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Challenges in Biotherapeutics

Regulatory pathways for biosimilar products

Innovative biotherapeutic products such as insulin, human growth hormone and erythropoietin offer promise for treating many of the life threatening chronic diseases that present major challenges to public health programmes in both developed and developing countries.

Until now, the high cost of biotherapeutics has often limited their use, particularly in low income countries. However, many of the current patents on these products are now expiring, offering an opportunity to manufacturers to produce and market "generic" products. This will improve availability and contribute to increased access at a more affordable price. Depending on the jurisdiction, biotherapeutic products produced and marketed in this way are referred to as 'similar biological medicinal products (bio-similars)', 'follow-on protein products', 'subsequent-entry products' or 'biogenerics'.

Worldwide, varying degrees of regulatory preparedness exist for the approval of biosimilars. In order to consolidate thinking on the current situation, a WHO informal consultation was organized in April 2007 by the Quality, Safety and Standards Team of the WHO Department of Immunization, Vaccines and Biologicals. The consultation was attended by national regulatory authorities from developing and developed countries, innovator and generic biopharmaceutical industries, and academia. The objectives of the meeting were to discuss the current status of so-called "similar" biological medicinal products — biosimilars — and to review regulatory pathways and challenges in evaluating the quality, safety and efficacy of these products.

It was soon realized that marked differences exist in the definitions and regulatory pathways for biosimilar products in many countries. For example, in some Asian countries, a number of biosimilar products such as interleukins, interferons, erythropoetins, growth factors, hormones, enzymes and even monoclonal antibodies, are available on the market. However, they are not defined as a class nor are they approved within a distinct regulatory framework. In the European Union (EU), a few biosimilar products have been approved so far through the European Medicines Agency (EMEA), which has the most well developed regulatory framework for biosimilars so far and which is supported by specific guidelines (1–3).

The existence of divergent approaches to the regulatory oversight of biosimilars in different countries has revealed a need for defining globally acceptable regulatory expectations for these products. It was agreed that WHO should develop a global regulatory guideline for biosimilar products to help WHO Member States meet the challenge of establishing appropriate national oversight (4).

Consequently, a drafting group has been organized and is developing a WHO guideline on Biosimilar/Follow-on protein/Subsequent-entry products. A number of key issues for future discussion were also highlighted during the meeting.

Terminology
Terminology currently used is not consistent between the various countries and jurisdictions. In the EU, the term 'similar

biological medicinal products', commonly referred to as 'biosimilars, is defined in the legislation. EU terminology and the EMEA regulatory guidelines for biosimilars have been adopted in Australia also. In the USA, biosimilars are termed 'follow-on protein products', and in Japan 'follow-on biologicals'. In Canada they are referred to as 'subsequent entry biologics'. In India and Iran, they are usually referred to as biogenerics. WHO aims to establish globally acceptable terminology. This issue is the starting point for defining the 'scope' of the international guideline, therefore, it will hopefully be resolved during the development of the draft. For convenience, the term 'biosimilars' is used in this document.

Concept of biosimilars

The term 'generic medicines' refers to chemically-derived products which are therapeutically equivalent to the agreed reference or originator product. For such generics, demonstration of bioequivalence with the originator product is usually appropriate to infer therapeutic equivalence. However, it is unlikely that biotherapeutics can generally follow this standard approach for generics because of their relatively large and complex molecular structures, which are more difficult to adequately characterize in the laboratory.

Based on current analytical techniques, two biologicals produced by different manufacturing processes cannot be shown to be identical, but similar at best. For these reasons, the standard generic approach is scientifically not applicable to development of biosimilar products and additional non-clinical and clinical data are usually required.

Principally, two different strategies for developing biosimilar products can be envisaged. The first scenario can be termed a 'full comparability approach' and corresponds to the EU pathway, which requires a thorough comparability exercise to generate evidence substantiating the similar nature, in terms of quality, safety and efficacy, of the new biosimilar product and the chosen reference or comparator product.

The second scenario considers that a thorough comparability exercise may not be required but rather reliance on publicly available information coupled with additional non-clinical and clinical studies to demonstrate similarity could be used. In the second approach, reliance on the reference product may not be as essential and a new biosimilar product approved with this approach would not be granted all the indications of the reference product. At the current time, it is considered that further clarity and real examples are needed to assist in development of this second scenario as a regulatory pathway.

Proof of similarity

In general, a biosimilar product may be approved following an abbreviated regulatory process based on the claim that it is similar to an existing licensed product. The key issue to agree is how much data are required to demonstrate similarity. There was consensus in the WHO meeting that a comparability programme should involve all aspects of development, with full analytical comparability of quality, and abridged studies for the non-clinical and clinical components of a licence application.

But there were clear differences between countries in the approach to non-clinical and clinical studies for biosimilars. Although there was a strong view that comparative studies remain central to an abbreviated regulatory process, in some countries non-clinical studies might be reduced to non-comparative studies for toxicity (single and/or repeat-dose), where the goal is solely to establish the non-clinical safety of biosimilars. For

clinical assessment, there was agreement that reduced studies compared to a full licence application for a biological medicine or novel biotherapeutic would be acceptable; however there was no clear consensus on the details of a reduced clinical assessment package.

Generally, confirmatory phase III studies for safety and efficacy involving pharmacokinetic and pharmacodynamic tests would be required, along with safe dose ranging. However, views varied as to the extent to which these studies need to be comparative or not. It was also unclear whether the studies should demonstrate non-inferiority or equivalence. It was also acknowledged that in some cases the effort that would be required to perform the comparability study might be greater than to seek licensure of the biotherapeutic as a stand-alone medicinal product. It would be the responsibility of the sponsor of biosimilars to choose the desired licensure pathway.

The reference or comparator product

A common feature in this process is the reference or comparator product. Generally, countries expect this to be a locally registered product, but it has to be considered that a company might wish to register the biotherapeutic in a country where the reference product is not (and is unlikely ever to be) licensed. The option of accepting reference products not licensed by the national regulatory authority (NRA) would increase opportunities for access to alternatives to innovator biologics and/or entry of biosimilars to some markets.

It is conceivable that scientific issues that limit their use could be addressed through the use of publicly available information, data provided by the manufacturers, and/or information obtained by the NRA via information sharing with other NRAs. However, this consideration may cause legal problems unless careful approaches are made.

All these issues will be discussed at the next WHO consultation on biosimilar in Seoul, Republic of Korea, May 2008. Progress in the development of the WHO guideline on biosimilar products will be reported to the Expert Committee on Biological Standardization (ECBS) at its meeting in October 2008.

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Pharmacovigilance Focus

WHO Programme for International Drug Monitoring: annual meeting

The annual meeting of representatives from national centres participating in the WHO Programme for International Drug Monitoring was recently convened in Buenos Aires, Argentina. Working groups were set up during the meeting to discuss points of immediate interest and to provide recommendations. A summary of the proceedings is set out below.

WHO adverse drug reactions database: public access

Requests for information are received at all twelve national centres represented in the working group but not all have procedures available for dealing with such inquiries.

Users of the data base have been identified as physicians, researchers, epidemiologists, lawyers, general public and patient organizations or the general public, media, and politicians. Queries range from very basic information (number of reports; number of fatal cases) to more detailed information, e.g. for specific rare adverse drug reactions, signals, or comparative data. National Centres need to improve their capacity to respond and to be more transparent by allowing the public access to decision-making processes. Such access would strengthen public trust.

There was no objection to information from the adverse drug reactions (ADR) data bases being provided to interested third parties, but it was felt that the responses should be tailored to the individual/organization requesting the data. It was important for data privacy to be rigorously preserved in accordance with national legislation, and it was recommended that rules and procedures be established to deal with third party requests. A caveat should also be created to set out the basic principles applicable to the practice of sharing information. To maintain data privacy, narratives should never be given to third parties, but may be given to the market authorization holder. Alternatively, a third party can be asked what specific fields they would need, while physicians often prefer summaries.

The Netherlands National Centre has already opened its database to the general public and was able to offer useful feedback (www.lareb.nl). Fore example, information provided by the Centre is restricted to age groups rather than specific ages since a specific age could be an identifier.

Extending open access to the signal document

A signal document is a publication of potentially interesting pharmacovigilance signals drawn from the WHO global individual case safety reports (ICSR) database, Vigibase. Signals are noted by the Uppsala Monitoring Centre Review Panel and distributed to a restricted audience of national pharmacovigilance authorities.

There are many advantages to providing open access to the signal document: information will reach a wider audience, will provide greater transparency, increase public confidence in pharmacovigilance, contribute to scientific re-

search, and give feedback to the reporters. Disadvantages include misinterpretation of information and possible creation of unnecessary concern. In providing open access to the document, it would be useful to describe how the reports are collected, how a signal is detected and how the results should be interpreted.

In conclusion, it was proposed that all signals should be published in the same journal, that marketing authorization holders should be allowed to comment and that national centres should be notified of signals in advance in order to be prepared. Signals could be graded to better assess impact, which may assessed by noting a change in number of reports or increased number of studies.

Exchange of information

It was agreed that there is a need to involve consumers and patients in pharmacovigilance practices. Concerns regarding patient reporting include the mixed quality of reports, incomplete information, which sources of information are being used by patients, and patient access to prescribers.

International experience indicates that in the majority of countries, patients are advised to make a report to their physician or to go to a pharmacist. Some patients are allowed to report directly to national centres. Although many national centres are not interested in accepting reports from patients/consumers, some may accept reports from special interest groups. In developing countries, patients need the assistance of a health professional to make a report. An Information Hotline is also available in some countries. EudraVigilance, in the European Union, does not accept reports from patients because they require reports to be medically confirmed.

Consumers/patients have rights and are acknowledged as end users. By involving patients, it is hoped to improve compliance, and by accepting patient reports one gets a closer view of patient safety. Mechanisms for reporting by patients must be suitable and user friendly. Empowering patients by providing information is an opportunity for national centres to improve their public health role. Consumer reports accepted by national centres should be reported to the WHO adverse drug reactions database at the Uppsala Monitoring Centre.

Direct to consumer advertising

With regard to direct-to-consumer advertising of pharmaceuticals, the group unanimously recommended prohibiting direct-to-consumer advertising.

Risks in special populations: women and children

Few data are available on the safety of medicines used in pregnant and lactating women. Women may be inadvertently exposed to unsafe products and there is a particular lack of information, education and guidance in resource-limited settings. Intensive monitoring systems could lead to creating pregnancy registries which would serve as a useful tool. “Congenital abnormalities” registers could also be used to collect information on congenital abnormalities, stillbirths, birth defects, etc.

In relation to medicines use in women of childbearing age there is an urgent need to educate health professionals, the general public and the media on safety issues. Establishment of a medical information centre would be desirable.

Children are vulnerable because they have unique physiological features and handle medicines differently. Extrapolation of adult data to children is often not appropriate nor backed by solid evidence. In resource poor settings, children are often malnourished and conditions such as marasmus and kwashiorkor are

common. Many medicines have not been developed in paediatric doses and are used off-label, so that dosage in children is often inaccurate. Fortunately, clinical trials in children are now required in some regions before marketing approval. Global networking and sharing of information, or pooling of data could contribute to better knowledge of the true extent of adverse drug reactions in children. Poison Centres are often a useful source of information for adverse drug reactions in children.

WHO has published a booklet promoting safety of medicines in children and, at the next International Conference of Drug Regulatory Authorities (ICDRA) in Switzerland, a two-day satellite meeting will focus on better medicines for children.

Medication errors: expanding the scope of pharmacovigilance centres

The role of pharmacovigilance centres in monitoring medication errors (ME) needs to be expanded and the ability to detect cases increased. Existing systems are limited by unharmonized terminology and unhelpful presentation of information. Pharmacovigilance centres are not yet responsive enough for root cause analysis and corrective action.

A proposal for a combined ADR and ME report form needs to be discussed further. There are areas which can be identified for focused analysis, or which may concentrate on patients presenting with allergy due to ME.

It was recommended that:

- national centres interact with relevant national bodies to ensure integration of activities related to ME
- national centres complete and return questionnaires to facilitate a comprehensive overview of data.
- the Uppsala Monitoring Centre should develop a web-page for ME activities, with links to relevant information.
- a special ad-hoc meeting should take place to review progress.
- co-operation should continue with the World Alliance for Patient Safety.

Communication and crisis management

Management of crises includes handling the impact of rumours, defining the role of the media, and managing the public perception of disasters. This is very important where coincidental adverse events following immunization occur or in the event of premature withdrawal or suspension of a product. Patients and professionals need to interact on the interpretation of science.

National centres need to oversee processes through guidelines, standard operating procedures and protocols to enable them to predict, prepare and plan for future events. These protocols should identify communications priorities and explain how to address a communications crisis. Trusted opinion leaders could be identified and recruited to help manage the crisis, and communication materials should be designed to target the issues. Training should focus on process management and communication skills.

In dealing with potential groups that are questioning the decisions of a public health authority, it is important to consider the context of culture and allow equal opportunities for these groups to articulate their concerns. When explaining the facts of a crisis, compassion and empathy were cited as critical components of a credible messenger.

Cohort Event Monitoring

Cohort event monitoring (CEM) is a methodology which analyses cohorts by

various means based on prescription records, public health programmes, and other health records and is a discipline which should be included in pharmacovigilance training. CEM has many additional needs in the area of terminology because CEM uses terms that are never reported or rarely used in spontaneous reporting. However, such terminology has to be in the context of local culture and programmes. A complete dictionary of 'adverse events' with a hierarchical structure should be developed.

The working group proposed to map WHO-ART terminology and the events dictionary developed by New Zealand's Intensive Medicines Monitoring Programme, to update WHO-ART correspondingly, with provisions on ongoing maintenance in accordance with progress in medical sciences, and to have the terminology available within a data management tool such as the Vigiflow (see www.who-umc.org). The data management tool should be adapted to receive reports from CEM.

Stimulated passive reporting

Stimulated passive reporting (SPR) has been used in South Africa as a way of encouraging reporting of adverse drug reactions to antiretrovirals. The objective of this working group was to determine whether SPR could be used as a methodology to improve spontaneous adverse drug reactions reporting.

The general consensus was that SPR was not a methodology *per se*, but could be used to encourage spontaneous reporting of adverse drug reactions. SPR could be used to suit country and/or product specific needs, to encourage spontaneous reporting of adverse drug reactions, and to increase awareness and culture of reporting. It could be effective if used appropriately to complement existing pharmacovigilance activities/systems.

However, SPR does not necessarily increase the quality of reporting, it can limit reporters to reporting specified adverse drug reactions only. It does not determine the incidence of adverse drug reactions and may limit information for signal generation.

Reference: *Pharmaceuticals Newsletter*, Number 6, 2007. http://www.who.int/medicines

Safety and Efficacy Issues

Recall of heparin products extended

United States of America — On 11 February 2008, the Food and Drug Administration (FDA) informed healthcare professionals of important warnings and instructions for heparin sodium injection use. On 28 February 2008, the FDA issued an update to inform the public that the manufacturer has extended its recall of multi-dose vials of heparin sodium for injection to also include single-dose vials of heparin sodium for injection.

There have been reports of serious adverse events including allergic or hypersensitivity-type reactions, with symptoms of oral swelling, nausea, vomiting, sweating, shortness of breath, and cases of severe hypotension. Most events developed within minutes of heparin initiation although the possibility for a delayed response has not been excluded. The reports have largely involved use of multiple-dose vials. However, there have been several cases in which products from multiple, single-dose vials have been combined to administer a bolus dose.

Heparin sodium is an anticoagulant used in patients undergoing kidney dialysis, certain types of cardiac surgery, and treatment or prevention of other serious medical conditions, including deep venous thrombosis and pulmonary emboli.

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Contaminated heparin products recalled

Canada — Health Canada testing of heparin products marketed in Canada has identified a contaminant in products from manufacturer B. Braun Medical Inc. The contaminant, oversulphated condroitin sulphate, has also been found in heparin products in the United States and Australia.

On 11 March 2008, Health Canada requested that all suppliers of heparin for sale in Canada test their heparin products using the same methodology that uncovered the contamination in the United States. Health Canada is continuing its testing of heparin products from all Canadian companies and will continue to update Canadians as needed.

Health professionals should only use heparin where it is medically essential after careful weighing of the risks and benefits for each individual patient. Patients should be monitored during and immediately following heparin administration for signs of allergy or anaphylactic reaction.

Reference: Advisory 2008-49, dated 20 March 2008. http://www.hc-sc.gc.ca

Dacart™ development terminated and Lapdap™ recalled

Data from two Phase III clinical trials assessing use of the artemisinin-based combination therapy Dacart™, a fixed-dose combination of chlorproguanil, dapsone and artesunate, currently in clinical development have shown disappointing results.

The first trial was primarily designed to establish the efficacy of Dacart™ versus Coartem™ (artemether–lumefantrine), currently the first-line antimalarial therapy in many endemic countries. The study, carried out in 1372 patients showed statistical non-inferiority with 94% efficacy at 28 days for Dacart™ and 97% for Coartem™. However, although the efficacy of Dacart™ was in line with expectations, the reduction of haemoglobin observed in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency taking Dacart™, was greater than that of Coartem™.

A reduction in haemoglobin can lead to anaemia which, in some severe incidences, may require treatment with blood transfusions. G6PD deficiency is a hereditary enzyme disorder which is estimated to impact 10–25% of the population in sub-Saharan Africa. The G6PD enzyme is important for the normal functioning of red blood cells and deficiency of the enzyme in certain individuals can only be detected using a blood test which is often not a practical option.

The second trial, in 892 patients, was designed to establish the efficacy of Dacart™ versus Lapdap™ (chlorproguanil and dapsone), another antimalarial product Glaxo SmithKline developed in partnership with the Medicines for Malaria Venture (MMV). Significant reductions in haemoglobin levels of patients with G6PD deficiency were observed for both products in this trial.

On the basis of these data, it has been decided to terminate further development of Dacart™. A product recall process has commenced at pharmacy level in Kenya, for Lapdap™, this being the only market with recent sales of the product.

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Varenicline and suicide attempts

European Union — The European Medicines Agency (EMEA) has concluded that updated warnings to doctors and patients are needed to increase awareness of cases of suicidal ideation and suicide attempts reported in patients using varenicline (Champix®), a medicine indicated for smoking cessation in adults.

At its December 2007 meeting, the Committee for Medicinal Products for Human Use (CHMP) concluded that there is a need to update the product information for Champix® to warn doctors and patients that depression has been reported. The symptoms of this depression may include suicidal ideation and suicide attempt.

The CHMP has requested that the marketing authorization holder submit a variation to the marketing authorization before 19 December 2007 to implement these changes to the product information. The EMEA will continue to keep this issue under close scrutiny and take appropriate actions if further concerns arise.

Reference: *Press Release*, Doc. Ref. EMEA/595516/2007. 14 December 2007 www.emea.europa.eu

Norelgestromin–ethinyl estradiol: infarction & thromboembolism

Canada — Evra® is a transdermal hormonal contraceptive system containing 6 mg of norelgestromin and 0.6 mg of ethinyl estradiol per patch. Since its introduction on the Canadian market in early 2004, 16 cases of thromboembolism and 1 of myocardial infarction suspected of being associated with the product have been reported to Health Canada. Two of the 17 patients died.

Hormonal contraception is a known risk factor for venous thromboembolism (VTE). Others include prolonged immobility, major surgery, family history of VTE, increasing age, smoking and obesity (1–5). The risks may be cumulative if more than one risk factor is present (1). An association between being overweight and thrombosis has also been observed among women using oral contraceptives (6) and the combined effect was greater than the expected risks based on their individual effects (6). The risk of VTE is also reported to be higher during the first 3 postpartum months than during pregnancy (7). The product monograph states that women should be encouraged to use a nonhormonal form of contraception in the 3 months following delivery (5).

Extracted from Canadian Adverse Reaction Newsletter, Volume 18(1), January 2008 at http://www.hc-sc.gc.ca

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Emerging cardiovascular concerns with rosiglitazone

Australia — The Australian Adverse Drug Reactions Advisory Committee (ADRAC) has drawn the attention of prescribers to an emerging concern about the cardiovascular safety of the thiazolidinedione (TZD) drug rosiglitazone.

TZD drugs (rosiglitazone, pioglitazone) improve glycaemic control and are approved for the treatment of Type 2 diabetes mellitus. Whether they have long term benefits in reducing the chronic complications of Type 2 diabetes remains an open question. It is well established that TZDs cause fluid retention and can exacerbate or precipitate cardiac failure.

Recently, three separate meta-analyses of data derived from pooled clinical trials of rosiglitazone have reported an increased risk of cardiac ischaemia (1–3), The product information for rosiglitazone (Avandia/Avandamet®) has been

amended to reflect these emerging results and the Therapeutic Goods Administration has now required the following boxed warning: "The use of Avandia/Avandamet® is not recommended in patients with known ischaemic heart disease, particularly in those taking nitrates. Avandia/Avandamet® has been shown to be associated with an increased risk of myocardial ischaemia (angina, infarction) in pooled short-term clinical studies, particularly in those who needed several antidiabetic drugs or nitrates."

The TGA has commissioned an additional review of the information. Pending the outcome of this review, prescribers should include this potential additional risk in their consideration of appropriate drug therapy for Type 2 diabetes, taking into account that rosiglitazone should not be prescribed for patients with known ischaemic heart disease or those considered to be at high risk for ischaemic heart disease.

Extracted from Australian Adverse Drug Reactions Bulletin, Volume 26, Number 6, December 2007. http://www.tga.gov.au

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Disclosure of transdermal patches

Australia — The Therapeutic Goods Administration has received a report of an inadvertent overdose of opioid medicines caused when subcutaneous morphine was administered pre-operatively to a patient who was wearing a Norspan® transdermal patch, delivering buprenorphine 20 µg/hour. Despite a thorough medical history, the patient omitted to tell the anaesthetist and other medical staff that she was using Norspan patches, and she had applied a fresh patch on the day of surgery. Medical staff discovered the patch when the patient became comatose with significant respiratory depression after the conventional dose of morphine was given.

Doctors are advised to remind their patients to disclose use of all medications, including those administered by non-conventional routes such as transdermal patches and subcutaneous implants. Physical examinations should include a check for topically applied or superficially implanted medicines.

Extracted from Australian Adverse Drug Reactions Bulletin, Volume 26, Number 6, December 2007. http://www.tga.gov.au

Statement on safety of HPV vaccine

European Union — The European Medicines Agency (EMEA) has received reports of deaths in women who had previously received the HPV vaccine, Gardasil®, including two reports concerning the sudden and unexpected deaths of two young women in the European Union

(EU). Gardasil® is a vaccine approved for the prevention of cervical cancer and other diseases caused by human papillomavirus (HPV) types 6, 11, 16 and 18.

The two European cases were reported as part of the continuous monitoring of the safety of medicines. One of the cases occurred in Austria and the other in Germany. In both cases, the cause of death could not be identified.

Reference: *Press Release,* Doc. Ref. EMEA/37479/2008, 24 January 2008 at: http://www.emea.europa.eu

IVIG: myocardial infarction, stroke and thrombosis

Canada — Use of intravenous immune globulin (IVIG) is reported to have increased by approximately 115% over the past 7–8 years, making Canada one of the highest per capita users of IVIG in the world (1). In this context of increasing use, it is important that health professionals recognize the serious adverse reactions (ARs) suspected of being associated with the use of these products.

IVIG consists mostly of concentrated IgG manufactured from large pools of human plasma. Health Canada has authorized the use of a number of commercial brands for such indications as replacement therapy for primary or secondary immunodeficiency syndromes and treatment of idiopathic thrombocytopenic purpura. In addition, IVIG is often used off-label either as a passive immunizing agent or as an immunomodulator for the treatment of a growing number of conditions (2).

From October 1997 to July 2007, 10 reports of stroke, 6 reports of thrombosis , 4 reports of myocardial infarction (MI), 2 reports of pulmonary embolus and 1 report of transient ischemic attack were suspected of being associated with IVIG. Two patients received IVIG for common variable immune deficiency, and 17 were prescribed it off-label. Strokes resulted in the most serious outcomes (1 death, 4 cases of persistent sequelae).

Serum viscosity has been shown to increase following IVIG administration (3). Although several possible mechanisms have been proposed (4), some authors have postulated that the change in serum viscosity during IVIG administration together with mild dehydration and other risk factors (e.g., age, atherosclerosis) contribute to the development of a "threshold" facilitating the production of thrombotic ARs (4). Five reports noted the concomitant use of diuretics, which may have contributed to a rise in serum viscosity.

Health care professionals are encouraged to report ARs suspected of being associated with the use of IVIG and to include any available information that could help characterize potential risk factors.

Extracted from Canadian Adverse Reaction Newsletter, Volume 18(1), January 2008 at http://www.hc-sc.gc.ca

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Erythropoietins: lower haemoglobin levels

Australia — Dosage instructions for the use of erythropoiesis-stimulating agents (erythropoietins) in patients with chronic kidney disease have been updated in line with evidence that higher haemoglobin levels may be associated with an increased risk of morbidity and mortality.

Erythropoietins currently available in Australia are erythropoietin alfa, erythropoietin beta, and darbepoetin alfa, approved for the treatment of anaemia associated with chronic renal failure and with the treatment of certain malignancies.

Recent studies and a meta-analysis have compared outcomes in patients with chronic kidney disease treated with an erythropoietin (1–3). The larger of the two randomized studies showed a lower incidence of adverse cardiovascular outcomes in the subnormal (113 g/L) compared to the normal (135 g/L) target haemoglobin group (1). The second study showed no difference in cardiovascular outcomes between the two groups, (2) and the meta-analysis of nine randomized trials showed a lower all-cause mortality and lower incidence of arteriovenous access thrombosis in patients in the lower target haemoglobin groups (3).

Product information documents for the three erythropoietins have been amended to indicate a target haemoglobin not exceeding 120 g/L in patients with anaemia due to chronic kidney failure.

Extracted from Australian Adverse Drug Reactions Bulletin, Volume 26, Number 6, December 2007. http://www.tga.gov.au

References

1. Singh AK, Szczech L, Tang KL, Barnhart H, Sapp S, Wolfson M, Reddan. Correction of anemia with epoetin alfa in chronic kidney disease. *NEJM* 2006; **355**: 2085-2098

2. Drueke TB, Locatelli F, Clyne N, Eckardt KU, Macdougall IC, Tsakiris D, Burger HU, Scherhag A. Normalization of hemoglobin level in patients with chronic kidney disease and anemia. *NEJM* 2006; **355**: 2071-2084.

3. Phrommintikul A, Haas SJ, Elsik M, Krum H. Mortality and target haemoglobin concentrations in anaemic patients with chronic kidney disease treated with erythropoietin: a meta-analysis. *Lancet* 2007; **369**: 381-388.

Erythropoiesis–stimulating agents

United States of America — On 8 November 2007, the Food and Drug Administration (FDA) strengthened the warning sections for Epogen/Procrit® and Aranesp® following results of six studies showing decreased survival and/or tumour progression in patients with cancer receiving an erythropoiesis-stimulating agent (ESA).

Findings from two additional clinical studies (PREPARE and GOG-191) now show an increase in mortality and shorter time to tumour progression in patients with cancer receiving an ESA. This new infor-mation further underscores the safety concerns regarding use of ESAs in patients with cancer.

On 30 November 2007, the manufacturer of epoetin alfa (Epogen® and Procrit®) and darbepoetin alfa (Aranesp®) notified FDA of findings from the PREPARE (Preoperative Epirubicin Paclitaxel Aranesp®) study in patients with primary breast cancer receiving chemotherapy prior to surgery and randomly assigned to a group that was to receive Aranesp® or no Aranesp®.

On 4 December 2007, the manufacturer notified FDA of the findings of GOG-191 (National Cancer Institute Gynecologic Oncology Group), a study in which 109 of a planned 460 patients with cervical cancer treated with chemotherapy and radiation were randomly assigned to a group that was either to receive an ESA or transfusions. The GOG-191 study stopped enrolling patients because of a higher rate of potentially life-threatening blood clots occurring in the patients who received an ESA.

Both the PREPARE study in breast cancer and the GOG-191 study in cervical cancer showed higher rates of death and or tumour progression in patients who received an ESA compared to patients who did not receive an ESA.

FDA is currently reviewing this information and will take additional actions as appropriate. FDA will hold another public advisory committee meeting in early 2008 to reevaluate the risk and benefit balance of ESAs for the treatment of patients with chemotherapy-induced anemia. In the interim, healthcare professionals should consider the risks of tumour progression and decreased survival observed when ESAs are used as supportive care in patients with cancer. These risks should be carefully weighed against the need for and potential risks of red cell blood transfusions.

Reference: FDA Medwatch. 3 January 2008 http://www.fda.gov/medwatch/

Pregabalin: hypersensitivity reactions

Australia — Pregabalin (Lyrica®) is approved for use in the treatment of neuropathic pain in adults and as adjunctive therapy in adults with partial seizures with or without secondary generalisation. Post-marketing reports of hypersensitivity reactions to pregabalin comprise 13% of all the pregabalin adverse reaction reports in The Australian Adverse Drug Reactions Advisory Committee (ADRAC) database, with a range of symptoms reported in 22 individuals (14F:8M). Presentations have included anaphylaxis and 7 reports of allergic skin rash. The others were angioedema of eyelids, tongue, mouth, face, lips or upper airway, with breathing difficulty when severe and widespread.

Of the 22 cases, 6 women developed symptoms within hours of their first dose of pregabalin. In 14 of the cases, pregabalin was the sole suspected drug. Four patients required emergency treatment, including adrenaline and/or parenteral steroids and IM or oral antihistamine. Three of the cases of skin reaction were confirmed by a positive dechallenge and subsequent rechallenge. There is insufficient information about the patients' histories of atopy or other allergies to comment on the predictive value of such a history.

The pregabalin Product Information includes a contraindication for patients who have demonstrated hypersensitivity to pregabalin or to any of the excipients. Pregabalin prescribers should be alert to the fact that acute allergic reactions may present early after its introduction and after any dose increases, and counsel patients accordingly.

Extracted from Australian Adverse Drug Reactions Bulletin, Volume 26, Number 6, December 2007. http://www.tga.gov.au

Cefepime: increased mortality?

United States of America — An article in a recent issue of *The Lancet Infectious Diseases* has raised the question about increased mortality with the use of cefepime. The Food and Drug Administration (FDA) is currently reviewing safety data and has requested additional data to

further evaluate the risk of death in patients treated with cefepime. Cefepime is a broad spectrum cephalosporin antibiotic currently approved for the treatment of a variety of infections due to susceptible strains of microorganisms.

FDA is working with the manufacturer of cefepime, to further evaluate the finding of increased mortality in patients who received cefepime. Until the evaluation is completed, healthcare providers who are considering the use of cefepime should be aware of the risks and benefits described in the prescribing information and the new information from this meta-analysis.

References

1. Yahav D, Paul M, Fraser A et al. Efficacy and safety of cefepime: a systematic review and meta-analysis. *Lancet Infect Dis* 2007; **7**: 338–48)

2. FDA Medwatch, 14 November 2007. http:/ www.fda.gov/medwatch

Mycophenolic acid: pregnancy loss and congenital malformation

United States of America — The manufacturer has informed prescribers that use of mycophenolic acid (MPA) (Myfortic®) during pregnancy is associated with increased risks of pregnancy loss and congenital malformations. This new important safety information involves: Increased risk of first trimester pregnancy loss and increased risk of congenital malformations, especially external ear and facial abnormalities including cleft lip and palate, and anomalies of the distal limbs, heart, oesophagus, and kidney.

This change is a result of postmarketing data from the United States National Transplantation Pregnancy Registry (NTPR) and additional postmarketing data collected in women exposed to systemic mycophenolate mofetil (MMF) during pregnancy. MMF is converted to MPA, the active ingredient in Myfortic®, following oral or IV administration. The prescribing information revisions are in response to a Food and Drug Administration (FDA) request sent to all marketed MMF and MPA products.

Reference: Communication from FDA at http:/ www.fda.gov/medwatch.

Carbamazepine and skin reactions

United States of America — The Food and Drug Administration (FDA) has informed patients that dangerous or even fatal skin reactions (Stevens Johnson syndrome and toxic epidermal necrolysis), that can be caused by carbamazepine therapy, are significantly more common in patients with a particular human leukocyte antigen (HLA) allele, HLA-B*1502.

This allele occurs almost exclusively in patients with ancestry across broad areas of Asia, including South Asian Indians. Genetic tests for HLA-B*1502 are already available. Patients with ancestry from areas in which HLA-B*1502 is present should be screened for the HLA-B*1502 allele before starting treatment with carbamazepine. If they test positive, carbamazepine should not be started unless the expected benefit clearly outweighs the increased risk of serious skin reactions. Patients who have been taking carbamazepine for more than a few months without developing skin reactions are at low risk of these events ever developing from carbamazepine. This is true for patients of any ethnicity or genotype, including patients positive for HLA-B*1502. This new safety information will be reflected in updated product labelling.

Reference: *FDA Alert*, 12 December 2007 at http://www.fda.gov/medwatch/report/

Canada Vigilance: a new name and database

Health Canada is pleased to announce Canada Vigilance as the new name for the Canadian Adverse Drug Reaction Monitoring Program. The Program is also implementing a new database that will provide an enhanced capacity for the postmarketing surveillance of adverse reactions (ARs). The Canada Vigilance database will contribute to the ongoing assessment and communication of health product safety information. Health Canada, through the Canada Vigilance Program, is responsible for the collection and assessment of AR reports that have been submitted by health professionals or consumers, either directly or through Market Authorization Holders. Since 1965, Health Canada has been gathering information on suspected ARs to health products (pharmaceuticals, biologics [e.g., fractionated blood products, and therapeutic and diagnostic vaccines], natural health products and radiopharmaceuticals).

Reference: *Canadian Adverse Reaction Newsletter*, Volume 18(1), January 2008 at http://www.hc-sc.gc.ca

Desmopressin and hyponatraemia

United States of America — The Food and Drug Administration (FDA) has requested that prescribing information for desmopressin includes important new information about severe hyponatraemia and seizures.

Certain patients taking desmopressin are at risk for developing severe hyponatraemia that can result in seizures and death. Children treated with desmopressin intranasal formulations for primary nocturnal enuresis (PNE) are particularly susceptible to severe hyponatremia and seizures. As such, desmopressin intranasal formulations are no longer indicated for the treatment of primary nocturnal enuresis and should not be used in hyponatraemic patients or patients with a history of hyponatremia. PNE treatment with desmopressin tablets should be interrupted during acute illnesses that may lead to fluid and/or electrolyte imbalance. All desmopressin formulations should be used cautiously in patients at risk for water intoxication with hyponatremia.

Reference: *FDA Alert*, 4 December 2007 at http://www.fda.gov/medwatch/report

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

Regulatory Action and News

Influenza virus vaccine: northern hemisphere winter

World Health Organzation — It is recommended that vaccines for use in the 2008-2009 influenza season (northern hemisphere winter) contain the following:

- an A/Brisbane/59/2007 (H1N1)-like virus.
- an A/Brisbane/10/2007 (H3N2)-like virus. (A/Brisbane/10/2007 is a current southern hemisphere vaccine virus).
- a B/Florida/4/2006-like virus. (B/Florida/4/2006 and B/Brisbane/3/2007 are current southern hemisphere vaccine viruses).

Reference: *Weekly Epidemiological Record*, No. 9, 2008, 83, 77–88. http://www.who.int/wer

Lumiracoxib–containing medicines: withdrawal

European Union — The European Medicines Agency (EMEA) has recommended withdrawal of the marketing authorizations for all lumiracoxib-containing medicines, because of the risk of serious side effects affecting the liver.

Lumiracoxib is a nonsteroidal anti-inflammatory drug (NSAID) that belongs to the group 'COX-2 inhibitors'. It is used for symptomatic relief in the treatment of osteoarthritis of the hip and knee.

The liver safety of lumiracoxib has been monitored continuously since its launch in 2005. In August 2007, the product was contraindicated for patients with potential liver problems and advice to doctors that they should frequently monitor patients treated with lumiracoxib for liver reactions. More spontaneous reports of serious liver problems have been received since then, which have increased the concerns regarding hepatic safety for lumiracoxib.

The CHMP's opinion will now be forwarded to the European Commission for the adoption of a decision.

Reference: *Press Release*. EMEA/CHMP/579301/2007 13 December 2007 www.emea.europa.eu

Thalidomide approved for multiple myeloma

European Union — The European Medicines Agency (EMEA) has recommended the approval of thalidomide (Thalidomide Pharmion®) for the treatment of multiple myeloma, a rare cancer of the bone marrow.

The Committee for Medicinal Products for Human Use (CHMP) concluded that the benefits of Thalidomide Pharmion® in combination with melphalan and prednisone outweigh its risks for the first-line treatment of multiple myeloma for patients over 65 years of age or those who cannot be treated with high-dose chemotherapy.

Clinical studies have shown that adding Thalidomide Pharmion® to melphalan and prednisone can prolong survival time by about 18 months in newly-diagnosed multiple myeloma patients over 65 years of age, as compared to patients who received conventional chemotherapy.

Thalidomide is teratogenic. Because of this, the CHMP consulted representatives of thalidomide victims and myeloma patient groups from across the European Union to develop measures that can effectively minimize the risk of foetal exposure to thalidomide and has approved a risk management plan.

Subject to the granting of a marketing authorization by the European Commission, Thalidomide Pharmion® will only be available by prescription, and treatment will be initiated and monitored by a doctor who has experience in the treatment of multiple myeloma.

Reference: *Press Release*. Doc. Ref. EMEA/33024/2008, 24 January 2008. http://www.emea.europa.eu

New genetic test for breast cancer

United States of America — The Food and Drug Administration has approved a test that helps in assessing the risk of tumour recurrence and long-term survival for patients with relatively high-risk breast cancer. The TOP2A FISH pharmDx® is the first approved device to test for the TOP2A (topoisomerase 2 alpha) gene in cancer patients.

The TOP2A gene plays a role in DNA replication. The TOP2A FISH pharmDx test uses fluorescently labelled DNA probes to detect or confirm gene or chromosome abnormalities, a technology known as fluorescent in situ hybridization (FISH).

The recurrence of cancer depends partly on certain genes whose activity may be altered by changes in the number of gene copies in the tumor. Changes in the TOP2A gene in breast cancer cells mean there is an increased likelihood that the tumor will recur or that long-term survival will be decreased.

The test is suitable for breast cancer patients who are premenopausal or for whom tumor characteristics, such as tumor size or lymph node involvement, suggest a higher likelihood of tumour recurrence or decreased survival.

Reference: FDA News, 14 January 2008, http://www.fda.gov

Natalizumab for moderate–to–severe Crohn disease

United States of America — The Food and Drug Administration has approved natalizumab (Tysabri®), currently approved for use in treating some forms of multiple sclerosis, for the treatment of moderate-to-severe Crohn disease in patients with evidence of inflammation who have had an inadequate response to, or are unable to tolerate, conventional Crohn disease therapies. Crohn disease patients using the drug must be enrolled in a special restricted distribution program.

Natalizumab carries a boxed warning for progressive multifocal leukoencephalopathy (PML), an opportunistic viral infection that affects the brain and can lead to death or severe disability.

Other serious adverse events that have occurred in patients include hypersensitivity reactions, such as anaphylaxis and liver injury. Serious opportunistic and other atypical infections have been observed in patients receiving immunosuppressants while on Tysabri. Serious herpes infections have also been observed. Common side effects include headache, fatigue, infusion reactions, urinary tract infections, joint and limb pain, and rash.

Reference: *FDA News*, 14 January 2008, http://www.fda.gov

First test to detect and identify 12 respiratory viruses

United States of America — The Food and Drug Administration has approved a test that simultaneously detects and identifies 12 specific respiratory viruses.

The test, called the xTAG Respiratory Viral Panel®, is the first test for the detection and differentiation of influenza A subtypes H1 and H3. Influenza A is the most severe form of influenza for humans, and has been the cause of major epidemics. The new panel is also the first test for human metapneumovirus (hMPV), newly identified in 2001.

The panel amplifies viral genetic material found in secretions taken from the back of the throat in patients with possible respiratory tract infections. In the test, specific beads, or microspheres, bind to the amplified viral genetic material. The beads are then sorted so that the specific virus can be identified. Other viruses identified by the panel:

- influenza B - one of three types of human influenza, less severe than influenza A
- respiratory syncytial virus subtype A and B (both are leading causes of infant pneumonia and bronchiolitis and often contribute to the development of long-term pulmonary disease)
- parainfluenza 1, 2 and 3 (all are leading factors in croup and the common cold)
- rhinovirus (the most common viral infective agent in humans and a cause of the common cold)
- adenovirus (a cause of respiratory tract infections often similar to strep throat or tonsilitis).

While the test is faster than conventional tests, it is specific to the dozen viruses listed and should be used with other diagnostics such as patient data, bacterial or viral cultures and X-rays. Positive results do not rule out other infection or co-infection and the virus detected may not be the specific cause of the disease or patient symptoms.

Reference: *FDA News*, 3 January 2008 http://www.fda.gov

Miglustat: withdrawal by manufacturer

European Union — The European Medicines Agency (EMEA) has been formally notified of the decision to withdraw an application for an extension of indication for the centrally authorized medicine miglustat (Zavesca®).

Miglustat was expected to be used for the treatment of neurological manifestations in patients with Niemann Pick type C disease, a rare inherited neurodegenerative disease of childhood and adolescence. Zavesca is an orphan medicinal product.

Zavesca® is currently authorized for the oral treatment of mild to moderate type 1 Gaucher disease and may be used only in the treatment of patients for whom enzyme replacement therapy is unsuitable.

The Committee for Medicinal Products for Human Use (CHMP) had given a negative opinion recommending the refusal of the type II variation to extend the indication on 18 October 2007. The company has stated it will resubmit for this indication in the near future with additional data.

Reference: *Press Release*. Doc. Ref. EMEA/95140/2008, 25 February 2008. http:/www.emea.europa.eu

Voluntary withdrawal of clobutinol cough syrup

Singapore —Clobutinol (Silomat®) was licenced in Singapore in 1999. It is an orally active non-opioid antitussive agent, and is indicated for the treatment of irritable, non-productive cough and inflammatory disorders of the airways.

In September 2007, the manufacturer voluntarily withdrew Silomat® from the Singapore market as a precautionary measure due to concerns of a potential increased risk of cardiac arrhythmias that could be associated with the active ingredient. Published experimental data have indicated the potential of clobutinol affecting the hERG (human ether-a-go-go related gene) potassium channels.

Preliminary findings from a recent clinical trial with clobutinol in adult healthy volunteers have shown a prolongation of the QTc interval in the ECG. As clobutinol is indicated for a non-serious disease condition and in view of the potentially life-threatening adverse effects, HSA agreed with the actions of the manufacturer to withdraw clobutinol from the worldwide market.

A Dear Healthcare Professional Letter (DHCPL) was issued by the company to alert healthcare professionals to the findings and the decision to recall and suspend the sales of Silomat®.

***Reference**: Adverse Drug Reaction News*, December 2007, Vol.9 No.3, at http://www.hpp.moh.gov.sg.

Current Topics

Proposed harmonized requirements: licensing vaccines in the Americas

A Vaccines Working Group of the Pan-American Network on Drug Regulatory Harmonization (PANDRH) was established in March 2005 to develop harmonized documents and approaches to the licensing of vaccines in the Americas.

At its first meeting, held in Panama, the Working Group, made up of national regulatory authorities of seven countries (Argentina, Brazil, Canada, Chile, Cuba, Mexico and Venezuela), proposed the development of harmonized registration requirements for vaccines for human use. Information derived from a survey conducted by the Pan-American Health Organization (PAHO) of licensing requirements for vaccines in 16 countries of the region was reviewed in detail.

A second meeting of the Working Group, held in December 2005 in Venezuela, proceeded to identify and agree upon the basic requirements and data which need to be submitted by a manufacturer to a National Regulatory Authority in support of an application for licensing. At the Group's third meeting, held in Canada, the first draft of a document on harmonized requirements for the licensing of vaccines in the region was reviewed and developed further, as was an accompanying guideline on the preparation of applications.

The two draft documents are: *Proposed Harmonized Requirements for Licensing of Vaccines in the Americas*, and an accompanying attachment entitled *Guidelines for Preparation of Applications*. They are available in Spanish, as well as in English and French versions. The information required is structured using the International Conference on Harmonization (ICH) Common Technical Document (CTD), specifically adapted to the market authorization of vaccines, and complemented by *Recommendations for vaccines* published in the World Health Organization's *Technical Report Series*. Because of their special characteristics, vaccines should always be considered as new products for the purpose of market authorization.

The purpose of these documents is to achieve greater harmonization in the information submitted in the application for market authorization of vaccines for human use. They apply to all vaccines to be registered, regardless of whether they are manufactured in the country of origin or not. Since the same information should be submitted to all countries in the Americas, the licensing process and ultimately the availability of vaccines should be facilitated. It is expected that having a common document will also benefit the region by making more efficient use of technical and financial resources, as well as facilitating mutual recognition processes where appropriate.

These draft documents are posted on the PAHO (http://www.paho.org) as well as the Health Canada (http://www/hc-sc.gc.ca) websites for the purpose of inviting comments and suggestions on the proposals . Comments proposing modifications to the texts should be addressed to Dra Maria de los Angeles Cortes, Regional Advisor on Vaccines and Biologicals, THR/EV, Pan American Health Organization, 525 23rd St. NW. Washington DC. 20037-2895 USA. cortesan@paho.org

Sixteen types of counterfeit artesunate circulating in South–east Asia

In the late 1990s counterfeits of artesunate, a vital life-saving antimalarial drug, were discovered circulating in South-east Asia. Surveys have suggested that 38% – 53% of shop-bought artesunate in mainland South-east Asia are fake and have been reported from Cambodia, the People's Republic of China, Lao PDR, Myanmar, Thai/Myanmar border, and Vietnam. The diversity of different types of fake hologram have increased and now 16 are recognized.

An article has recently been published in *PLoS Medicine* which includes an updated warning sheet describing these holograms and stickers Greater action by governments and international organizations is strongly urged to combat this under-recognized and serious public health problem.

Reports of counterfeit artemisinin derivatives and ACTs in Africa are also extremely alarming and could undermine the effectiveness of these medicines for malaria control in Africa.

References

1. *A Collaborative Epidemiological Investigation into the Criminal Fake Artesunate Trade in South East Asia.* PLoS Medicine e32 doi:10.1371/journal.pmed.0050032. http://medicine.plosjournals.org or: http://www.tropicalmedicine.ox.ac.uk

3. The Pharmacy and Poisons Board, Republic of Kenya Ministry of Health. 2007. Available at: http://www.pharmacyboardkenya.org.

4. Fake antimalarials in Southeast Asia are a major impediment to malaria control: multinational cross-sectional survey on the prevalence of fake antimalarials. *Trop Med Int Hlth,* 2004 **9**:1241–1246

5. Fake artesunate in southeast Asia. *Lancet*, 2001 **357**:1948–1950.

6. USP (2005) Fake antimalarials found in Yunnan Province, China, 2004. Available at: http://www.uspdqi.org/pubs

7. AED-SATELLIFE. Center for Health Information and Technology. http://www.healthnet.org

Eastern Mediterranean Ministers tackle high medicines prices

Medicines prices, availability, affordability and other component issues were recently discussed by delegates at a meeting of the Regional Committee for WHO's Eastern Mediterranean Region, held in Cairo 20–23 October 2007.

Results were presented from 11 surveys undertaken in the region using the WHO/HAI medicine price measurement methodology.

Key findings showed:

- Substantial differences in government procurement prices across countries in the region.
- Government purchasing of expensive originator brands, as well as cheaper generics, in all but 3 countries. On average, originator brands were about 3 times more expensive than generics. Prices of generics were often high.
- Availability in public sector facilities was very poor e.g. 16 of the 35 surveyed medicines were not found in any outlet surveyed in Yemen, and 23 of 29 medicines were not found in over 50% of the outlets in Pakistan.
- Excessive prices in the private sector for originator brands and lowest priced generics, e.g. Sudanese patients were paying 18 times international reference prices for originator brands. Lowest priced generics were over 5 times the reference prices in most countries.

- Most treatments purchased in the private sector were unaffordable (based on the salary of the lowest paid unskilled government worker).
- Some countries were applying taxes to essential medicines.

A lengthy discussion followed with comments from delegates of 16 countries. They acknowledged the many problems related to medicines prices in both the public and private sectors. Many also noted that the TRIPS Agreement had contributed to rising prices and diminished access to medicines, especially in developing countries.

Various policy and programme options were mentioned including the increased use of quality generics to improve affordability, regressive mark-ups to encourage the dispensing of lower priced generics, pooled procurement, greater transparency and the sharing of price information. A number of options were proposed for countries to consider to reduce prices. Countries were urged to develop, implement and enforce sound evidence-based policies and programmes and monitor their impact, and to ensure medicines are affordable and available to all.

A resolution was passed that featured the establishment of a web-based medicines prices hub in the region to share information on medicine prices and pricing structures, as well as best practices in medicine management. This innovative approach is welcomed as it will improve price transparency and empower governments to negotiate for more favourable prices. The resolution also urged governments to strengthen pricing policies (including public procurement of generics, and enhanced competition amongst suppliers) and rationalize supply chain costs in the private sector. WHO EMRO resolved to support Members States in this work including the development of guidelines on pricing policies and sharing information on best practices from other regions.

References

1. The resolution and the technical paper *Medicine prices and access to medicines in the Eastern Mediterranean region* is available on WHO EMRO's website at http://www.emro.who.int/rc54/

2. Survey data is available on HAIs website: http://www.haiweb.org/medicineprices

ATC/DDD Classification

ATC/DDD Classification (temporary)

The following anatomical therapeutic chemical (ATC) classifications and defined daily doses (DDDs) were agreed by the WHO International Working Group for Drug Statistics Methodology in 24-25 October 2007. Comments or objections to the decisions from the meeting should be forwarded to the WHO Collaborating Centre for Drug Statistics Methodology at whocc@fhi.no. If no objections are received, the new ATC codes and DDDs will be considered final and included in the January 2009 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
New ATC level codes (other than 5th levels):		
Other cephalosporins		J01DI
Other diuretics		C03X
Vasopressin antagonists		C03XA
New ATC 5th level codes:		
	Alitretinoin	D11AX19
	Azacitidine	L01BC07
	Calcium acetate and mmagnesium carbonate	V03AE04
	Ceftobiprole medocaril	J01DI01
	Clevudine	J05AF12
	Combinations	G03GA30
	Conivaptan	C03XA02
	Eszopiclone	N05CF04
	Etravirine	J05AG04
	Fluorodopa (^{18}F)	V09IX05
	Glycyrrhizic acid	A05BA08
	Hyaluronic acid	R01AX09
	Influenza, live attenuated	J07BB03
	Lubiprostone	A06AX03
	Metformin and vildagliptin	A10BD08
	Nicotinic acid, combinations	C10AD52
	Olmesartan medoxomil and amlodipine	C09DB02
	Paclitaxel poliglumex	L01CD03
	Pramlintide	A10BX05
	Rivaroxaban	B01AX06
	Romidepsin	L01XX39
	Satraplatin	L01XA04

ATC level	INN/Common name	ATC code
	Sugammadex	V03AB35
	Temsirolimus	L01XE09
	Terguride	G02CB06
	Tolvaptan	C03XA01
	Vorinostat	L01XX38

INN/common name	Previous ATC	New ATC
ATC code changes:		
Benfluorex	C10AX04	A10BX06
Bupropion	N07BA02	N06AX12
Methoxyflurane	N01AB03	N02BG09
Tedisamil	C01EB12	C01BD06

New DDDs:

INN/common name	DDD	Unit	Adm.R	ATC code
Alfa1 antitrypsin	0.6	g	P	B02AB02
Aliskiren	0.15	g	O	C09XA02
Ambrisentan	7.5	mg	O	C02KX02
Apomorphine	20	mg	P	N04BC07
Aripiprazole	15	mg	P	N05AX12
Betaine	6	g	O	A16AA06
Darunavir	1.2	g	O	J05AE10
Fesoterodine	4	mg	O	G04BD11
Maraviroc	0.6	g	O	J05AX09
Melatonin	2	mg	O	N05CH01
Methoxy polyethylene glycol-epoetin beta	4	mcg	P	B03XA03
Paliperidone	6	mg	O	N05AX13
Paricalcitol	2	mcg	O	A11CC07
Prulifloxacin	0.6	g	O	J01MA17
Rufinamide	1.4	g	O	N03AF03
Sitagliptin	0.1	g	O	A10BH01
Stiripentol	1	g	O	N03AX17
Telbivudine	0.6	g	O	J05AF11

ATC/DDD Classification

ATC/DDD Classification (final)

The following anatomical therapeutic chemical (ATC) classifications and defined daily doses (DDDs) were agreed by the WHO International Working Group for Drug Statistics Methodology in March 2007. They will be included in the January 2008 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 at whocc@fhi.no

ATC level	INN/Common name	ATC code
New ATC level codes (other than 5th levels):		
Melatonin receptor agonists		N05CH
New ATC 5th level codes:		
	Aliskiren and hydrochloro thiazide	C09XA52
	Azithromycin	S01AA26
	Diphtheria-hemophilus influenzae B-pertussis-tetanus-hepatitis B-meningococcus A	CJ07CA13
	Lacosamide	N03AX18
	Maraviroc	J05AX09
	Nitazoxamide	P01AX11
	Raltegravir	J05AX08
	Ramelteon	N05CH02
	Risedronic acid, calcium and colecalciferol, sequential	M05BB04
	Sitimagene ceradenovec	L01XX37
	Tafluprost	S01EE05

Change of ATC codes:

INN/common name	Previous ATC	New ATC
Melatonin	N05CM17	N05CH01

New DDDs:

INN/common name	DDD	Unit	Adm.R	ATC code
Argatroban	0.2	g	P	B01AE03
Carbetocin	0.1	mg	P	H01BB03
Dexrazoxane	1.5	g	P	V03AF02
Exenatide	15	mcg	P	A10BX04
Levetiracetam	1.5	g	P	N03AX14
Lumiracoxib	0.1	g	O	M01AH06
Nitazoxanide	1	g	O	P01AX11
Phentolamine	1	mg	P	G04BE05
Risedronic acid, calcium and cole-calciferol, sequential	5	mg[1]	O	M05BB04
Sitaxentan	0.1	g	O	C02KX03
Sodium phenyl-butyrate	20	g	O	A16AX03

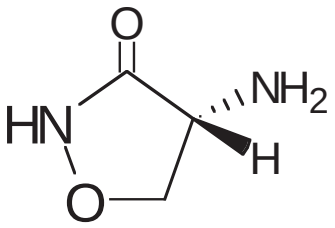
[1] *refers to risedronic acid*

Consultation Document

The International Pharmacopoeia

CYCLOSERINUM
CYCLOSERINE

Draft proposal for the *International Pharmocopoeia* (November 2007). Please address any comments to Quality Assurance and Safety: Medicines, PSM, World Health Organization, 1211 Geneva 27, Switzerand. Fax +4122 791 4730 or e-mail to rabhouansm@who.int



C3H6N2O2

Relative molecular mass. 102.1

Chemical name. (R)-(+)-4-Amino-3-isoxazolidinone; (R)-4-aminoisoxazolidin-3-one; CAS Reg. No. 68-41-7.

Other name. Orientomycin, PA-94, 106-7, Closina, Farmiserina, Micosetina, Oxamycin, Seromycin.

Description. A white or pale yellow, crystalline powder.

Solubility. Freely soluble in water; slightly soluble in methanol R and propylene glycol R; very slightly soluble in ethanol (~750 g/l) TS; practically insoluble in chloroform R and in ether R.

Category. Antibacterial drug.

Storage. Cycloserine should be kept at a temperature between 2 ˚ and 8 ˚C in a tightly closed container.

Additional information
Cycloserine is slightly hygroscopic and deteriorates upon absorbing water. Its solution is dextrorotatory.

REQUIREMENTS

Definition. Cycloserine is an analogue of the amino acid D-alanine with broad-spectrum antibiotic and glycinergic activities produced by *Streptomyces garyphalus* and *S. orchidaceus* or obtained by synthesis.

Cycloserine contains not less than 98.0% and not more than 100.5% of $C_3H_6N_2O_2$, calculated with reference to the dried substance.

Identity tests

Either test A, or tests B and C may be applied.

A. Carry out the examination as described under 1.7 Spectrophotometry in the infra-red region. The infrared absorption spectrum is concordant with the spectrum obtained from cycloserine RS or with the reference spectrum of cycloserine.

B. Dissolve about 1 mg in 10 ml of sodium hydroxide (0.1 mol/l) VS. To 1 ml of resulting solution add 3 ml of acetic acid (~60 g/l) TS and 1 ml of recently prepared mixture of equal volumes of a 40 mg/ml solution of sodium nitroprusside R and sodium hydroxide (~200 g/l) TS; a blue colour is developed gradually.

C. The absorption spectrum of a 25 µg/ml solution in hydrochloric acid (0.1mol/l) VS, when observed between 215 nm and 360 nm, exhibits a maximum at about 219 nm; the specific absorbance ($A_{1cm}^{1\%}$) is between 327 and 361.

Specific optical rotation. Use a 50 mg/ml solution in sodium hydroxide (~80 g/l) TS and calculate with reference to the dried substance; [á]D 20 ˚C = +108˚ to +114˚.

Heavy metals. Use 2.0 g for the preparation of the test solution as described under 2.2.3 Limit test for heavy metals, Procedure 3; determine the heavy metals content according to Method A; not more than 10 µg/g.

Sulfated ash. Not more than 5.0 mg/g.

Loss on drying. Dry at 60 ˚C under reduced pressure (not exceeding 0.6 kPa or about 5mm of mercury) for 3 hours; it loses not more than 10 mg/g.

pH value. pH of a 100 mg/ml solution in carbon-dioxide-free water R, 5.5-6.5.

Related substances
Carry out the test as described under 1.14.4 High performance liquid chromatography, using a stainless steel column (25 cm x 4.6 mm) packed with base-deactivated octadecylsilyl silica gel for chromatography R (5 ìm).

Mobile phase A: 4 volumes of acetonitrile R, 70 volumes of 0.02 mol/l sodium octanesulfonate R solution, 10 volumes of phosphate buffer pH 2.8 and 16 volumes of purified water.

Mobile phase B: 17 volumes of acetonitrile R, 70 volumes of 0.02 mol/l sodium octanesulfonate R solution, 10 volumes of phosphate buffer pH 2.8 and 3 volumes of purified water.

Prepare the sodium octanesulfonate solution by dissolving 4.7 g of sodium octanesulfonate R in 1000 ml of purified water.

Prepare the phosphate buffer pH 2.8 by dissolving 27.2 g of potassium dihydrogen phosphate R in 800 ml of purified water, adjust the pH to 2.8 by adding phosphoric acid (~20 g/l) TS and dilute to 1000 ml with purified water.

Use the following conditions for gradient elution:

Time (min)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comments
0 – 16	100	0	Isocratic
16 – 18	100 to 0	0 to 100	Linear gradient
18 – 22	0	100	Isocratic
22 – 24	0 to 100	100 to 0	Return to initial conditions
24 – 30	100	0	Isocratic re-equilibration

Prepare the following solutions using mobile phase A as diluent. For solution (1) use 0.5 mg of the test substance per ml. For solution (2) dilute a suitable volume of solution (1) to obtain a concentration equivalent to 0.5 ìg of cycloserine per ml.

For the system suitability test: prepare solution (3) by diluting a suitable volume of solution (1) to obtain a concentration equivalent to 25 ìg of cycloserine per ml, heat carefully in a boiling water-bath for 30 minutes.

Operate with a flow rate of 1.0 ml per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 219 nm.

Maintain the column temperature at 45 ˚C.

Inject 50 ìl of resolution solution. The test is not valid unless the resolution between the principal peak and the large degradation peak with a relative retention of about 3.2 is not less than 35. If necessary adjust the amount of acetonitrile in mobile phase A.

Inject alternatively 50 µl each of solutions (1) and (2).

In the chromatogram obtained with solution (1), the area of any peak, other than the principal peak, is not greater than twice the area of the principal peak obtained with solution (2) (0.2%). The sum of the areas of all peaks, other than the principal peak, is not greater than five times the area of the principal peak obtained with solution (2) (0.5%). Disregard any peak with an area less than 0.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

Assay
Dissolve about 0.1 g, accurately weighed, in 5 ml of water. Add 75 ml of 2-propanol R and titrate with carbonate-free sodium hydroxide (0.1 mol/l) VS using thymolphthalein/ethanol TS as indicator. Perform a blanc determination and make any necessary correction.

Each ml of sodium hydroxide (0.1 mol/l) VS is equivalent to 10.21 mg of $C_3H_6N_2O_2$.

CYCLOSERINI CAPSULAE
CYCLOSERINE CAPSULES

Draft proposal for the *International Pharmocopoeia* (November 2007). Please address any comments to Quality Assurance and Safety: Medicines, PSM, World Health Organization, 1211 Geneva 27, Switzerand. Fax +4122 791 4730 or e-mail to rabhouansm@who.int

Category. Antibacterial drug.

Storage. Cycloserine capsules should be kept in a tightly closed container and stored at a temperature between 2˚ to 8˚C.

Additional information. Strength in the current WHO Model list of essential medicines: 250 mg.

Requirements

Comply with the monograph for “Capsules”.

Definition. Cycloserine capsules contain Cycloserine. They contain not less than 90.0% and not more than 110.0% of the amount of $C_3H_6N_2O_2$ stated on the label.

Manufacture. The manufacturing process and the product packaging are designed and controlled so as to minimize the moisture content of the capsules. They ensure that, if tested, the contents of the capsules would comply with a loss on drying limit of not more than 20 mg/g when determined by drying a quantity of the capsules containing 0.1 g of cycloserine for 3 hours under reduced pressure (not exceeding 0.6 kPa or about 5 mm of mercury) at 60 ˚C.

Identity tests

Either tests A or tests B and C may be applied.

A. Examine the chromatograms obtained in the assay. The principal peak in the chromatogram obtained with the test solution is similar in retention time to the principal peak in the chromatogram obtained with the reference solution.

B. Shake a quantity of the contents of the capsules equivalent to 10 mg of cycloserine with 100 ml of sodium hydroxide (~40 g/l) TS and filter. To 1 ml of the filtrate add 3 ml of acetic acid (~60 g/l) TS and 1 ml of recently prepared mixture of equal volumes of a 40 mg/ml solution of sodium nitroprusside R and sodium hydroxide (~200 g/l) TS; a blue colour is developed gradually.

C. The absorption spectrum of the solution obtained in the assay, when observed between 215 nm and 360 nm, exhibits a maximum at about 219 nm.

Related substances
Carry out the test as described under 1.14.4 High performance liquid chromatography, using a stainless steel column (25 cm x 4.6 mm) packed with base-deactivated octadecylsilyl silica gel for chromatography R (5 ìm).

Mobile phase A: 4 volumes of acetonitrile R, 70 volumes of 0.02 mol/l sodium octanesulfonate R solution, 10 volumes of phosphate buffer pH 2.8 and 16 volumes of purified water.

Mobile phase B: 17 volumes of acetonitrile R, 70 volumes of 0.02 mol/l sodium octanesulfonate R solution, 10 volumes of phosphate buffer pH 2.8 and 3 volumes of purified water.

Prepare the sodium octanesulfonate solution by dissolving 4.7 g of sodium octanesulfonate R in 1000 ml of purified water.

Prepare the phosphate buffer pH 2.8 by dissolving 27.2 g of potassium dihydrogen phosphate R in 800 ml of purified water, adjust the pH to 2.8 by adding phosphoric acid (~20 g/l) TS and dilute to 1000 ml with purified water.

Use the following conditions for gradient elution:

Time (min)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comments
0 – 16	100	0	Isocratic
16 – 18	100 to 0	0 to 100	Linear gradient
18 – 22	0	100	Isocratic
22 – 24	0 to 100	100 to 0	Return to the initial conditions
24 – 30	100	0	Isocratic re-equilibration

Prepare the following solutions using mobile phase A as diluent. For solution (1) mix the contents of 20 capsules and transfer a quantity equivalent to about 50 mg of cycloserine, dissolve, dilute to 100 ml and filter. For solution (2) dilute a suitable volume of solution (1) to obtain a concentration equivalent to 0.5 ìg of cycloserine per ml.

For the system suitability test: prepare solution (3) by diluting a suitable volume of solution (1) to obtain a concentration equivalent to 25 µg of cycloserine per ml, heat carefully in a boiling water-bath for 30 minutes.

Operate with a flow rate of 1.0 ml per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 219 nm.

Maintain the column temperature at 45 ˚C.

Inject 50 µl of solution (3). The test is not valid unless the resolution between the principal peak and the large degradation peak with a relative retention of about 3.2 is not less than 35. If necessary adjust the amount of acetonitrile in mobile phase A.

Inject alternatively 50 ìl each of solutions (1) and (2).

In the chromatogram obtained with solution (1), the area of any peak, other than the principal peak, is not greater than four times the area of the principal peak obtained with solution (2) (0.4%). The sum of the areas of all peaks, other than the principal peak, is not greater than ten times the area of the principal peak obtained with solution (2) (1.0%). Disregard any peak with an area less than 0.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

Assay
Either method A or method B may be applied.

A. Determine by High performance liquid chromatography as described in the test for related substances with the following modifications.

Prepare solutions as follows. For solution (1) mix the contents of 20 capsules and transfer a quantity equivalent to about 10 mg of cycloserine, dissolve, dilute to 100 ml and filter. For solution (2) dissolve cycloserine RS in mobile phase A to obtain a concentration of 0.1 mg/ml.

Inject alternatively 50 µl each of solutions (1) and (2).

Calculate the content of cycloserine ($C_3H_6N_2O_2$) from the declared content of $C_3H_6N_2O_2$in cycloserine RS.

B. To a quantity of the mixed contents of 20 capsules equivalent to 0.250 g of cycloserine, accurately weighed, add sufficient hydrochloric acid (0.1mol/l) VS to produce 200 ml, shake for 10 minutes and filter. Dilute 2 ml of the filtrate to 100 ml with hydrochloric acid (0.1mol/l) VS.

Measure the absorbance of this solution in a 1-cm layer at the maximum at about 219 nm against a solvent cell containing hydrochloric acid (0.1mol/l) VS. Calculate the percentage content of $C_3H_6N_2O_2$in the capsules, using the absorptivity value of 34.3 (A1cm 1% = 343). [Note from Secretariat: This has to be checked by WHO Collaborating Centre, Sweden.]

Dissolution. Carry out the test as described under 5.5 Dissolution test for solid oral dosage forms.

Recent Publications, Information and Events

Assessing the quality of herbal medicines: contaminants and residues

This WHO guideline *Assessing the quality of herbal medicines: with reference to contaminants and residues* presents a general overview of potentially hazardous contaminants and residues in herbal medicines and includes guiding principles for assessing the quality of herbal medicines in terms of major contaminants and residues. It also recommends analytical methods for qualitative and quantitative determination of such contaminants and residues.

Within the overall context of quality assurance, these guidelines are intended to provide general technical guidance to countries. The objectives of the guideline are to provide:

- guiding principles for assessing the quality and safety of herbal medicines, with specific reference to contaminants and residues;
- model criteria for identifying possible contaminants and residues;
- examples of methods and techniques; and
- examples of practical technical procedures for controlling the quality of finished herbal products.

The scope of these guidelines does not cover issues of adulteration of herbal medicines and/or counterfeit products.

The annexes present several examples of suitable methodologies found in national or regional pharmacopoeias and in WHO documents.

Reference: *Assessing the quality of herbal medicines: with reference to contaminants and residues.* http://www.who.int/medicines

Launch of procurement and supply management website

The AIDS Medicines and Diagnostic Service (AMDS) of WHO and its partner organizations have initiated development of a unique procurement and supply management website for HIV-related health commodities: the PSM Toolbox.

The PSM Toolbox website features a user-friendly search engine, regularly updated content, a forum to share tool use experiences and more. You are invited to submit tools via the website for review by the project working group and possible inclusion on the website.

An offline, CD-ROM version of the PSM Toolbox is also available at cmorris@idasolutions.org or amds@who.int.

Reference: http://www.psmtoolbox.org/

Malaria research collection published

Leading research scientists, physicians, and public health specialists from around the world have published papers on new insight into the international burden of malaria and how the global community can best combat the disease.

The collection of latest research is presented in a 340-page supplement to the *American Journal of Tropical Medicine and Hygiene* entitled “Defining and

Defeating the Intolerable Burden of Malaria III: Progress and Perspectives." The supplement contains 42 articles and features a diverse range of contributors, including epidemiologists, entomologists, microbiologists, economists and social scientists.

This publication is available free to scientists, researchers, and other interested parties worldwide and describes the latest developments on a broad range of malaria issues.

Additional papers explore malaria advocacy efforts and international cooperation, examining the gains made by the Multilateral Initiative on Malaria and the Global Fund, and making recommendations for a long-term vision for global malaria prevention and control.

The third in a series, the new supplement contains data contributed by malaria researchers from around the world, including many in malaria-endemic areas.

Reference: Defining and Defeating the Intolerable Burden of Malaria III: Progress and Perspectives. http://www.fic.nih.gov/news/press_releases/malaria_eradication1-08.htm

New pricing bulletin

Since publishing the WHO/HAI survey tool in mid-2003, over 50 surveys have been conducted worldwide measuring medicine prices, availability, affordability, and price components in the supply chain from manufacturer to patient. More surveys are planned for 2008. A number of countries are considering policy changes in response to survey findings, and some are now regularly monitoring prices and availability.

The purpose of the pricing bulletin is to inform on this work — survey results, workshops, advocacy campaigns, policy changes, monitoring work, project activities and publications etc. It is appreciated that people lack time to read lengthy documents, so each bulletin will only be 4 pages long, and produced quarterly.

Reference: http://www.haiweb.org/medicineprices/

How to improve the use of medicines by consumers

A revised version of the WHO guide *How to improve the use of medicines by consumers* is now available on the WHO Medicines website.

Influencing human behaviour is a complex undertaking that requires careful groundwork and carries responsibility for improving public health. To develop an intervention capable of delivering measurable changes requires working with communities to find the answers to eight basic questions:

1. What is current medicine use?
2. What are the problems related to current medicines use and what are the critical factors underlying these problems?
3. What practices put people most at risk and are a priority for an intervention?
4. What solutions are possible that will build on existing perceptions and understandings to motivate changes in individual and social behaviour?
5. Who needs to be addressed?
6. What channels of communication and what materials/approaches are likely to be most effective?
7. What other measures might be needed?
8. How will the intervention be monitored and evaluated?

Having found appropriate answers, the work then starts, with the people most affected, to put into practice an intervention that will encourage rational use of

medicines in the community to help everyone attain the best possible level of health."

Reference: How to improve the use of medicines by consumers. http://www.who.int/entity/medicines/publications/WHO_PSM_PAR_2007.2.pdf

Model quality assurance system for procurement agencies

The Model quality assurance system for procurement agencies was developed by WHO through an extensive consultative process. The final guide was endorsed by the WHO Expert Committee on Specifications for Pharmaceutical Preparations in 2005 and published as Annex 6 of the Technical Report Series Number 937 (1).

In 2003, the WHO Expert Committee also adopted a procedure (2) that allows the assessment of procurement agencies as well as guidelines for the preparation of a procurement agency information file (3). These texts are available on the web and provide a basic tool to enable an official assessment process.

References:

1. WHO Expert Committee on Specifications for Pharmaceutical Preparations. A model quality assurance system for procurement agencies. Annex 6. Technical Report Series, No. 937 (2006). http://whqlibdoc.who.int/trs/WHO_TRS_937_eng.pdf#page=217

2. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Procedure for assessing the acceptability, in principle, of procurement agencies for use by United Nations agencies. Annex 6. Technical Report Series No. 917 (2003). http://whqlibdoc.who.int/trs/WHO_TRS_917_annex6.pdf

3. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Guidelines for the preparation of a procurement agency information file. Annex 7, Technical Report Series No. 917 (2003). http://whqlibdoc.who.int/trs/WHO_TRS_917_annex7.pdf

Training courses in management and supply

Managing drug supply in developing countries
Managing drug supply in developing countries is a training course covering the complete drug management cycle. The course is run by IDA solutions and WHO and is designed to expose participants to modern management techniques of drug supply systems and to teach them how to apply them to their own specific situation; to provide practical tools to decision makers in essential drugs programmes to improve their level of performance; and to encourage the exchange of views and experiences between senior officers and decision makers

Dates & Location 2008

- June 23 – July 5. The Netherlands. (French)
- October 6 –18. The Netherlands. (English)

Supply chain management of HIV and AIDS medicines and supplies
This course covers the Drug Management Cycle with emphasis on HIV/AIDS Project/Programme management
Course objectives: to expose participants to issues specific to planning the procurement and distribution of ARVs - provide programme managers with skills in programme planning and management - teach participants how to apply those skills in their own country - provide practical tools to decision-makers in essential medicine programmes to improve their level of performance - exchange views and experiences between senior decision-makers.

Dates & Location 2008

- November 24 – December 6. The Netherlands. (French)
- South-Africa (English) http://www.aa4a.co.za
- In-country Lusophone version

Reference: IDA Solutions. http://www.idasolutions. org

Pharmacists work to improve use of generics

Pharmacists in Singapore have linked up with the Consumer Association, CASE, to educate and empower patients on generic products, and advocate generics as a cost-saving solution. Joint initiatives have included public forums and publication of drug prices.

Pharmacists have also contributed articles on generic medicines to the CASE newsletter as well as to a weekly supplement on healthcare in the national newspaper. Individual institutions too have their own initiatives.

There is also discussion on whether physicians should deliver a prescription allowing the patient to choose where they would like to buy their medicines, and whether to obtain generic or branded products. Currently, physicians are allowed to sell and dispense drugs from their clinics and they charge for a prescription when a patient requests one.

References

1. http://www.pss.org.sg/main/content/view/490/

2. CASE Public Forum. Know Your Medicine, Understand Your Options. http://www.pss.org.sg/main/content/view/502/ and http://www.case.org.sg

Announcement

The 13th International Conference of Drug Regulatory Authorities (ICDRA) will be hosted by the Swiss Agency for Therapeutic Products (Swissmedic) in collaboration with the World Health Organization

The ICDRA will take place in Berne, Switzerland from 16 to 19 September 2008

Updated information is availabel at:
http://www.icdra.ch

or

http://www.who.int/medicines/icdra