the World Health Organization is reflected in Article 58, which states:

“The Agency may give scientific opinion, in the context of cooperation with the World health Organization, for the evaluation of certain medicinal products for human use intended exclusively for markets outside the Community. For this purpose, an application shall be submitted to the Agency in accordance with the provisions of Article 6. The Committee for Medicinal Products for Human Use may, after consulting the World Health Organization, draw up a scientific opinion in accordance with Articles 6 and 9. The provisions of Article 10 shall not apply),

Additionally, Article 27 on pharmacovigilance provides that “The Agency shall collaborate with the World health Organization in matters of international pharmacovigilance and shall take the necessary steps to submit to it, promptly, appropriate and adequate information regarding the measures taken in the Community which have a bearing on public health protection in third countries ...”

Reference: Regulation (EC) No 2003 of the European Parliament and Council

Atypical antipsychotics warning

United States of America — In 2003, the Food and Drug Administration (FDA) asked all manufacturers of atypical antipsychotic medications, to add a warning on the increased risk of hyperglycaemia and diabetes in patients taking these medications..

The manufacturer of quetiapine fumarate (Seroquel®) tablets has advised of changes to prescribing information in the form of a warning for hyperglycaemia and diabetes mellitus. Hyperglycaemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics, including quetiapine fumarate. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycaemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycaemia-related adverse events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycaemia-related adverse events in patients treated with atypical antipsychotics are not available.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment.

Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycaemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycaemia during treatment should undergo fasting blood glucose testing. In some cases, hyperglycaemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of antidiabetic treatment despite discontinuation of the suspect drug.

Reference: Communication from AstraZeneca 4 May 2004 on <http://www.fda.gov/medwatch>

Tegaserod maleate: updated precautions

United States of America — The manufacturer of tegaserod maleate tablets (Zelnorm®) has advised prescribers of an important drug warning and prescribing information. Tegaserod maleate is a serotonin 5-HT₄ receptor partial agonist indicated for the short-term treatment of women with irritable bowel syndrome (IBS) whose primary symptom is constipation.

This new information relates to a warning for serious consequences of diarrhoea and a precaution for rare reports of ischaemic colitis in post marketing use. Serious consequences of diarrhoea, including hypovolaemia, hypotension, and syncope, have been reported in clinical trials and during marketed use. Tegaserod maleate should be discontinued immediately in patients who develop hypotension or syncope.

Reference: *FDA Talk Paper*; T04–10. 28 April 2004. Communication from Novartis. 26 April 2004 at <http://www.fda.gov/medwatch/index.html>

Rotavirus vaccine ready for licensing

In 1999, the oral rotavirus vaccine, Rotashield® was withdrawn from the market by the manufacturer following reports of intussusception (1, 2). The US National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health (NIH), has now announced a new license agreement for global commercialization of RotaShield® (3).

Worldwide, rotavirus is implicated in more than 135 million episodes of diarrhoea each year in infants and children younger than 5 years of age, resulting in almost 600 000 deaths annually. Rotaviruses are egalitarian viruses: they readily infect and cause illness in infants and young children in both developed and developing countries. The overall consequences of these illnesses, however, are quite different. Approximately 1600 rotavirus-related deaths each day occur predominantly in the developing countries

Rotavirus infection develops quickly and in addition to diarrhoea, may include vomiting, fever and dehydration. The resulting dehydration can

be reversed through oral rehydration therapy or, in more serious cases, through hospitalization and intravenous fluids. Although effective, these therapies are not readily available or used in many parts of the developing world. Children in developing countries are more vulnerable to severe and fatal illness.

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Tenofovir approved for HIV

Canada — Health Canada has issued a marketing authorization for tenofovir disoproxil fumarate (Viread®), a new nucleotide reverse transcriptase inhibitor which is conditional on the conduct of confirmatory studies to verify the clinical benefit seen to date. Tenofovir is indicated for the treatment of HIV-1 infection in combination with other antiretroviral agents in patients 18 years of age and older who have experienced virologic failure on other regimens.

Routine monitoring of renal function is recommended and particular caution should be exercised when administering to patients with known risk factors for renal disease or a history of renal dysfunction (although cases of renal failure have also been reported in patients with no known risk factors). Tenofovir should not be used concurrently with a nephrotoxic agent nor be administered to patients with renal insufficiency (creatinine clearance < 60 mL/min).

Co-administration of tenofovir and didanosine should be undertaken with caution because the C_{max} and AUC of didanosine increases approximately 48 to 64%. Increases in didanosine concentration of this magnitude could potentiate didanosine-associated adverse events, including pancreatitis, lactic acidosis, and neuropathy. Patients receiving this combination should be monitored closely and didanosine should be discontinued in patients who develop didanosine-associated adverse events.

Early virologic failure and high rates of resistance mutations have been reported in HIV-infected patients receiving once-daily triple nucleotide reverse transcriptase inhibitor regimens containing tenofovir disoproxil fumarate/lamivudine/didanosine, and tenofovir DF/lamivudine (investigational as once-daily) abacavir. Tenofovir DF in combination with didanosine and lamivudine or abacavir and lamivudine as a triple antiretroviral therapy is not recommended when considering a new treatment regimen for patients with HIV infection.

The most common adverse events in patients receiving tenofovir in clinical studies were mild to moderate gastrointestinal events, such as nausea, diarrhoea, vomiting and flatulence. In general, laboratory abnormalities observed in clinical studies occurred with similar frequency in the tenofovir and placebo-treated groups.

Adverse events reported during clinical practice include renal insufficiency, kidney failure, Fanconi syndrome, increased creatinine levels, asthenia, pancreatitis, hypophosphataemia, lactic acidosis, dizziness, dyspnoea and rash.

Reference: Communication from the manufacturer dated 8 March 2004 under a Health Canada advisory on <http://www.hc-sc.gc.ca>

Rosuvastatin: revised package insert

United States of America — The manufacturer of rosuvastatin (Crestor®) has released a revised package insert for use in 22 member countries of the European Union (EU). The changes to the European labeling are in response to post-marketing spontaneous adverse event reports in patients receiving rosuvastatin and highlight certain patient populations who may be at an increased risk for serious muscle toxicity (myopathy) associated with use, especially at the highest approved dose of 40 mg.

Rosuvastatin is a cholesterol-lowering drug approved in the USA in August 2003. At that time, the FDA identified that an increased baseline risk for myopathy warranted more careful monitoring, and labeling included a specific section on myopathy/rhabdomyolysis. Elderly patients (≥ 65 years) with hypothyroidism, and/or renal insufficiency should be considered to be at greater risk for developing myopathy while receiving a statin. Physicians are warned to prescribe rosuvastatin

with caution in these patients, particularly at higher doses, as the risk of myopathy increases with higher drug levels.

Healthcare professionals are reminded of the following key safety messages: start doses and maintenance doses of drug should be based on individual cholesterol goals and apparent risks for side-effects; all patients should be informed that statins can cause muscle injury, which in rare, severe cases, can cause kidney damage and other organ failure that are potentially life-threatening; and patients should be told to promptly report to their physician signs or symptoms of muscle pain and weakness, malaise, fever, dark urine, nausea, or vomiting. The current FDA-approved label can be obtained at http://www.fda.gov/cder/foi/label/2003/21366_crestor_lbl.pdf

Reference: *FDA Public Health Advisory*, 9 June 2004.

Sulphur hexafluoride: contraindicated in heart disease

European Union — Severe allergy and heart problems have been reported as rare side effects occurring within minutes of sulphur hexafluoride administration (Sonovue®), a diagnostic contrast medium for use with ultrasound imaging where study without contrast enhancement is inconclusive. As such, it is only used in the hospital or clinical setting. On the basis of reported adverse events and as a precautionary measure, the European Medicines Agency has restricted use by a temporary suspension in heart imaging pending further evaluation.

Sulphur hexafluoride is now contraindicated in patients with known coronary artery disease, myocardial infarction, unstable angina, acute cardiac failure, class II/IV cardiac failure, severe rhythm disorders, acute endocarditis and prosthetic valves. Patients should be kept under close medical supervision during and for at least 30 minutes following administration of sulphur hexafluoride.

Adverse events included severe hypotension, bradycardia, cardiac arrest and acute myocardial infarction, in the context of an idiosyncratic hypersensitivity reaction.

Reference: EMEA Public statement. 19 May 2004 on <http://www.emea.eu.int>

Oxandrolone and warfarin

United States of America — The manufacturer of oxandrolone (Oxandrin®) has provided new safety information when used concurrently with the oral anticoagulant warfarin for systemic anticoagulation. Oxandrolone, a synthetic derivative of testosterone, is indicated as adjunctive therapy to promote weight gain after weight loss following extensive surgery, chronic infections, or severe trauma, and in some patients who without definite pathophysiologic reasons fail to gain or to maintain normal weight, to offset the protein catabolism associated with prolonged administration of corticosteroids, and for the relief of the bone pain frequently accompanying osteoporosis.

As a class, anabolic androgenic steroids may increase susceptibility, specifically to oral anticoagulants, with reduction of the anticoagulant dosage necessary to maintain the desired prothrombin time (PT). No specific directions have previously been available for any anabolic androgenic agents. A recent clinical study conducted by Savient demonstrated a significant decrease (80–85%) in the warfarin dose needed to achieve therapeutic effect in subjects also treated with oxandrolone. The recommendations are specific and cannot be presumed to be applicable for other anabolic androgenic steroids.

Concurrent dosing of oxandrolone and warfarin may result in unexpectedly large increases in the International Normalized Ratio (INR) or PT. When oxandrolone is prescribed to patients being treated with warfarin, doses of warfarin may need to be decreased significantly to maintain a desirable INR level and diminish the risk of potentially serious bleeding.

Physicians should instruct patients to report immediately any use of warfarin and any bleeding. Furthermore, in patients receiving both drugs, careful monitoring of the INR or PT, and adjustment of the warfarin dosage if indicated, are recommended when the oxandrolone dose is changed or discontinued. Patients should be closely monitored for signs and symptoms of occult bleeding.

Reference: *FDA Safety Alert*. 20 April 2004 at <http://www.fda.gov/medwatch/index.html>.

Oseltamivir: new preclinical findings

Singapore — Oseltamivir (Tamiflu®, Roche) was recently licensed for the treatment of uncomplicated illness due to influenza infections in children

one year of age and older who have been symptomatic for no more than 2 days. It has been licensed for use in adults since October 2000. The findings of a recent preclinical study alerts potential concerns pertaining to the use of Tamiflu® in very young children.

The manufacturer has recently released findings of its preclinical study carried out in juvenile rats (7-day old) and highlighted the concerns to the regulatory authorities regarding the use of Tamiflu® in infants. Juvenile rats that were treated with a single dose of 1000 mg/kg oseltamivir (about 250 times the recommended total daily dose) died due to the unusually high levels of oseltamivir and its phosphate salt found in the brain of these young animals. The concentrations of oseltamivir phosphate were approximately 1500 times those seen in adult rats given the same dose. It is likely that these high exposures are related to an immature blood brain barrier of the juvenile rats. Studies showed no death or other significant effects in older juvenile rats given the same or higher doses of Tamiflu®.

HSA's recommendation

The clinical significance of these data to human infants is uncertain. Due to the uncertainty in predicting the exposures in infants with immature blood brain barrier, prescribers are advised that Tamiflu® should not be given to children under 1 year of age. The above findings have been included in the package insert of Tamiflu®.

Reference: Product safety alerts, 15 March 2004. Health Sciences Authority, Singapore on <http://www.hsa.gov.sg>

Muromonab: nervous system complications

Canada — The manufacturer of muromonab-CD3 (Orthoclone OKT*3®) has informed Canadian hospitals of important new safety information. Muromonab is used to treat acute rejection from liver, kidney, and heart transplants that do not respond to other therapies.

Muromonab is not approved for use in children in Canada. Children treated with muromonab may be at increased risk of nervous system complica-

tions, most notably a buildup of excess fluid in the brain (cerebral oedema) that may result in a fatal condition called cerebral herniation. Children may also be at increased risk of lymphomas and infections.

Since 1986, a total of nine (9) cases of cerebral oedema have been reported around the world in children, with subsequent cerebral herniation and death in 6 of the 9 cases. The majority of the cases of cerebral herniation in paediatric patients occurred within a few hours to one day after the first injection. Signs of cerebral oedema and cerebral herniation may include the sudden appearance of severe headache, seizures, impaired mental function, drowsiness and lethargy, coma.

Patients with high blood pressure and excess fluid buildup in their bodies (fluid overload) are at increased risk of developing these conditions.

Reference: Communication from manufacturer on <http://www.hc-sc.gc.ca> dated 17 May 2004.

Domperidone and unapproved use

United States of America — In response to reports that women may be using an unapproved drug, domperidone, to increase milk production (lactation), the Food and Drug Administration (FDA) is warning breastfeeding women not to use this product because of safety concerns. The FDA has also issued six letters to pharmacies that compound products containing domperidone and firms that supply domperidone for use in compounding.

FDA has become aware that some women are purchasing domperidone to increase breast milk production. Domperidone may increase the secretion of prolactin, a hormone that is needed for lactation. The potential public health risks associated with domperidone include cardiac arrhythmias, cardiac arrest, and sudden death in patients receiving an intravenous form of domperidone. The oral form of domperidone by breastfeeding women can expose a breastfeeding infant to unknown risks. Domperidone is not approved in the USA for any indication.

Reference: *FDA Talk paper*, T04-17, 2004.

Safety of Medicines

Combating counterfeit medicines*

Substandard medicines are products whose composition and ingredients do not meet the correct scientific specifications and which may consequently be ineffective and often dangerous to the patient. Substandard products may occur as a result of negligence, human error, insufficient human and financial resources or counterfeiting.

Counterfeit medicines are part of the broader phenomenon of substandard pharmaceuticals. The difference is that they are deliberately and fraudulently mislabeled with respect to identity and/or source. Counterfeiting can apply to both branded and generic products and counterfeit medicines may include products with the correct ingredients but fake packaging, with the wrong ingredients, without active ingredients or with insufficient active ingredients. In wealthier countries, new expensive medicines are frequently counterfeited such as hormones, corticosteroids, cancer drugs or antiretrovirals. In developing countries, the most counterfeited medicines are those used to treat life-threatening conditions such as malaria, tuberculosis and HIV/AIDS.

Trade in these medicines is more prevalent in countries with weak drug regulation control and enforcement, scarcity and/or erratic supply of basic medicines, unregulated markets and unaffordable prices (<http://www.who.int/medicines>). It is estimated that counterfeits make up a significant proportion of the global medicines market and are present in both industrialized and developing countries. Industry figures estimate annual earnings from the sales of counterfeit and substandard medicines at over US\$ 32 billion globally.

International action against counterfeiting

A workshop on counterfeit medicines, was held from 13 to 14 February 2004 in Madrid, Spain on the occasion of the International Conference of Drug Regulatory Authorities (ICDRA).

The workshop was attended by national drug regulatory authorities, international organizations, nongovernmental organizations, industry associations, and the media. The programme included presentations on national experience, investigation and action against counterfeits, control of e-commerce counterfeiting, and perspectives from regulatory authorities and international organizations. A draft concept paper on a framework convention against counterfeiting was debated and recommendations proposed. A summary of

highlights is set out on the following pages and a full report of the event is available at <http://www.who.int/medicines>

Industry response to counterfeiting

The view of a leading multinational pharmaceutical company was presented. It is generally agreed that counterfeit drugs endanger health, threaten the reputation of drug companies and undermine regulatory action to control counterfeiting. The presence of counterfeits can also cause a loss of trust in the public health system by patients. Strong internal company strategies to combat counterfeiting are therefore a responsive solution. These may include formal investigative procedures, anti-counterfeiting features in packaging, maintaining secure manufacturing and supply sources, and conduct of market surveys. External strategies may include consumer education, tougher laws, strengthened enforcement and stricter penalties. Both covert and overt measures are available to companies to combat counterfeiting. Measures taken should be difficult

* Views expressed during meeting reports do not necessarily reflect WHO position, policy or endorsement.

to copy, combinatorial, easy to incorporate, and not require regulatory approval and may include user education or deterrents to counterfeiting.

The Pharmaceutical Security Institute (PSI) represents a group of multinational pharmaceutical companies. Its role is to combat counterfeiting through collection, collation and dissemination of information and to identify and satisfy training needs. Drug investigations by law enforcement agencies are often under-resourced due to other crime priorities. PSI key findings in 2003 concluded that of 327 reported incidents of crime in pharmaceuticals, 81% involved counterfeits. Most incidents occurred in the USA, followed by India and China. A key trend indicates that counterfeiting operations are small. In all, 363 people were arrested with an average value of seizure at US\$ 3 million. Fifty-three percent of arrests were made at the point of sale; 13% were manufacturers and 5% were at borders. The US market is predicted to become an attractive target for counterfeit medicines and drug diversion. International mail is highlighted as a distribution corridor readily exploited by medicine traffickers.

A presentation from the self medication industry provided statistical information in relation to the prevalence of counterfeits in Latin America and globally. It confirmed that counterfeit drugs pose a significant public health risk and stated that counterfeiting involves established, sophisticated, regional criminal organizations and international organized crime. Factors that make counterfeiting a widespread activity are:

- Lack of access to many drugs, making low-priced counterfeit products attractive.
- Possibility of selling counterfeit drugs from varied outlets.
- Sale of products without a physician's prescription facilitates the selling of fake or counterfeit products
- Outside of pharmacies, vendors do not possess the same ability to detect counterfeit products as pharmacists do.
- Counterfeiting is not a specific crime and inadequate penalties are applied to drug counterfeiting.
- Lack of intellectual property protection.

- Existence of free trade zones.
- Internet sales leading to cross-border trade in counterfeits.

Factors that are successful in combating counterfeiting are:

- Interagency cooperation.
- Categorizing counterfeiting as a specific crime.
- Establishment of stiffer penalties.
- Monitoring of wholesalers and pharmacies.
- The development of best practice manuals on distribution and dispensing of medicines.
- Consumer education.

In conclusion, essential benefits could be gained from collaboration between the pharmaceutical industry and regulators through development of a comprehensive plan.

E-commerce and challenges to pharmaceutical trading

Sale of drugs on the Internet has both positive and negative aspects. Prescription drug sales on the Internet can provide benefits to consumers, especially to the disabled or homebound patients who cannot move easily. It is convenient for shopping 24 hours a day and gives privacy and anonymity to those who do not want to discuss their medical condition in a public place. However, the negative aspects include possible sale of unapproved new drugs, absence of doctor/patient relationship and possibility of obtaining information on correct use, dispensing of prescription drugs without prescription, and availability of products with fraudulent claims.

The United States Food and Drug Administration has taken steps to customize and expand its enforcement efforts by setting priorities, improving data acquisition, and coordinating case assessment. This has resulted in the evaluation of over 400 websites and an increased number of civil and criminal actions, improved collaboration with international regulatory officials and the issuance of cyber letters. Hard copies of each cyber letter are sent to the website operator, the US Customs Service and the regulatory authority officials in the country in which the operator is based. Other

strategies used to control the sale of drugs on the Internet include, collaboration with other law enforcers and regulatory partners, professional organizations, public outreach-media campaigns, and public education.

In the Netherlands, the Internet plays an important role in the distribution of medicinal products that are being used without prescription. However, where normal safeguards are bypassed, consumers are put at risk. The greatest areas of risk were identified as lifestyle and similar drugs such as anabolic steroids, drugs used for weight loss and hair loss. To maintain public confidence in the health care system it is necessary to prevent unreliable products from entering the Internet, which is by definition a highly volatile mechanism for mass cross-border trade and difficult to police.

In Thailand, websites offering pharmaceuticals for sale provide detailed information on products, as well as order procedures. In Thailand, three main organizations are involved in the purchasing and controlling procedures for pharmaceutical trade via e-commerce: Food and Drug Administration, Customs and the information technology department. Laws are in place to enforce website activity and cooperation to trace the offenders.

The control procedure includes a check of the website for illegal electronic advertisement and sale, and follow up on complaints received from individuals in the form of a letter, telephone, e-mail and random spot checks. If the website is located in Thailand, an e-mail message is sent ordering them to stop illegal advertisement and distribution. In addition, an investigation and inspection of the company and storage site is carried out. FDA personnel also check mail parcels randomly in collaboration with customs and the post office.

Impediments to effective control of illegal trade in pharmaceuticals via the Internet include:

- Servers located in other countries.
- Use of incorrect company name or address.
- Clandestine pharmaceutical storage/unlicensed drug stores.
- Limited resources.
- Insufficient cooperation and collaboration among government agencies.
- Sites close and open easily.

International perspectives

The Interpol Intellectual Property Crime Action Group (IIPCAG) is a multi-agency Action Group made up of different partners such as the European Union, World Customs Organization, World Intellectual Property Organization, REACT UK, law enforcement agencies, and customs officials from Canada, China, Europol, Finland, Ireland, Northern Ireland, Italy and USA. IIPCAG is involved in training and best practices promotion, information and intelligence sharing, and raising public awareness. The Action Group has carried out several successful investigations based on information received from industry and law enforcement agencies. It has developed reporting systems, trained national authorities, and developed a guide on best practices. Increasing scale-up is proof of organized crime and organized criminal activity.

The World Customs Organization (WCO) aims to provide an effective response to fraud or any other form of transnational criminal activity, in particular counterfeiting and piracy. The WCO has developed a strong working relationship with the private sector and has developed model legislation to help countries in drafting or revising their existing customs legislation. A specific website has also been created to provide a full range of international property rights services, including on-line applications for customs protection.

The International Chamber of Commerce (ICC) Counterfeiting Intelligence Bureau provided examples of incidences that occurred in different countries as a result of counterfeit medicines. In many cases, the problem of counterfeiting is difficult to solve due to lack of resources and corruption. Counterfeiting of medicines involves both backstreet and more advanced production facilities and increasingly involves organized crime. In some developing countries, such as Argentina, Mexico or Colombia, 40% of medicines on the market are counterfeit and in many parts of West Africa up to 70% of the market is awash with counterfeits.

The ICC publishes a Counterfeit Pharmaceutical Digest hosts a dedicated website, and collaborates with governments, law enforcement and customs who can assist in tracking pharmaceutical counterfeits. In order to combat counterfeiting, information sharing is vital with a need for greater public awareness and political will.

The global approach of the World Intellectual property organization (WIPO) to address counter-

feiting includes coordination at the international level, as well as training, awareness, and information exchange. At the national level, WIPO will assist Member States in concluding effective public/private partnerships, educate consumers and help develop judicial infrastructures under which counterfeiters will receive deterrent sanctions and right holders will obtain adequate relief and/or compensation.

The World Health Organization's (WHO) is very active in supporting countries to combat counterfeit drugs. Guidelines have been developed, while training on detection and investigation of counterfeit drugs has been carried out in several countries. WHO has also established a working group with pharmaceutical industry associations and nongovernmental organizations which has carried out advocacy and awareness activities. At present, WHO is operating a programme in six countries in the Greater Mekong area. Activities include promoting public awareness, surveillance of the quality of medicines, training of inspectors in detection and investigation of counterfeit medicines, promoting cooperation between drug regulatory authorities and other law enforcement agencies such as the police, customs and prosecutors.

International framework convention to combat counterfeiting of medicines

A draft concept paper on the establishment of an international framework convention to combat counterfeit medicines was presented for debate. The aim of such a framework is to encourage collaboration, including the application of universal jurisdiction, whereby suspected counterfeiting criminals could be prosecuted where they are found, rather than where they had committed the crime. The convention could also be used to form international organizations as well as promote uniformity of sanctions. Drug regulatory authorities have important roles to play in development of the framework.

The convention would clearly define medicines as public health goods while outlining the moral and commercial concerns at stake. The convention would need to concentrate on regional differences and concerns for public access to good quality, safe and effective medicines.

The following issues were discussed and considered relevant to development of a convention:

- Adoption of a convention would assist countries that did not have a legal framework in place and would be an important tool for regulators to show how counterfeiting is a major transnational crime and not only a public health matter. Additionally, establishment of a convention would remove jurisdictional problems amongst countries and help in intelligence gathering.
- Although the focus of a convention should be international, it would also urge national authorities to act on non-compliance and unauthorized use of intellectual property rights within their own country and to introduce laws to protect public health. Counterfeiting thrives in areas of regulatory weakness. Strengthened international cooperation could lead to improved domestic effectiveness, particularly where requirements for registration of medicines, implementation of good manufacturing practice, or licensing of producers has so far been lacking.
- Disparities in sophistication between regions would make centralized discussions difficult for less prominent countries. However, countries could be involved as members of sub-committees, technical advice groups or common interest country blocs. A procedure within the framework of the International Conference of Drug Regulatory Authorities (ICDRA) could also be considered. Regulators must remain engaged in development of the convention until its finalization.
- There is a need to make information on counterfeits available to the public and a convention should make it mandatory for members to report cases.

In conclusion:

- Delegates agreed on a need to urgently endorse the concept for an international framework convention on counterfeiting of medicines.
- Regulatory authorities should be actively engaged in development of the concept.
- Improvement of existing structures was to be encouraged.
- A secretariat should be established to coordinate implementation.

Summary

Participants of the meeting appreciated the efforts made by governments, WHO and other international organizations, nongovernmental organizations and pharmaceutical industries to combat the circulation of counterfeit medicines in national and international markets. However, greater cooperation at all levels should be engaged. The following preliminary action points were identified:

- clarify national definitions and seek harmonization for law enforcement purposes;
- aggregate databases, increase transparency and functionality;
- build on and coordinate existing structures;
- consider the feasibility of having a functioning secretariat to administer and coordinate cooperation and collaboration;
- review and analyse national and international laws relating to counterfeiting.
- Convene a meeting prior to the Twelfth ICDRA to consider progress on development of the concept paper.

Recommendations from the meeting

Participants should:

- Follow the *WHO Guidelines on Developing Measures for Combating Counterfeit Drugs* and make counterfeiting pharmaceuticals a specific crime punishable with appropriate sanctions.
- Establish effective pharmaceuticals regulation including export controls and licensing of establishments engaged in the manufacture, import, export, distribution, supply and sale of drugs; product registration, inspection, quality surveillance, etc.
- Increase local and international cooperation.
- Raise public and political awareness of counterfeiting of medicines as a serious public health risk.
- Develop and implement best practice manuals regarding distribution and dispensing of medicines.
- Publish and provide information on drugs to consumers, health professionals and retailers
- Report any suspected cases of counterfeit drugs to the appropriate body and publish and disseminate information.
- Raise awareness of consumers and policy makers to the links between counterfeiting and organized crime
- exchange data and information between all interested parties.

The World Health Organization should:

- Collaborate with all stakeholders in the development of a concept paper proposing an international framework convention on counterfeit medicines.

Current Topics

New oral rehydration solution adopted by WHO and UNICEF

For more than 25 years, WHO and UNICEF have recommended a single formulation of glucose based oral rehydration solution to prevent or treat diarrhoeal dehydration, no matter from what cause or affected age group. This solution has played a major role in dramatically reducing global mortality due to diarrhoea. During this time, researchers have sought to develop an 'improved' ORS formulation that was as safe and effective as the original in preventing and treating diarrhoeal dehydration but also reduced stool output or offered additional clinical benefits. Reducing the concentrations of glucose and salt in the solution accomplished this goal (see article below).

Because of the improved effectiveness of reduced osmolarity oral rehydration solution, especially for children with acute, non-cholera diarrhoea, WHO and UNICEF are recommending that countries manufacture and use the following formulation in place of the previously recommended oral rehydration solution.

Composition of reduced osmolarity ORS

Reduced osmolarity ORS grams/litre

Sodium chloride	2.6
Glucose, anhydrous	13.5
Potassium chloride	1.5
Trisodium citrate, dihydrate	2.9
Total weight	20.5

Reduced osmolarity ORS mmol/litre

Sodium	75
Chloride	65
Glucose, anhydrous	75
Potassium	20
Citrate	10
Total osmolarity	245

A single oral rehydration solution for global use?

Diarrhoeal diseases remain important causes of death and morbidity in developing countries, with an estimated 1.5 billion episodes and 1.5 million to 2.5 million deaths each year among children younger than 5 years (1–4). A critical factor in reducing diarrhoeal deaths has been the widespread adoption of oral rehydration solution (ORS) programmes for the treatment and prevention of diarrhoea-associated dehydration (5, 6). An article recently appearing in the *Journal of the American Medical Association* (7) has proposed that the composition of oral rehydration solution is now in need of a revision and proposes the following argument.

The composition of oral rehydration solution has proven to be both safe and effective in worldwide use, based on its efficacy in replacing water and electrolytes in individuals with cholera infection. However, concern that the sodium concentration of 90 mEq/L was too high for the lower salt losses of viral and other causes of childhood diarrhoea (8) was invoked to explain its low acceptance among paediatricians in industrialized countries who were concerned about the possible occurrence of hypernatraemia (9). Some authors also noted that the standard WHO ORS was occasionally associated with hypernatraemia in children in developing countries (10).

Based on relevant data, WHO and UNICEF convened a meeting in 2001 to review all published studies comparing standard and reduced-osmolarity ORS (11). The conclusions were as follows:

1. Reduced osmolarity ORS was more effective than standard ORS for acute noncholera diarrhoea in children, as measured by clinically important outcomes such as reduced stool output, reduced vomiting, and reduced need for supplemental intravenous therapy. Although data were more limited, reduced-osmolarity ORS also appeared safe and effective for children with cholera;
2. Among adults with cholera, clinical outcomes were not different among those treated with reduced-osmolarity ORS compared with standard ORS, although the risk of transient asymptomatic hyponatraemia was noted;
3. Given the programmatic and logistical advantages of using a single ORS composition globally, it was recommended that this be a reduced-osmolarity ORS (Table 1); and
4. Further monitoring, including postmarketing surveillance studies, were strongly encouraged to better assess any risk of symptomatic hyponatraemia in cholera-endemic parts of the world (11).

A number of randomized controlled trials have established the superiority of reduced-osmolarity ORS over standard ORS in the management of diarrhoeal diseases in children. Concerns about the safety of reduced-osmolarity ORS centre on its use in patients with cholera, especially adults. While the provision of 17% less sodium to patients with cholera may lead to a slightly greater negative sodium balance at the end of treatment, this deficit should be rapidly corrected when a normal diet is resumed. Experience to date provides no evidence that transient hyponatraemia, which may

also occur with standard ORS, has significant adverse clinical consequences for cholera patients.

The benefits of promoting the use of a single ORS solution for all patients with diarrhoea, including cholera, are enormous, as has been clearly established with standard ORS. It is recognized, however, that any single ORS formulation, including standard ORS, that is promoted for use in patients of all ages and with diarrhoea of any aetiology must be a compromise that takes into consideration both the substantial differences in stool sodium losses that occur across the spectrum of diarrhoeal disease as well as substantial differences in the global burden of cholera vs noncholera diarrhoea.

It is estimated that acute noncholera diarrhoea in children causes 1.5 million to 2.5 million deaths per year, whereas cholera causes significantly fewer deaths in all age groups. Reduced-osmolarity ORS has the potential to substantially reduce childhood deaths from noncholera diarrhoea due to the reduced requirement for supplementary intravenous fluids. Although reduced-osmolarity ORS may not have the same benefit for cholera patients, clinical trials show it to be as effective as standard ORS. It is the authors view that the current evidence demonstrates the benefits of reduced-osmolarity ORS for the world's children, and that use of the revised formulation is fully justified.

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Table 1 Composition of oral rehydration solutions

Component	Standard WHO (1975)	Reduced osmolarity WHO (20002)	Glucose plus glycine
glucose, mmo/L	111	75	110
sodium, mEq/L	90	75	120
potassium, mEq/L	20	20	15
chloride, mEq/L	80	65	72
base	10 ¹	10 ¹	48 ² (15 ³)
glycine, mmo/L			110
osmolarity, mOsm/L	311	245	510

WHO = World Health Organization

¹ Citrate in mmol/L

² The base was bicarbonate in the original study (9)

³ Potassium citrate

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Principles for fixed-dose combination drug products

A statement has been issued by the Southern African Development Community (SADC), United Nations Joint Programme on HIV/AIDS (UN-AIDS), US Department of Health and Human Services (HHS) and the World Health Organization (WHO) on the scientific and technical principles for fixed-dose combination drug products.

In March 2004, officials and representatives of drug regulatory agencies from 23 countries, the research-based and generic pharmaceutical industries, public health leaders, health care providers, advocacy groups, academia and members of nongovernmental organizations met in Botswana to discuss the scientific and technical principles for fixed-dose combination drug products (FDCs) for use in the treatment of HIV/AIDS, tuberculosis and malaria.

Combination therapies, either using single drugs administered together, or FDCs are considered by many to be essential for treating these diseases as well as to limiting the development of drug resistance. Among other advantages, FDCs simplify dosing which could result in better patient adherence to therapy.

An expert panel had previously met in Cape Town, South Africa, in February 2004 to develop a working draft of shared scientific and technical principles for evaluating FDCs. This draft was then posted on the web for comment.

Before and during the conference, concerns were raised that this initiative was biased towards favouring innovator above generic manufacturers, in a way that might negatively affect access to badly needed medicines. However, it was agreed that the principles, in whatever final form, were not intended to impede access to safe, efficacious and quality FDCs and progress was made towards drafting a document based on comments provided by conference participants and those who submitted feedback electronically. In mid-April this revised draft document was posted for two weeks at: <http://www.globalhealth.gov/fdc.shtml> for further comment via e-mail. An expert panel will consider these additional comments and proceed to write the final document which is expected to be made available in mid-May 2004.

It is anticipated that the document will be of use to regulatory agencies around the world, as well as to pharmaceutical companies and other organizations involved in developing and evaluating FDCs. It is not intended to be a therapeutic or regulatory guideline, nor address the procurement and distribution of specific products.

Reference: <http://www.globalhealth.gov/fdc.shtml>. 8 April 2004.

Mozambique issues compulsory license for HIV antiretrovirals

The HIV/AIDS pandemic constitutes a serious handicap in Mozambique's struggle against hunger, illness, underdevelopment and misery. High rates of morbidity and mortality have put Mozambique among the ten countries in Africa worst hit by HIV. It is estimated that by the end of 2002 over 1.5 million Mozambicans were infected by HIV, of whom more than 100 000 are suffering from full-blown AIDS. The AIDS death toll is so far well over 200 000 and about 360 000 children have been orphaned by the pandemic. Despite vigorous prevention campaigns, HIV is still spreading,

On 14th November 2001, WTO Members adopted the Ministerial Declaration on the TRIPS Agreement and Public Health (the Doha Declaration) which affirmed the right of each Member to take measures to protect public health, and in particular to promote access to medicines, by using the flexibilities and public health safeguards contained in the TRIPS Agreement. These flexibilities include the use of compulsory licences, and the Doha Declaration confirms that each Member has the right to grant compulsory licences and the freedom to determine the grounds upon which such licences are granted (that is to say that the granting of compulsory licences is not only limited to cases of national emergencies).

Antiretroviral drugs are available which prolong the lives of those infected with HIV/AIDS. However, such drugs are not accessible at affordable prices to large numbers of the Mozambican population. In view of the above, the Mozambique Ministry of Industry and Commerce, in a notice dated 5 April 2004, granted a compulsory licence (No. 01/MIC/04) for the local manufacture of a triple combination of lamivudine, stavudine and nevirapine; antiretrovirals which have proved to be the most effective and economical treatments. The compulsory license will expire as soon as conditions of national emergency and extreme urgency created by the HIV/AIDS pandemic have come to an end.

Other countries have also used the flexibilities in the TRIPS Agreement to protect public health and promote access to medicines. On 29 October 2003, the Ministry of Domestic Trade and Consumer Affairs, Malaysia issued a notice of Section

84 of the Patents Act, to authorize the import of generic antiretrovirals from India, under compulsory licence. In 2002, Zimbabwe declared an emergency (Declaration of Period of Emergency on (HIV/AIDS) Notice 2002, General Notice 240 of 2002) for a period of five years, taking effect from 1 January 2003, for the purpose of enabling local manufacture or import of 'any patented drug used in the treatment of persons suffering from HIV/AIDS or HIV/AIDS-related conditions'.

Reference: Communications and letters posted at Consumer Project on Technology <http://www.cptech.org>

Improved use of medicines

Over 450 leading multi-disciplinary researchers, national and international policy makers, patient advocates and clinicians representing nearly 80 countries recently gathered in Thailand for the Second International Conference on Improving Use of Medicines (ICIUM 2004).

Participants reported on the many advances made during the past years but expressed concern over the continued, widespread improper use of medicines. They cautioned that increased access to quality drugs is beneficial only if the medicines are used properly. Overuse, underuse, and misuse of medicines along with poor patient adherence to therapy are contributing to the emergence and rapid spread of disease strains that are resistant to currently available treatment. Resistance to conventional drugs has been observed in patients with respiratory infections, HIV/AIDS, diarrhoeal diseases, tuberculosis, and malaria along with other ailments. Once the ability to use important drugs is lost due to resistance, their effectiveness is lost to every patient, whether in Africa, Asia or anywhere else in the world.

Members of the international community who assembled for ICIUM 2004 reviewed research generated since the first International Conference on Improving Use of Medicines in 1997. The previous conference was a milestone which resulted in unprecedented consensus on interventions to improve medicine use and a definitive global research agenda to increase understanding of issues that impact the appropriate use of medicines.

Reference: www.icium.org

Rapid TB diagnostic test by 2005

The Foundation for Innovative New Diagnostics (FIND) has announced development of a rapid economical TB test aimed to provide tuberculosis results within 48 hours, rather than weeks. The new TB test is expected to be available in 2005.

Following the launch of FIND in May 2003 at the World Health Assembly, a first development agreement has been signed with Biotec Laboratories Ltd, an established independent UK company with expertise in the development of a number of diagnostic products.

FIND's involvement will accelerate the development, evaluation and demonstration of two improved diagnostic tests. One of these tests will enable rapid and sensitive detection of tuberculosis in patients seeking a diagnosis, while the other will be used to detect multi-drug resistance directly from sputum.

The development target is a test that is as accurate as culture, the current internationally recognized standard, but that gives results in 48 hours rather than several weeks, while using a simple manual procedure that is easy to perform in routine laboratories. The FIND investment will be used primarily to enhance the capacity of Biotec's R&D facilities in Cape Town, South Africa, which will accelerate the development of these tests.

This technology has the potential to replace existing slow culture methods, boosting TB case detection far above that achieved with microscopy alone by bringing a rapid and sensitive test to developing country laboratories.

FIND, a non-profit organisation, will leverage its development investment with Biotec to ensure affordability of the tests for low-income countries where they are most urgently needed. Under the terms of this agreement, FIND has obtained a

royalty-free license for the use of this technology in the public health sector of low-income countries, with Biotec retaining exclusive rights for the private health sector in low-income countries and all markets in high income countries.

One use of the new FASTPlaque tests is to screen for rifampicin resistant strains directly from sputum. FIND is collaborating with the UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR) to evaluate the accuracy and effectiveness of this newly developed test for drug resistance.

The announcement coincides with the release of the World Health Organization's third global report on 'Anti-TB Drug Resistance in the Developing World' which highlights the utility of rapid rifampicin resistance tests in TB to predict multi-drug resistance in areas where it is prevalent.

Reference: http://www.finddiagnostics.org/news/docs/clinica_may04.pdf

Research bioethics training

The Johns Hopkins University Bloomberg School of Public Health and Bioethics Institute, in collaboration with the US National Institutes of Health (NIH), Department of Clinical Bioethics, are pleased to announce the availability of a one year training programme in research ethics for scientists and professionals from sub-Saharan Africa. This training programme is supported by the Fogarty International Center, US National Institutes of Health (NIH). The training programme will provide funding for African scientists, professionals, and senior scholars to study bioethics and research ethics, and also to do an independent project in their home country related to research ethics.

Reference: <http://www.hopkinsmedicine.org/bioethics/research/ire/fogarty.html>

Consultation Document

The International Pharmacopoeia: monographs for antiretrovirals (second draft)

Within the framework of the Pilot Procurement Project for Quality and Sourcing of HIV Drugs (<http://www.who.int/medicines>), the International Pharmacopoeia is collaborating with manufacturers, independent analytical drug quality control laboratories, national and regional pharmacopoeial bodies, research, governments, and regulatory bodies to provide specifications and monographs for the following antiretroviral agents:

abacavir, didanosine, efavirenz, indinavir, lamivudine, nelfinavir,
nevirapine, ritonavir, saquinavir, stavudine, zidovudine

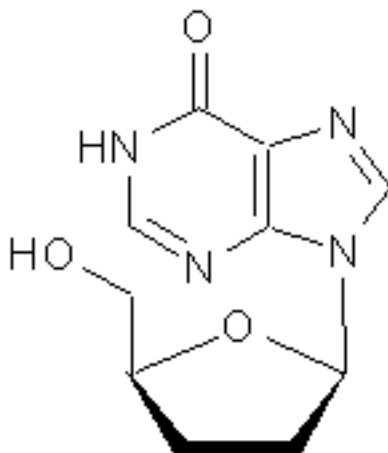
Specifications for the respective dosage forms are now being developed and a draft monograph for didanosine is now available for consultation as presented below. This second draft monograph has been developed following comments received on the first draft published in WHO Drug Information, Vol. 17, No. 3 2003. Comments should be sent to: Quality and Safety: Medicines, World Health Organization, 1211 Geneva 27, Switzerland or kopps@who.int.

DIDANOSINUM ***Didanosine***

Molecular formula: C₁₀H₁₂N₄O₃

Relative Molecular Mass: 236.23

Graphic formula:



Chemical name: 9-[(2*R*,5*S*)-5-(hydroxymethyl)tetrahydrofuran-2-yl]-1,9-dihydro-6*H*purin-6-one; 9-(2,3-dideoxy-β-D-*glycero*-pentofuranosyl)-1,9-dihydro-6*H*purin-6-one; 2',3'-dideoxyinosine (DDI); CAS Reg. No. 69655-05-6.

Description: A white to almost white powder.

Solubility: Sparingly soluble in water; slightly soluble in methanol R and ethanol (95 per cent) R

Melting point: about 170 °C with decomposition.

Category: Antiretroviral (nucleoside reverse transcriptase inhibitor).

Storage: Didanosine should be kept in a tightly closed container.

REQUIREMENTS

Didanosine contains not less than 98.5% and not more than 101.0% of $C_{10}H_{12}N_4O_3$ calculated with reference to the dried substance.

Identity test

Carry out the examination as described under "Spectrophotometry in the infrared region" (Vol. 1, p. 40*). The infrared absorption spectrum is concordant with the spectrum obtained from didanosine RS or with the *reference spectrum* of didanosine.

If the spectra are not concordant, use didanosine RS. Dissolve the sample in a small amount of methanol R, evaporate and carry out the IR spectrum as mentioned above. Treat didanosine RS in the same way. The infrared absorption spectrum is concordant with the spectrum obtained from didanosine RS.

Specific Optical Rotation. Use a 10 mg/ml solution and calculate with reference to the dried substance; $[\alpha]_D^{20} = -24^\circ$ to -28° .

Heavy metals. Use 1.0 g for the preparation of the test solution as described under "Limit test for heavy metals", Procedure 1 (Vol. 1, p. 118*); determine the heavy metal content according to Method A (Vol. 1, p. 119*); not more than 20 µg/g.

Sulfated ash. Not more than 1.0 mg/g.

Loss on drying. Dry for 4 hours at 105 °C; it loses not more than 5 mg/g.

Related Substances

Note: Prepare fresh solutions and perform the tests without delay.

Carry out the test as described under "High-performance liquid chromatography" (Vol. 5, p. 257*), using a stainless steel column (25 cm x 4.6 mm), packed with octadecylsilyl base-deactivated silica gel for chromatography R (5µm). (Hypersil BDS is suitable.)

Maintain the column temperature at 20 – 25 °C.

The mobile phases for gradient elution consist of a mixture of aqueous phase (Mobile phase A) and methanol (Mobile phase B), using the following conditions :

Mobile phase A: A 0.05 M solution of ammonium acetate R adjusted to pH 8.0 using a 20% v/v ammonia solution.

Mobile phase B: Methanol.

* Refers to *The international Pharmacopoeia*

Time (min)	Mobile phase A (%)	Mobile phase B (%)
0	92	8
18	92	8
25	70	30
45	70	30
50	92	8
60	92	8

Prepare the following solutions in a mixture of 92 volumes of mobile phase A and 8 volumes of mobile phase B (dissolution solvent).

For solution (1) dissolve 5 mg of hypoxanthine R and 5 mg of inosine R in the dissolution solvent and dilute to 100.0 ml with the same solvent. Dilute 1.0 ml in 10.0 ml with the same solvent. For solution (2) dissolve 25 mg of Didanosine in the dissolution solvent and dilute to 50.0 ml with the same solvent. For solution (3) dilute 5.0 ml of solution (2) to 50.0 ml with the dissolution solvent. Then dilute 5.0 ml of this solution to 50.0 ml with the same solvent.

Operate with a flow rate of 1.0 ml per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of about 254 nm.

Inject 20 µl of solution (1). The test is not valid unless the resolution factor between the peaks due to hypoxanthine and inosine is greater than 8.0, if necessary reduce the amount of methanol in the mobile phase and adjust the proportion of aqueous phase pH 8.0 accordingly.

Inject separately 20 µl of solution (3) in replicate injections in the chromatographic system. The relative standard deviation for peak areas of didanosine in replicate injections of solution (3) is not more than 5.0%.

Inject separately 20 µl each of solution (2) and of mobile phase in the chromatographic system. Examine the mobile phase chromatogram for any extraneous peaks and disregard the corresponding peaks observed in the chromatogram obtained with solution (2).

In the chromatogram obtained with solution (2), the following peaks are eluted at the following relative retention with reference to didanosine: hypoxanthine (A) = about 0.08; inosine (B) = about 0.23; 2'-deoxyinosine (C) = about 0.30; 2',3'-didehydrodidanosine (D) = about 0.71; didanosine acetate (E) = about 1.85.

Measure the areas of the peak responses obtained in the chromatograms from solutions (2) and (3), and calculate the content of related substances as a percentage. For the calculation of limit contents, multiply the peak areas of the following impurities by the corresponding correction factor: hypoxanthine (A) = 0.6. For any other peaks eluting apart from the above mentioned relative retention, apply a response factor of 1.

In the chromatogram obtained with solution (2) the area of any individual peaks corresponding to A, B, C, D and E is not greater than 0.3 times the area of the principal peak obtained with solution (3) (0.3%). Any other impurity peak is not greater than 0.1 times the area of the principal peak obtained with solution (3) (0.1%). The sum of the areas of all peaks, other than the principal peak, is not greater than the area of the principal peak obtained with solution (3) (1.0%). Disregard any peak with an area less than 0.05 times the area of the principal peak obtained with solution (3) (0.05%).

* Refers to *The international Pharmacopoeia*

Assay

Dissolve about 0.200 g, accurately weighed, in 50 ml glacial acetic acid R1 and titrate with perchloric acid (0.1 mol/l) VS as described under "Non-aqueous titration"; Method A (Vol. 1, p.131*) determining the end point potentiometrically.

Each ml of perchloric acid (0.1 mol/l) VS is equivalent to 23.62 mg of $C_{10}H_{12}N_4O_3$.

Tested impurities

- A. "Hypoxanthine" = 1,7-dihydro-6H-purin-6-one
- B. "Inosine" = 9-β-D-ribofuranosyl-1,9-dihydro-6H-purin-6-one
- C. "2'-Deoxyinosine" = 9-(2-deoxy-β-D-*erythro*-pentofuranosyl)-1,9-dihydro-6H-purin-6-one
- D. "2',3'-Didehydrodidanosine" = 9-[(2*R*,5*S*)-5-(hydroxymethyl)-2,5-dihydrofuran-2-yl]-1,9-dihydro-6H-purin-6-one; 9-(2,3-dideoxy-β-D-*glycero*-pent-2-enofuranosyl)-1,9-dihydro-6H-purin-6-one
- E. "Didanosine acetate" = [(2*S*,5*R*)-5-(6-oxo-1,6-dihydro-9H-purin-9-yl)tetrahydrofuran-2-yl]methyl acetate; 9-(5-*O*-acetyl-2,3-dideoxy-β-D-*glycero*-pentofuranosyl)-1,9-dihydro-6H-purin-6-one
- F. "3'-Deoxyinosine" = 9-(3-deoxy-β-D-*erythro*-pentofuranosyl)-1,9-dihydro-6H-purin-6-one
- G. "Olefine" = [(2*S*,5*R*)-5-(6-oxo-1,6-dihydro-9H-purin-9-yl)-2,5-dihydrofuran-2-yl]methyl acetate; 2',3'-didehydrodidanosine acetate; 9-(5-*O*-acetyl-2,3-dideoxy-β-D-*glycero*-pent-2-enofuranosyl)-1,9-dihydro-6H-purin-6-one
- H. "Dioxolane" = 9-[(2*RS*,3*aR*,4*R*,6*R*,6*aR*)-6-(hydroxymethyl)-2-methoxy-2-methyltetrahydrofuro[3,4-*d*]-1,3-dioxol-4-yl]-1,9-dihydro-6H-purin-6-one; 2',3'-*O*-(1-methoxyethylidene)inosine; 9-[2,3-*O*[(1*RS*)-1-methoxyethylene]-β-D-ribofuranosyl]-1,9-dihydro-6H-purin-6-one
- I. "Bromoesters" = mixture of 9-(3,5-di-*O*-acetyl-2-bromo-2-deoxy-β-D-arabinofuranosyl)-1,9-dihydro-6H-purin-6-one and 9-(2,5-di-*O*-acetyl-3-bromo-3-deoxy-β-D-xylofuranosyl)-1,9-dihydro-6H-purin-6-one

Reagents

Hypoxanthine R. 1,7-dihydro-6H-purin-6-one; $C_5H_4N_4O$.

A commercially available reagent of suitable grade.

Description. A white, crystalline powder.

Solubility. Very slightly soluble in water, sparingly soluble in boiling water, soluble in dilute acids and in dilute alkali hydroxide solutions.

Melting point. Decomposes without melting at about 150°C.

Thin-Layer Chromatography. Examine as prescribed in the monograph on Mercaptopurine (Vol. 4, p.77-79*); the chromatogram shows only one principal spot.

* Refers to *The international Pharmacopoeia*

Inosine R. 9-β-D-ribofuranosyl-1,9-dihydro-6H-purin-6-one; C₁₀H₁₂N₄O₅.

A commercially available reagent of suitable grade.

Description. A crystalline powder. Dihydrate, long rectangular plates from water, melting point = 90 °C. Anhydrous needles from 80% alcohol, decomposition 218 °C (rapid heating).

Solubility. Sparingly soluble in water.

Specific optical rotation. $[\alpha]_D^{18^\circ} = -49^\circ$ (c = 0.9 in H₂O with c = concentration by volume, g/100 ml after optical rotation only).

Silica gel for chromatography, octadecylsilyl, base-deactivated

A very finely divided silica gel, pretreated before the bonding of octadecylsilyl groups to minimize the interaction with basic components.

ATC/DDD Classification (Final)

The following final anatomical therapeutic chemical (ATC) classifications and defined daily doses (DDDs) were agreed at a meeting of the WHO International Working Group for Drug Statistics Methodology which took place in October 2003. They came into force on 1 March 2004 and will be included in the January 2005 issue of the ATC index. The inclusion of a substance in the lists does not imply any recommendation of use in medicine or pharmacy. The WHO Collaborating Centre for Drug Statistics Methodology can be contacted through e-mail: whocc@nmd.no.

ATC level	INN/Common name	ATC code
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New ATC level codes (other than 5th level):

Other hormone antagonists and related agents	L02BX
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New ATC 5th level codes:

abarelix	L02BX01
aprepitant	A04AD12
aripiprazole	N05AX12
buprenorphine, combinations	N07BC51
cetuximab	L01XC06
enfuvirtide	J05AX07
enoxolone	D03AX10
flutrimazole	G01AF18
fosamprenavir	J05AE07
ibuprofen	C01EB16
insulin glulisine	A10AB06
methazolamide	S01EC05
micafungin	J02AX05
olmesartan medoxomil	C09CA08
sacrosidase	A16AB06
strontium ranelate	M05BX03
temoporfin	L01XD05
undecylenic acid, combinations	D01AE54

New DDDs:

INN/common name	DDD	Unit	Adm.R	ATC code
adalimumab	2.9	mg	P	L04AA17
apraclonidine	0.3	ml		S01EA03
clofoctol	1.5	g	R	J01XX03
colistin	3	MU	Inhal. sol.	J01XB01
enfuvirtide	0.18	g	P	J05AX07
everolimus	1.5	mg	O	L04AA18

New DDDs (continued):

INN/common name	DDD	Unit	Adm.R	ATC code
laronidase	1	TU	P	A16AB05
methazolamide	0.2	g	O	S01EC05
olmesartan medoxomil	20	mg	O	C09CA08
paracetamol	3	g	P	N02BE01
rokitamycin	0.8	g	O	J01FA12
sacrosidase	68	TU	O	A16AB06
testosterone	50	mg	TD gel	G03BA03

ATC/DDD Classification (temporary)

The following temporary anatomical therapeutic chemical (ATC) classifications, defined daily doses (DDDs) and alterations were agreed at a meeting of the WHO International Working Group for Drug Statistics Methodology which took place on 22–23 March 2004. Comments or objections to the decisions from the meeting should be forwarded to the WHO Collaborating Centre for Drug Statistics Methodology, e-mail: whocc@nmd.no before 1 September 2004. If no objections are received before this date, the new ATC codes and DDDs will be considered final and be included in the January 2005 issue of the ATC index. The inclusion of a substance in the lists does not imply any recommendation of use in medicine or pharmacy.

ATC level	INN/Common name	ATC code
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New ATC level codes (other than 5th level):

First-generation cephalosporins	J01DB
Fourth-generation cephalosporins	J01DE
Second-generation cephalosporins	J01DC
Third-generation cephalosporins	J01DD

New ATC 5th level codes:

anecortave	S01XA16
atorvastatin, combinations	C10AA55
bevacizumab	L01XC07
cefoperazone, combinations	J01DA82
cromoglicic acid	D11AX17
darifenacin	G04BD10
eplerenone	C03DA04
hydroxybutyric acid	N07XX04
insulin detemir	A10AE05
mecobalamin	B03BA05
melatonin	N05CM17
olmesartan medoxomil and diuretics	C09DA08
pemetrexed	L01BA04
pravastatin, combinations	C10AA53
rasagiline	N04BD02
sulfamerazine and trimethoprim	J01EE07
typhoid – hepatitis A	J07CA10
ziconotide	N02BG08

Change of ATC codes (operational January 2005):

INN/common name	Previous ATC	New ATC
cefacetrile	J01DA34	J01DB10
cefaclor	J01DA08	J01DC04

INN/common name	Previous ATC	New ATC
cefadroxil	J01DA09	J01DB05
cefalexin	J01DA01	J01DB01
cefaloridine	J01DA02	J01DB02
cefalotin	J01DA03	J01DB03
cefamandole	J01DA07	J01DC03
cefapirin	J01DA30	J01DB08
cefatrizine	J01DA21	J01DB07
cefazedone	J01DA15	J01DB06
cefazolin	J01DA04	J01DB04
cefdinir	J01DA42	J01DD15
cefepime	J01DA24	J01DE01
cefetamet	J01DA26	J01DD10
cefixime	J01DA23	J01DD08
cefmenoxime	J01DA16	J01DD05
cefmetazole	J01DA40	J01DC09
cefodizime	J01DA25	J01DD09
cefonicide	J01DA17	J01DC06
cefoperazone	J01DA32	J01DD12
cefotaxime	J01DA10	J01DD01
cefotetan	J01DA14	J01DC05
cefotiam	J01DA19	J01DC07
cefoxitin	J01DA05	J01DC01
cefpiramide	J01DA27	J01DD11
cefpirome	J01DA37	J01DE02
cefpodoxime	J01DA33	J01DD13
cefprozil	J01DA41	J01DC10
cefradine	J01DA31	J01DB09
cefroxadine	J01DA35	J01DB11
cefsulodin	J01DA12	J01DD03
ceftazidime	J01DA11	J01DD02
ceftezole	J01DA36	J01DB12
ceftibuten	J01DA39	J01DD14
ceftizoxime	J01DA22	J01DD07
ceftriaxone	J01DA13	J01DD04
ceftriaxone, combinations	J01DA63	J01DD54
cefuroxime	J01DA06	J01DC02
latamoxef	J01DA18	J01DD06
loracarbef	J01DA38	J01DC08

ATC name change:

Previous	New	ATC code
Morbilli vaccines	Measles vaccines	J07BD
Morbilli, combinations with parotitis and rubella, live attenuated	Measles, combinations with mumps and rubella, live attenuated	J07BD52
Morbilli, combinations with parotitis, live attenuated	Measles, combinations with mumps, live attenuated	J07BD5
Morbilli, combinations with rubella, live attenuated	Measles, combinations with rubella, live attenuated	J07BD53
Morbilli, live attenuated	Measles, live attenuated	J07BD01
Parotitis vaccines	Mumps vaccines	J07BE
Parotitis, live attenuated	Mumps, live attenuated	J07BE01

New DDDs:

INN/common name	DDD	Unit	Adm.R	ATC code
aprepitant	95	mg	O	A04AD12
aripiprazole	15	mg	O	N05AX12
atomoxetine	80	mg	O	N06BA09
benzathine benzylpenicillin	3.6	g	P	J01CE08
benzathine phenoxymethylpenicillin	2	g	O	J01CE10
brodimoprim	0.2	g	O	J01EA02
buprenorphine	1.2	mg	TD	N02AE02
cefmenoxime	2	g	P	J01DA16
ceftezole	6	g	P	J01DA36
cloperastine	60	mg	O	R05DB21
clotiapine	80	mg	O,P	N05AX09
flumequine	1.2	g	O	J01MB07
flurithromycin	0.75	g	O	J01FA14
levosulpiride	0.4	g	O	N05AL07
methotrexate	2.5	mg	O	L04AX03
nesiritide	1.5	mg	P	C01DX19
rufloxacin	0.2	g	O	J01MA10
sodium folinate	60	mg	P	V03AF06
solifenacin	5	mg	O	G04DB08
sulfamazone	1.5	g	O,R	J01ED09

Change of DDDs (operational January 2005)

INN/common name	DDD	Unit	Adm.R	ATC code
alosetron	2	mg	O	
(new)	1	mg	O	A03AE01
amoxicillin and enzyme inhibitor	1	g	P	
(new)	3	g	P	J01CR02
esomeprazole	20	mg	O	
(new)	30	mg	O	A02BC05
fentanyl	0.6	mg	TD	
(new)	1.2	mg	TD	N02AB03
levitiracetam	2	g	O	
	1.5	g	O	N03AX14

Recent Publications and Sources of Information

Specifications for pharmaceutical preparations

The latest report from the WHO Expert Committee on Specifications for Pharmaceutical Preparations has now been published. The report contains recommendations on the quality assurance of pharmaceuticals, including good manufacturing practices, inspection, distribution and trade, risk analysis and drug supply. The report is complemented by the following annexes.

- International chemical reference substances and infrared reference spectra.
- Good trade and distribution practices for pharmaceutical starting materials.
- WHO pharmaceutical starting materials certification scheme: guidelines on implementation.
- Procedure for assessing the acceptability, in principle, of quality control laboratories for use by United Nations agencies.
- Guidelines for the preparation of a procurement agency information file.
- Interim guidelines for the assessment of a procurement agency.

World Health Organization. Thirty-eighth report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations. Technical Report Series, No. 917, (2004) Available from Marketing and Dissemination, 1211 Geneva 27, Switzerland or publications@who.int

WHO model formulary

The 2004 edition of the WHO Model Formulary is now available. This is an indispensable source of independent information on essential medicines for policy makers and prescribers.

It describes how to make effective use of medicines on the WHO Model List of Essential Medicines by improving patient safety and limiting unnecessary medical spending. For each medi-

cine, the Model Formulary provides information on use, dosage, adverse effects, contraindications and warnings with guidance on selecting medicines.

World Health Organization. Model Formulary (2004) Available from Marketing and Dissemination, 1211 Geneva 27, Switzerland or publications@who.int

Guidance on risk management

The US Food and Drug Administration (FDA) has announced the availability of three draft guidances to help industry develop risk management activities when needed for some drugs and biological products. The documents, *Premarketing Risk Assessment, Development and Use of Risk Minimization Action Plans*, and *Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment*, address safety issues that can arise throughout a product's entire lifecycle, including its development, the review and approval process, and after it is available on the market.

The draft guidances describe additional safety testing, monitoring, and interventions that may be helpful in selected circumstances and address premarket risk assessment; the development, implementation, and evaluation of risk minimization action plans (called RiskMAPs); and good pharmacovigilance practices and assessment of reported adverse events.

For example, the draft guidance on premarket risk assessment focuses on measures sponsors might consider during the later stages of clinical development of products that are known to, or might, present special safety issues. The recommended risk assessment strategies for such cases can include long-term controlled safety studies, enrolment of diversified patient population, and phase 3 trials with multiple dose levels.

The draft guidance on development and use of RiskMAPs describes how industry can address specific risk-related goals and objectives. This guidance also suggests various tools to minimize

the risks of drug products. The draft guidance on heightened postmarketing vigilance identifies recommended reporting and analytical practices involving adverse events associated with high-risk drug and biological products.

The agency invites written or electronic comments on the draft guidances until 6 July 2004. FDA is specifically soliciting public comment on how to best characterize the types and levels of risk that might suggest the need for a risk management plan.

Reference: Federal Register Notice, 5 May 2004, on <http://www.fda.gov>

Clinical trial fellowships

The European & Developing Countries Clinical Trials Partnership (EDCTP) is an initiative by European Union Member Countries and Norway to reinforce research into the development of new clinical interventions against HIV/AIDS, tuberculosis and malaria in developing countries. A Partnership Board (PB) will oversee the scientific aspects.

EDCTP will focus activities on accelerating the clinical evaluation of candidate new interventions including conducting controlled trials of new and improved drugs and vaccines against target diseases, and increasing the capacity of scientists and institutions to undertake such trials.

A major objective is to encourage and facilitate networking and coordination of clinical trial activities on the target diseases within Europe and sub-Saharan Africa. The EDCTP intends to identify and support senior researchers capable of building up teams in African institutions that will be internationally competitive and capable of winning grants from international funding bodies for research on the three major poverty-related diseases in Africa (HIV/AIDS, tuberculosis and malaria).

EDCTP Fellows will undertake applied research in clinical trial related disciplines such as epidemiology, clinical medicine, virology, immunology, parasitology, pharmacology and molecular biology.

Reference: <http://www.edctp.org>

On-line course in medicines management

Management of medicines in International health is a new distance learning course provided by InWEnt in English, French, Spanish and German. It is being run currently as a pilot with more than 30 students. The InWEnt website (<http://www.gc21.de/ibt/opengc21/ibt/index.htm>) leads to information about online courses

InWEnt is a German organization for international human resources development, advanced training and dialogue. The Federal Government of Germany is its main partner and the Federal Ministry for Economic Cooperation and Development its chief commissioning authority. The health division of InWEnt also offers training programmes for capacity development, supporting individuals, institutions and governments for improving health service delivery.

E-learning, developed by InWEnt, provides a unique opportunity where participants who are separated by huge geographic distances and work in different parts of the health sector can learn together as a cyber group. The "Management of medicines in International health" is especially suitable for such an international and interdisciplinary learning process. The course is accessed through the internet but does not require continuous access because modules can be downloaded.

The structure consists of 3 phases.

1. The Contact Phase is focused on the participant interaction and their special needs. Participants get to know each other, analyse their needs and become familiar with the course.
2. The Online Course consists of 7 modules with one main-topic each followed by tests.
3. After a successful online course participants are invited to a workshop to reinforce learning and develop a project proposal to improve a specific medicine management problem in the working environment.

Reference: health@inwent.org or claudia.kornahrens@inwent.org