

# WHO Drug Information

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# Pharmacovigilance Focus

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## **Biosimilar medicines and safety: new challenges for pharmacovigilance**

Regulatory experience of approving and monitoring the safety of biosimilar medicines varies across the world. Recently, the European Union (EU) took the lead in establishing a transparent regulatory process for approving biosimilars. To date, the EU has approved a number of biosimilars such as formulations of somatotropin, epoietin and, most recently, filgrastim. The prevailing view among regulators is that proteins are much more complex than small molecule medicines and it may not be possible to demonstrate the identical nature of two biological products originating from different manufacturing sources solely based on quality information.

This has led to the view that follow-on biological products manufactured by generic manufacturers after expiry of patent and other exclusivity rights cannot be approved using the same simplified regulatory procedures as applied for small molecule-based generic drugs. Generating additional nonclinical and clinical data to demonstrate that these medicines have an equivalent, or similar, safety and efficacy profile to the originator product is needed. However, several parties have raised concerns that such regulatory procedures may not be enough to ensure the safety and efficacy of these products. This article gives an overview of regulatory experience as well as the main principles and issues concerning quality, safety and efficacy of these products.

Biological medicinal products (biopharmaceuticals) have a successful record in treating many life threatening and chronic diseases. However, their cost has often been high, thereby limiting their access to patients, notably in developing countries. More recently, the expiration of patents and/or data protection for the first major group of innovative biotherapeutics is stimulating development of products “similar” to the original biological products which rely for their licensing, in part, on data from originator products licensed on a full registration dossier.

A variety of terms, such as ‘biosimilars’, ‘follow-on protein products’ and ‘subsequent-entry biologics’ have been used by different jurisdictions to describe these products. The term ‘generic’ medicine is used extensively for chemical, small molecule medicinal products that are structurally and therapeutically equivalent to an originator product whose patent and/or data protection period has expired.

### **Current situation**

In many countries, a regulatory pathway for the approval of generic medicines has been established. Since biological medicinal products consist of large and highly complex molecular entities that are difficult to characterize, the approach established for small molecule generic medicines is not fully appropriate for development, evaluation and licensing of biosimilars — as they are called in the EU. The fine structure of a biotherapeutic medicine is very sensitive to various production parameters and the full understanding of all processes involved is complicated. Thus, it is unlikely that one

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*\* This article does not necessarily reflect the policies and views of the World Health Organization.*

manufacturer will be able to precisely reproduce a biotherapeutic medicine manufactured by another company. Indeed, an increasingly wide range of biosimilars are under development or already licensed in many countries.

As stated, the EU has taken the lead in establishing a regulatory process for approving biosimilars and EU legislation now differentiates between “generic medicinal products” and “similar biological medicinal products”. It also defines the regulatory approach for EU marketing authorization of biosimilar medicinal products. Both general [1–3] and product-specific guidelines dealing with recombinant erythropoietin [4], granulocyte colony stimulating factor (G-CSF) [5], human somatotropin [6] and human insulin [7] have been issued by the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA). Draft guidelines have also been issued for interferon alfa [8] and low molecular weight heparins [9]. All these guidelines have one common feature — identifying the need for at least some clinical data to support the approval of biosimilar medicinal products.

In the USA, there is currently no set of guidelines comparable to those of the EU for biosimilars. The Food and Drug Administration (FDA) has approved Omnitrope<sup>®</sup>, a growth hormone biosimilar, but this was done using the abbreviated new drug application (ANDA) procedure which essentially defines biosimilars as “chemical” generic drugs rather than biopharmaceuticals [10]. However, this method of approval is rather exceptional as specific US regulatory guidelines for approval of biosimilars do not currently exist. Also, in most other countries a comparative set of guidelines to those of the EU is absent.

The need for additional global regulatory guidelines for evaluation and overall

regulation was formally recognized by the World Health Organization (WHO) in 2007. Since then, WHO has been working with regulators from many countries on a draft document that provides guidance for the development and evaluation of biological therapeutic products that may be subject to abbreviated licensing pathways [11]. The document is expected to be finalized later in 2009.

### **Generic medicines and biosimilars: similarities and differences**

Multisource (generic) medicines are formulated when patent and other exclusivity rights expire. These medicines have an important role to play in public health as they are well known to the medical community and usually more affordable due to competitive availability.

The key requirement for authorization of generic medicines is therapeutic interchangeability with the originator product. To ensure therapeutic interchangeability, generic products must contain the same amount of active ingredient and have the same dosage form and be bioequivalent to the originator product. Bioequivalence is usually established using comparative *in vivo* pharmacokinetic studies with the originator product (or reference product). A detailed description of how this is carried out is described in respective WHO and national regulatory guidelines [12, 13]. Well-resourced regulatory authorities require that a multisource (generic) medicine must meet certain regulatory requirements. In a well established setting, a generic medicine in general must:

- contain the same active ingredients as the innovator drug;
- be identical in strength, dosage form, and route of administration;
- have the same use indications;
- be bioequivalent (as a surrogate marker for therapeutic interchangeability).

- meet the same batch requirements for identity, strength, purity and quality, and
- be manufactured under the same standards of good manufacturing practice (GMP) required for innovator products.

Traditional generic medicines are small, organic molecules with a well-characterized structure which can be more easily defined by their atomic structure than their manufacturing processes. In the case of more complicated generic medicines, processes of synthesis are used. For example, biotechnological methods are applied to produce large molecule medicines such as antibiotics (for example, streptomycin). Sometimes, several methods of synthesis are combined, including the use of genetically engineered microorganisms in fermentation. What makes a difference is how well the resulting active pharmaceutical ingredient (API) can be characterized without risking unidentified impurities and subtle structural changes resulting in different safety and efficacy profiles.

The current challenge facing international development of a programme for biosimilars is that there is no way of confirming that the reference product on the market in one region complies with requirements in other regions. It is true that even identifying a global comparator for generic “chemical” medicines is sometimes very challenging. Above all, the essential characteristics of a biosimilar are not yet perfectly defined. For example, some consider that only fully characterized proteins with no major differences in their structure or impurity profile can be considered biosimilar. However, EU regulators have accepted a degree of difference provided it can be justified. For example, Valtropin® (somatotropin) is expressed from yeast whereas its reference product, Humotrope®, is expressed from *Escherichia coli*. This

necessarily implies different host cell impurities as a minimum but the regulator has accepted the product as biosimilar [14]. Differences with other products have been justified as being within the range of natural variants without major clinical impact.

Originator products can go through a number of variations during product development and the post marketing period. However, it is difficult to ascertain whether major process variations (e.g. cloning, selection of a suitable cell line, fermentation, purification and formulation) will affect the end product. Thus, a biosimilar may differ significantly from the originator product. In principle, some of the variations applied by originators can be more substantial than those applied by generic manufacturers. When assessing and accepting variations applied to the manufacture of originator products, regulators can acquire valuable information for assessing biosimilars.

At present, lack of consistency between originator epoietins and products manufactured in countries outside well regulated markets (such as the EU and USA) was demonstrated at the World Congress of Nephrology in 2007 [15, 16]. Some products were identified as containing additional basic isoforms — more than 4% aggregates and bacterial endotoxin contamination. These findings may affect efficacy, immunogenicity and patient safety, respectively [16, 17]. Finally, some of these biosimilar products were not approved under a specific well-defined and transparent regulatory framework. Biopharmaceutical safety and efficacy data are difficult to transcribe into a discernable format and it is a challenge demonstrating that a biosimilar product is as safe or effective as the originator. It is hoped that rapid advances in science and knowledge obtained from regulatory practice may make this task easier in the future.

**Safety of biosimilars: specific points of concern**

The two main issues of concern with biosimilar agents involve variable potency/response and immunogenicity thought to be due to one of three main mechanisms: glycosylation, contamination or changes to three-dimensional structure. Immunogenicity is generally the primary safety concern, but variation in potency can also raise safety issues in the case of substitution of the original molecule with biosimilars, e.g. variability in haemoglobin values seen with original epoietin [18] and its possible association with increased mortality in dialysis patients [19]. The issues of safety and efficacy cannot easily be separated as binding of an agent by immune system molecules will often decrease its clinical effect and changes to the shape or structure of a protein can alter binding to immune system receptors as well as to its physiological target. Therefore, biosimilars could induce immune responses which may be either clinically irrelevant or could have severe and potentially lethal consequences.

The glycosylation of recombinant proteins can influence degradation, exposure of antigenic sites and solubility, as well as immunogenicity. Changes in degradation can produce novel antigenic epitopes not found in the parent molecule with potentially increased immunogenicity and biological activity and metabolic half-life also affected. The degree of glycosylation depends primarily on the host cell expression system. For example, recombinant G-CSF expressed in *Escherichia coli* is non-glycosylated, whereas that expressed in Chinese hamster ovary cells is glycosylated. Similarly, proteins manufactured in yeast cells contain high levels of mannose sugar groups, rendering them more prone to degradation and thereby decreasing their half-life. [See references 20 and 21 for more details about effects of immunogenicity.]

Another important factor is potential contamination during manufacturing. Impurities in biopharmaceuticals may derive from chemicals or antibiotics used during manufacture or may result from microbial or viral contamination. Impurities such as endotoxins or denatured proteins, for example, may give a danger signal to T cells which may then send activating signals to B cells leading to an immune response.

An important lesson was learned in the case of an increasing incidence of antibody-mediated pure red cell aplasia (PRCA) observed outside the USA between 2000 and 2002 which revealed that a small change in the formulation of a well-established innovator biopharmaceutical product (epoietin alfa) with extensive patient years experience may have significant clinical consequences [22]. The sharp increase in incidence occurred primarily among those on Eprex®/Erypo®, and coincided with replacement of human serum albumin as a stabilizer by glycine and polysorbate 80. Subsequent withdrawal of the SC formulation of epoietin alfa led to a considerable decrease in the incidence of PRCA cases. A number of possible mechanisms have been proposed to explain the observed upsurge of PRCA but it is likely the modification in formulation played a major role [23].

Alterations to the three-dimensional structure of a protein may also have important effects on immunogenicity. Major sources of such changes include protein aggregation (which has been suggested as one possible explanation of the PRCP epidemic described above), oxidation and deamidation. Likely aggregation is of particular concern as it may lead to the immune system recognizing the protein as non-self and mounting a response [24]. This is probably because the repeating structure of protein aggregates more closely resembles the micro-

bial structures that the immune system is primed to act against [25]. The process by which the body becomes reactive to the protein can be very slow: antibodies to products such as interferon and erythropoietin may be detected for more than a year after treatment cessation [26].

### **Clinical safety data and pharmacovigilance**

The concerns raised above have been addressed, as far as possible and in line with present scientific knowledge, in EU regulatory guidance. For example, erythropoietin is a more complex molecule compared to either insulin or growth hormone. The respective guidelines reflect this complexity and, in order to identify potential immunogenicity, advocate conducting at least two randomized controlled trials confirming safety data collected over a minimum of 12 months from at least 300 patients. Within the EU authorization procedure, the applicant should present a risk management programme/pharmacovigilance plan in accordance with current EU legislation and pharmacovigilance guidelines.

In order to further study the safety profile of the biosimilar medicinal product, data for rare adverse events should be collected from a cohort of patients representing all approved therapeutic indications. Specific reference is made to include assessment of the incidence of PRCA within the pharmacovigilance plan for epoietin biosimilars [4]. It is clear that with 300 patients PRCA may not be detected due to the relatively small number of patients involved as compared to the rarity of this complication. Consequently, EMEA guidelines for epoietins also require immunogenicity testing and pharmacovigilance programmes to monitor the efficacy and safety of biosimilar products during post-approval.

Nonetheless, some adverse effects may take more than a year to appear [26] and

even very small changes in manufacturing can have major consequences for a product's adverse effects [27]. Pharmacovigilance is thus likely to be a long-term project for any biosimilar medicine. Overall, routine pharmacovigilance is recommended for products where no special concerns have arisen, whereas additional pharmacovigilance activities and action plans will be required for medicinal products with important established risks, potential risks or missing information.

Spontaneous reporting still remains the cornerstone of pharmacovigilance but has several weaknesses. Often, only the international nonproprietary name (INN) is used as the sole product identifier and in the case of several products with the same INN (originator, plus generics or biosimilars) it may be difficult to trace the exact manufacturer of the product. A much better traceability of products is needed [28], particularly in the case of biosimilars.

Recent developments within the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) raise hopes that a harmonized set of product identifiers will become available soon and could improve future traceability. Recently, the ICH Steering Committee recognized the benefits of continuing to work with International Standard Development Organizations in developing harmonized electronic messages to transfer regulatory information with a view to developing harmonized formats for Individual case safety reports (ICSR) and identification of medicinal products [29]

Different versions of biopharmaceuticals have been available in both India and China for several years [30]. It is important to note that both India and China are considered to have less stringent regulatory standards than the EU and the USA.

Unfortunately, both countries have under-developed pharmacovigilance systems and provide only small number of adverse drug reaction reports to the WHO International Programme on Drug Monitoring database managed by the Uppsala Monitoring Centre [31].

### Conclusions

The cost of providing effective therapies in different disease areas increases progressively and biosimilar medicines may offer considerable advantages to hard-pressed health-care budgets globally. Regulatory decisions to permit clinical use should be based on rigorous and highly competent case by case scientific assessments and presence of appropriate systems for pharmacovigilance. Clearly this area of rapidly evolving regulatory science would benefit from better cooperation and information exchange between different regulators internationally. Safety has to come first and effective pre- and post-marketing safety monitoring remains the key.

Sufficient regulatory tools are currently available to ensure safety of biosimilars but the proper implementation of these tools may prove challenging, particularly outside well established and resourced regulatory settings. Even in the EU, applying pharmacovigilance programmes with uniform excellence across the region remains a challenge. Pharmacovigilance is a responsibility that is shared among actors in the pharmaceutical industry, physicians and pharmacists, with input from appropriately educated and informed patients. Much better cooperation between all stakeholders is needed to ensure that everyone involved fully understands the complex scientific arguments and regulatory decisions applying to biosimilar products. This would hopefully lead to safer use and better qualitative and quantitative reporting of suspected adverse reactions. Biosimilar medicines clearly have a future

but patients should not be expected to bear the burden of excessive trial-error incidents.

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# Blood and Biomedicines

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## Availability, quality and safety of blood and blood products

Blood has been collected, stored, tested, and transfused as a therapeutic since the beginning of the Twentieth century. Until the 1950s, activities concentrated on improving storage of cells and ensuring blood group compatibility. Thereafter, methods were developed for preparing therapeutic products from human blood and plasma, for use in treating life-threatening diseases, and to support complex surgical procedures and transplantation.

For the past 25 years, efforts have focused on improving the safety and efficacy of components derived from blood and plasma, developing and validating new methods, and seeking new therapeutic uses. Blood products such as blood clotting factors and human immunoglobulins (polyvalent and specific) are now included in the World Health Organization's (WHO) *Model List of Essential Medicines*. This reflects the importance of blood and blood products in treating congenital, immune-acquired life-threatening diseases, and conditions such as bleeding or trauma. In vitro diagnostic devices for sensitive detection of infectious disease markers play a role in successfully screening donor blood and testing plasma pools prior to fractionation, as well as in clinical diagnosis.

Transmission of infectious diseases by blood (notably HIV, hepatitis B (HBV) and hepatitis C (HCV)) has underscored the importance of quality systems and effective regulation in the preparation of plasma as a raw material for use in the

manufacture of medicinal products and in supply of other blood components such as platelets and red cells.

Developed countries have implemented procedures, policies and methods to ensure the safety, quality and availability of all products derived from blood. This has facilitated wider access to a comprehensive range of safe blood products for patients with bleeding, immunological or other severe diseases. Additionally, good manufacturing practices (GMP) have been introduced into plasma fractionation centres and are now also applied in blood establishments. Improvements in health and transfusion safety have been documented by haemovigilance and pharmacovigilance programmes. Conversely, comparable levels of availability, quality and safety do not yet exist in many developing countries (1).

Equitable and universal access to blood and blood products of assured quality and efficacy will contribute to achievement of the UN Millennium Development Goals relating to reduction of maternal and child mortality, as well as to efforts to prevent HIV, HBV and HCV transmission.

## Specific issues requiring action

### Wastage of blood plasma

Several reasons account for the lack of blood products in developing countries. Plasma collected in developed countries is restricted and the potential for generating surplus products sufficient to meet the needs of developing countries is small. Moreover, such products would be too expensive. Developing countries must therefore create their own sustainable supplies of blood products using blood

plasma collected by their own blood establishments from their own populations. Currently, however, a large percentage of the plasma collected in developing countries is categorized as a waste material and destroyed. This is because appropriate technology and enforcement of GMP are not available. Fractionation capacity could, however, become available if plasma production complied with internationally-agreed standards.

### **Risk of transfusion-transmitted diseases**

If rigorous standards for donor selection, testing and donation are not applied, blood products and blood transfusion remain potent vectors for transmission of infectious diseases. Unfortunately, current arrangements for blood plasma collection, processing and testing are inadequate in a vast number of developing countries. In addition, increasing international mobility of populations and globalization of the blood industry highlight the need to introduce and strengthen quality assurance regulations.

The history of blood transfusion has amply demonstrated the risks. Examples include transmission of HIV, HCV and HBV, bacteria, trypanosoma and malarial parasites, as well as emerging and re-emerging diseases. Although worldwide expansion of human blood plasma collection and processing of blood products has the capacity to save lives, without appropriate control and standardization it can also amplify public health risks.

### **Poor regulation of blood products in developing countries**

Developing countries recognize the need to regulate blood products and assure blood safety. Blood establishments should be subject to inspection and audit by national regulatory authorities and fractionators should demonstrate effective control and traceability of plasma raw

material. Substantial improvement will prevail through introduction and enforcement of appropriate independent and transparent quality assurance regulations and inspection procedures.

### **Cross-border threats**

The risks of disease migration are escalating due to changes in habitat, increasing mobility of populations, wars and global climate change. Pandemic infections may also affect the supply of blood and blood products in different ways. These factors underscore the need to introduce and strengthen quality assurance regulations in developing countries. The trend towards global regulatory convergence favours sharing of best practices and the creation of internationally agreed regulations. International coordination, notably in areas such as the manufacture of blood products, is therefore becoming increasingly important.

### **WHO activities**

For more than 50 years, WHO has been closely involved in setting quality and safety standards and training regulators in the manufacture and quality control of biological and blood products. The overall technical responsibility for these activities lies with the WHO Expert Committee on Biological Standardization (ECBS). Guidelines on the manufacture and quality control of blood and blood products have been developed, updated and promoted by WHO (2–4). They represent global consensus on the part of manufacturers, regulators, professional international societies and national blood programmes with respect to production and quality assurance procedures for blood and blood products.

International biological reference preparations (5) to assist in establishing the quality and safety of blood products and related in vitro diagnostic devices have also been adopted following validation in global coordinated studies. The value of

reliable internationally agreed reference materials is that manufacturers, regulators and blood establishments can compare results worldwide despite the increasing diversity of products.

Public health challenges demonstrate the need for international collaboration and cooperation and the need to create regulatory networks to support dissemination of regulatory actions, knowledge transfer and organization of training programmes. The International Conference on Drug Regulatory Authorities (ICDRA) provides regulatory authorities of WHO Member States with a forum to meet and discuss ways to strengthen collaboration. In 2005, the WHO Blood Regulators Network was established in response to the request by ICDRA participants and the ECBS. The Network was set up to foster development of international consensus on effective regulatory approaches.

Recognizing the importance of the provision of safe blood, blood components and plasma derivatives, the Fifty-eighth World Health Assembly in 2005 (Resolution 58.13) expressed its support for “full implementation of well organized, nationally coordinated and sustainable blood programmes with appropriate regulatory systems” and stressed the role of “voluntary, non-remunerated blood donors from low-risk populations”.

## **Improving access to blood and blood products**

In order to ensure the availability of safe blood products in developing countries, Member States should be alerted to the risks of inadequate regulation and guidance should be provided on establishing regulatory oversight of blood systems. Efforts should be made to increase the transfer of validated technology and to build capacity with the overall aim of improving access to safe, effective and affordable blood products.

As a first step, up-to-date mechanisms for implementing and enforcing quality standards relating to blood products and blood safety-related in vitro diagnostic devices will need to be introduced in countries. Activities should be supported by WHO guidelines for the production of blood plasma for fractionation, complemented with additional guidelines to promote and support implementation of GMP. Work should also be undertaken to review existing national regulations for blood products and to support and further develop technical upgrading of medicines regulatory authorities. Furthermore, strategies should be sought to share the expertise and experience already generated in developed countries and to develop regional regulatory networks.

The dimension and complexity of the situation requires a multifaceted strategy incorporating input from partners at national, regional and international levels. WHO is well placed to secure the support of international and nongovernmental organizations, international professional associations and other agencies devoted to finding solutions for health problems.

Creating sustainable blood and plasma programmes with appropriate regulatory systems will ensure both specific and wider public health benefits including:

- optimal use of donated blood plasma;
- safer blood components;
- sustainable and affordable supply of safe essential products for the treatment of congenital diseases, trauma and immunologically mediated conditions;
- reduction of infectious disease transmission via blood-borne pathogens, both within countries and across national borders;
- improved quality and safety of all products from blood establishments

through the enforcement of national (and international) quality assurance regulations;

- substantial contribution to national/regional public health programmes through, for example, improved population epidemiology for infectious diseases such as HIV, HBV and HCV, prevention and control of disease transmission, and blood donor health monitoring;
- potential application of quality systems and GMP principles to other medical laboratory disciplines, and
- inclusion of developing countries in the international transfusion community and in activities of associated plasma fractionation industries.

The strategic goal is to improve public health by providing safe and effective medicine to the world's population. A risk-benefit analysis must ensure that sufficient quantities of the required products are available at a cost that does not limit access.

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# New Regulatory Challenges

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## Contribution of clinical pharmacologists to government: opportunities and challenges

Clinical pharmacology is a scientific discipline that focuses on evaluating the effect of medicines in humans. Within a wider context of promoting safety, maximizing efficacy and minimizing side-effects, the work of the clinical pharmacologist is particularly valuable in clinical trials. Other branches of the discipline involve pharmacovigilance, pharmacokinetics, drug metabolism, pharmacoepidemiology and, more recently, pharmacoconomics. The clinical pharmacologist collaborates closely with other clinicians, pharmacists, biologists, analytical chemists, statisticians, epidemiologists and health economists. The clinical pharmacologist receives training in the evaluation of drug therapy and drug products and this makes the profession valuable in a number of public activities such as drug approval, post-marketing surveillance, drug therapy selection, reimbursement decisions and ethical review of research projects.

Faced with the task of regulating increasingly complex medicines and biomedicines markets, many regulatory authorities and health departments in developing countries rely for advice on pharmacists who may have a limited medical background and lack the resources to access and assess information on the latest clinical research. On the other hand, clinical pharmacologists have a rigorous medical and scientific training which enables them to evaluate evidence and produce new data through well designed studies and interaction with other healthcare professionals. A clinical pharmacologist can provide the link between government and health care outcomes, serving also as a powerful advocate of evidence-based medicine. They can be invaluable in addressing current challenges such as assessing new medicines, providing unbiased medicines-related information, contributing to treatment guideline development, identifying preventable adverse drug reactions through promoting rational use of medicines and improving prescribing practices. Politicians are often unaware of the valuable role that clinical pharmacology can play in improving performance of regulatory and health systems through closing the gap between current medical practices and latest clinical science.

### Regulation and clinical pharmacology: emerging alliances

As a function of protecting and promoting public health, a government must consider the ethical, scientific and developmental aspects of medicines. Activities in these three dimensions are complimen-

tary and provide the means of attaining the health and wellbeing of citizens.

In a broad sense, the role of regulatory agencies is multidimensional. The World Health Organization (WHO) proposes that regulatory goals are achieved through ensuring the safety, efficacy and quality of medicines, rational use, and providing

appropriate medicines information to the public and health professionals (1). Similarly, the European Medicines Agency (EMA) coordinates the work of national experts and has *inter alia* the following far reaching responsibilities (2):

“In the context of continuing globalization, to protect and promote public and animal health by:

- developing efficient and transparent procedures to allow rapid access by users to safe and effective innovative medicines and to generic and nonprescription medicines through a single European marketing authorization;
- controlling the safety of medicines for humans and animals, in particular through a pharmacovigilance network and the establishment of safe limits for residues in food-producing animals;
- facilitating innovation and stimulating research, hence contributing to the competitiveness of the EU-based pharmaceutical industry, and
- mobilizing and coordinating scientific resources throughout the EU to provide high-quality evaluation of medicinal products, to advise on research and development programmes, to perform inspections for ensuring fundamental GXP (good clinical practice, good manufacturing practice and good laboratory practice collectively) provisions are consistently achieved, and to provide useful and clear information to users and healthcare professionals.

### **The ethical dimension**

In addition to their role in ensuring the safety, efficacy and quality of medicines, governments are also tasked with the responsibility of exerting an ethical influence on processes in the development and marketing of medicines. The regulatory authority is responsible for

many essential and interrelated activities which underpin the most important role of the government in the broader sense: i.e., to protect the health and wellbeing of its citizens through ensuring and promoting effective public health.

Governments and their respective institutions are responsible for ensuring basic human rights of citizens. In the event of research conducted within a country, they are expected to protect patients and trial participants by maintaining effective systems for granting clinical research authorization and oversight of trials. This challenging task involves assessment of whether the clinical research planned is based on scientific principles and considerations of safety and whether it will offer the desired benefits to patients while identifying and minimizing any possible risks. This task forms the *ethical dimension* of the government's role.

### ***Milestones in the current ethical research environment***

The International Covenant on Civil and Political Rights (1966) states that ... “no one shall be subjected without his free consent to medical or scientific experimentation”. These principles were developed with a particular focus on risk/benefit in the World Medical Association's Declaration of Helsinki and have been incorporated into national and international laws and regulations.

In 1949, the Council for International Organizations of Medical Sciences (CIOMS) was founded under the auspices of WHO and the United Nations Educational, Scientific and Cultural Organization (UNESCO). The most important of CIOMS publications is its *International Ethical Guidelines for Biomedical Research Involving Human Subjects*. The latest version was published in 2002 (3) and, based on the Declaration of Helsinki, is designed to be of use in defining the ethics of biomedical research, applying ethical standards in

local circumstances, and establishing or redefining adequate mechanisms for ethical review of research involving human subjects. The Guidelines are targeted to ethics committees, and review boards, sponsors and investigators. The CIOMS guidelines — to which several clinical pharmacologists have contributed — also provide the basis for government thinking about clinical research, especially in resource poor settings.

Good clinical practice (GCP) is a “standard for the design, conduct, performance, monitoring, auditing, recording, analysis and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that rights, integrity and confidentiality of trial subjects are protected.” Many national and regional GCP guidelines are based on, or refer to, the Declaration of Helsinki, including WHO GCP Guidelines published in 1995 (4) and the International Conference of Harmonization (ICH) GCP (E6) from 1996 (5).

A priority requirement for the ethical review of a scientific study, research or clinical trial involving human subjects is submission of a research proposal for independent evaluation by scientific, regulatory and ethical review committees. Nowadays, many governments define procedural aspects of the work of the ethics committees in detail.

For example, the European Commission has laid down strict timelines for processing research applications that affect the work of ethical review committees in all 27 European Union countries. This can be perceived as the European Commission’s attempt to facilitate and promote clinical research. Clinical pharmacologists can be particularly valuable as members of the ethical review committee because of their extensive knowledge of the effects of medicines and the related area of clinical research.

Above all, governments have to ensure that only effective and safe good quality medicines are used to treat their citizens. Nowadays, all medicines are subject to marketing authorization prior to being prescribed. Approval is based on assessment of quality, safety and efficacy of the product. The safety monitoring of medicines during their whole life-cycle (from marketing authorization to potential withdrawal from the market) is also a task for governments. Usually, these and other medicines-related regulatory functions are carried out by specialized governmental agencies, such as the Food and Drug Administration (FDA) in the USA or the European Medicines Agency (EMA).

### **Scientific dimension**

It is important for regulators involved in the evaluation of medicines prior to marketing to have the best possible scientific education and background or to be able to call on expertise which is relevant to the work in hand. A critical scientific review of the clinical data will address the known and unknown aspects of an assessment and provide relevant conclusions. The larger regulatory agencies possess their own clinical pharmacology units. For example, the US FDA has in its Center for Drug Evaluation and Research (CDER) Office of Clinical Pharmacology. Safety surveillance and pharmacovigilance is also entrusted to regulatory agencies, and here, also, expertise in clinical pharmacology is essential.

Governments, either directly or through their specialized agencies, are also involved in taking decisions about medicines selection for public procurement, developing national treatment guidelines and proposing inclusion of medicines in reimbursement lists. This work may also involve composing and updating national essential medicines lists as promoted by WHO. The real life performance of drugs following regulatory approval requires a

cost-effectiveness assessment by highly qualified specialists using different models and again calls on the expertise of the clinical pharmacologist.

These various activities support the rational use of medicines, sometimes also called "quality use" (6). Governmental institutions involved in such activities include the National Institute for Health and Clinical Excellence (NICE) in the United Kingdom. Activities are based on the best possible scientific methodologies and knowledge and are part of the *scientific dimension* of the Government's obligation to its citizens. Clinical pharmacologists are well prepared to meet the challenges needed in the complex assessment of medicines.

#### **Developmental dimension**

Lastly, governments carry the responsibility of improving the health of their citizens. Stimulating the necessary research and developing research capacities is therefore a regulatory function. Action should be directed to facilitating research in areas where lack of effective or safer health care interventions impedes improvement to public health. Recent examples provide evidence that private sector initiatives and funding are insufficient in developing and promoting public health through medicines research. Thus, governments may also be involved in providing financial support to stimulate clinical research in medicines. Clinical pharmacologists are well positioned to help make appropriate judgements on the scientific value of government funding of research proposals.

An important emerging issue is the adoption of electronic patient health records implemented or planned to be implemented in many countries. Although these may be perceived as mostly administrative tools, they hold scientific potential for monitoring of safety and quality medicines therapy. There is already first-

hand evidence that electronic health records can offer added value for pharmacogenetic research and pharmacovigilance (7). Clinical pharmacologists should be actively involved in designing electronic patient health records due to their potential for future clinical research use, including monitoring of rational use and safety.

Government efforts to create a research friendly environment should include legal and other systems with effective functioning and well-informed scientific government backup. Due to the relative lack of new therapies and pressure from patient groups and industry, governments have been exorted to grant "early market approvals" under certain preconditions. However, effective methodologies for pharmacovigilance and safety studies in the context of early market access have yet to be created and tested and clinical pharmacologists have an important role to play here (8, 9). Clinical pharmacology also contributes to the discipline of pharmacoepidemiology, which is sometimes the only available method to evaluate the benefits and risks of long term pharmacotherapy. Similarly, pharmacoeconomics attempts to give a financial cost and value to everyday medicines use and contributes to rational reimbursement systems.

In the implementation of these various dimensions, governments create various tools, including laws and regulations, infrastructure and institutions, with supporting resource allocations. A key resource is properly trained specialists who are capable of taking decisions based on the best possible scientific methodology and evidence. These dimensions are interrelated and interdependent. Good ethics cannot do without good science and developmental goals cannot be achieved without following ethical principles and a sound science base.

The clinical pharmacologist is thus a unique specialist and ally who can serve the public best by ensuring that only safe and effective medicines are authorized for use, as well as facilitating cost effective prescribing and improving rational use of drugs. In order to meet the needs of various governmental services and ensure that the best scientific knowledge is used to make decisions, clinical pharmacology as a discipline should be harmonized with the objectives and policies of governments to ensure a benefit to public health

Equally, governments of emerging economies and developing countries may benefit hugely from the expertise of clinical pharmacologists and experience has shown that a qualified clinical pharmacologist can make a great difference at country level.

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# Safety and Efficacy Issues

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## Etanercept: histoplasmosis and invasive fungal infections

**Canada** — The manufacturer of etanercept (Enbrel®) has informed healthcare professionals of the risk of invasive fungal infections, including histoplasmosis. Etanercept is indicated for the treatment of rheumatoid arthritis, psoriatic arthritis, juvenile idiopathic arthritis, ankylosing spondylitis and plaque psoriasis.

There have been reports of serious pulmonary and disseminated histoplasmosis, coccidioidomycosis, blastomycosis infections, sometimes with fatal outcomes, in patients taking TNF blockers, including etanercept. Histoplasmosis and other invasive fungal infections have not been recognized consistently in patients taking TNF blockers. This has led to delays in instituting appropriate treatment, sometimes resulting in death.

For a patient taking a TNF blocker who presents with signs and symptoms of systemic illness, such as fever, malaise, weight loss, sweats, cough, dyspnoea, and/or pulmonary infiltrates, the healthcare professional should ascertain if the patient has lived or worked in or travelled to areas of endemic mycoses, and appropriate empiric antifungal treatment may be initiated while a diagnostic workup is being performed. As with any serious infection, the TNF blocker should be stopped until the infection has been diagnosed and adequately treated.

Prescribers should discuss with patients and their caregivers the risk for infections while receiving TNF blockers, including infections caused by viruses, fungi, or bacteria including tuberculosis (TB).

**Reference:** Communication from Amgen. 21 April 2009 at Health Canada. [http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/\\_2009/index-eng.php](http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/_2009/index-eng.php)

## Zonisamide: metabolic acidosis

**United States of America** — Following a review of updated clinical data, the Food and Drug Administration (FDA) has determined that treatment with zonisamide can cause metabolic acidosis in some patients. Zonisamide (Zonegran® and generics) is indicated as adjunctive therapy in the treatment of partial seizures in adults with epilepsy.

Chronic metabolic acidosis can have adverse effects on the kidneys and on bones, and can retard growth in children. Patients with predisposing conditions or therapies, including renal disease, severe respiratory disorders, diarrhoea, surgery, ketogenic diet, or certain other drugs may be at greater risk for developing metabolic acidosis following treatment with zonisamide. The risk of zonisamide-induced metabolic acidosis appears to be more frequent and severe in younger patients. Although not approved by the FDA, zonisamide is sometimes used in children. Metabolic acidosis increases the risk for slowed growth in children and could reduce the overall height that they achieve.

The FDA recommends that healthcare professionals measure serum bicarbonate before starting treatment and periodically during treatment, even in the absence of symptoms. If metabolic acidosis develops and persists, consideration should be given to reducing the dose or discontinuing zonisamide (using

dose tapering), and modifying the patient's antiepileptic treatment as appropriate. If the decision is made to continue, then alkali treatment should be considered.

**Reference:** *FDA Alert*, 23 February 2009 at <http://www.fda.gov/medwatch>

## Progressive multifocal leukoencephalopathy

**United Kingdom** — Progressive multifocal leukoencephalopathy (PML) is a rare and usually fatal re-infection of the CNS characterized by progressive damage and inflammation of the white matter in the brain, in multiple locations. PML is caused by a type of human polyoma virus known as the JC, or John Cunningham virus. The JC virus is widespread, with about 70–90% of adults presenting antibodies.

The virus usually remains latent in healthy individuals, only causing disease when the immune system is severely compromised. PML has been studied in patients with HIV infection, where incidence is approximately 5% of the disease population. PML also occurs in patients with cancer and those who have received kidney or bone-marrow transplants. In PML, gradual destruction of the myelin sheath covering nerve axons leads to impaired transmission of nerve impulses. PML causes rapidly progressive focal neurological deficits including:

- cognitive and behavioural changes;
- paraesthesia;
- visual problems;
- gait abnormalities and loss of limb coordination, and
- hemiparesis.

The Medicines and Healthcare Products Regulatory Agency (MHRA) has previ-

ously identified an association between PML and use of some monoclonal antibodies such as natalizumab (Tysabri®, used to treat multiple sclerosis) and rituximab (MabThera®, indicated for non-Hodgkin lymphoma and severe active rheumatoid arthritis). An association has also now been identified between PML and efalizumab (Raptiva®).

Up to 6 January 2009, the MHRA has received 19 suspected reports of PML, in three of which PML was listed as the fatal suspected reaction.

**Reference:** Medicines and Healthcare Products Regulatory Agency, Drug Safety Update, Volume 2, Issue 8 March 2009 at <http://www.mhra.gov.uk/Safetyinformation/>

## Severe adverse reactions with intravenous immunoglobulin

**Australia** — Intravenous immunoglobulin, normal (human) (IVIG) is used to treat a variety of deficiencies and disorders with an immune (or presumed immune) aetiology. IVIG preparations, including Intragam P®, Sandoglobulin®, and Octagam®, have been available since the 1980s. Use worldwide and in Australia has more than doubled over the past decade (1) partly due to increasing use in off-label indications.

Nausea and vomiting are most commonly observed with IVIG, as are hypersensitivity reactions which may include anaphylaxis. Those with IgA deficiency have a higher risk of hypersensitivity to IVIG due to the presence of IgA antibodies. Less common but also serious reactions are aseptic meningitis, haemolysis and transfusion-related acute lung injury — one case has been reported in Australia and one in Canada (2). Recently, Health Canada highlighted an association between IVIG and thromboembolic events (3).

To date, the Therapeutic Goods Administration (TGA) has received 356 reports of

adverse reactions associated with IVIG: IVIG was the sole suspected agent in 90% of reports. Thirty-five per cent describe serious reactions, including where the outcome was fatal due to: stroke/myocardial infarction, myocardial infarction, convulsions, hepatic and renal failure, and respiratory failure respectively. In fatal cases, patients generally had thrombogenic risk factors such as hypertension, obesity, increasing age, or past history of stroke.

The TGA has also received substantial numbers of reports describing pyrexia (58), chills (41), haemolysis or anaemia (32), meningitis (20), neutropenia (12), hepatic disorders (11), and renal failure/impairment (8). In some of the cases, the reactions — particularly those suggesting hypersensitivity — occurred during the IVIG infusion and improved with slowing or stopping the infusion.

Before and during the use of IVIG, any pre-existing thrombogenic risk factors should be assessed and all patients should be monitored closely during infusion. A slow infusion rate of IVIG should be considered for all patients with risk factors (as recommended in the PI).

*Extracted from the Australian Adverse Drug Reactions Bulletin, Volume 28, Number 2, April 2009 at <http://www.tga.gov.au/adr/aadrb/aadr0904.htm>*

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3. Intravenous immune globulin: myocardial infarction and cerebrovascular and thrombotic adverse reactions. *Canadian Adverse Reactions Newsletter* Jan 2008; 18/1.

## Exenatide: risk of severe pancreatitis and renal failure

**United Kingdom** — Exenatide (Byetta®), an incretin mimetic, is a glucagon-like-peptide-1 analogue that stimulates insulin release from pancreatic cells in a glucose dependent manner. Exenatide is indicated for treatment of type 2 diabetes mellitus in combination with metformin, with or without sulphonylureas in patients who have not achieved adequate glycaemic control on maximally tolerated doses of these oral therapies.

Exenatide should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis. It should not be used in patients with type 2 diabetes who require insulin therapy due to cell failure.

Suspected adverse reaction reports of necrotizing and haemorrhagic pancreatitis have been received in association with exenatide. Some of these reports had a fatal outcome. If pancreatitis is diagnosed, exenatide should be permanently discontinued. Reports of renal impairment, including acute renal failure and worsened chronic renal failure have also been received. Exenatide is not recommended for use in patients with end-stage renal disease or severe renal impairment

**Reference:** Medicines and Healthcare Products Regulatory Agency, Drug Safety Update, Volume 2, Issue 8 March 2009 at <http://www.mhra.gov.uk/Safetyinformation/>

## Benefits of methylphenidate continue to outweigh risks

**United Kingdom** — The EMEA's Committee for Medicinal Products for Human Use (CHMP) concluded that on the basis of currently available data, the benefits of methylphenidate continue to outweigh the risks when used in its licensed indication. Methylphenidate is indicated as part of a

comprehensive treatment programme for attention deficit/hyperactivity disorder (ADHD) in children aged 6 years or older and adolescents who are diagnosed according to DSM-IV criteria or guidelines in ICD-10 and when remedial measures alone are insufficient.

Treatment must be under the supervision of a specialist in childhood behavioural disorders. Patients should be monitored during treatment, which should be interrupted at least once a year to determine whether continuation is needed.

Contraindications—methylphenidate should not be used in patients with:

- Diagnosis or history of severe depression, anorexia nervosa or anorexic disorders, suicidal tendencies, psychotic symptoms, mania, schizophrenia, severe mood disorders, or psychopathic or borderline personality disorder.
- Diagnosis or history of severe and episodic (type I) bipolar (affective) disorder that is not well-controlled.
- Pre-existing cerebrovascular disorders — e.g., cerebral aneurysm and vascular abnormalities, including vasculitis or stroke.
- Unless specialist cardiac advice has been obtained, in pre-existing cardiovascular disorders, including severe hypertension, heart failure, arterial occlusive disease, angina, haemodynamically significant congenital heart disease, cardiomyopathies, myocardial infarction, potentially life-threatening arrhythmias, and dysfunction of cardiac ion channels

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2. Further information on brands of methylphenidate available in the UK, see BNF, p 216 (edn 56; [www.bnf.org](http://www.bnf.org)).

3. Information on DSM-IV criteria is at <http://www.psychiatryonline.com/>; information on ICD-10 is at <http://www.cdc.gov/nchs/about/otheract/icd9/abctcd10.htm>

4. Medicines and Healthcare Products Regulatory Agency, Drug Safety Update, Volume 2, Issue 8 March 2009 at <http://www.mhra.gov.uk/Safetyinformation/>

### Chromic phosphate P32: acute lymphocytic leukaemia

**Canada** — Information has been provided on important new safety information concerning Chromic phosphate P32 suspension (Phosphocol® P32) which is authorized for intracavitary instillation for the treatment of peritoneal or pleural effusions caused by metastatic disease.

Physicians should be vigilant for signs and symptoms of leukaemia in patients who have received Phosphocol® P32. The Canadian product monograph will be updated to include the following warning.

**Leukaemia:** Phosphocol® P32 may increase the risk of leukaemia in certain situations. Two children (ages 9 and 14) with haemophilia developed acute lymphocytic leukaemia approximately 10 months after intra-articular injections. Phosphocol® P32 is not indicated in the treatment of haemarthroses.

In addition, the product monograph will be updated to include post-marketing reports of radiation injury (necrosis and fibrosis) to the small bowel, caecum, and bladder following peritoneal administration of Phosphocol® P32.

**Reference:** Health Canada, Alert dated 25 March 2009. at [http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/\\_2009/index-eng.php](http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/_2009/index-eng.php)

## Warning for metoclopramide-containing drugs

**United States of America** — The Food and Drug Administration (FDA) has announced that manufacturers of metoclopramide, a drug used to treat gastrointestinal disorders, must add a boxed warning to labelling about the risk of long-term or high-dose use. Chronic use of metoclopramide has been linked to tardive dyskinesia even after the drugs are no longer taken.

Metoclopramide works by speeding up the movement of the stomach muscles, thus increasing the rate at which the stomach empties into the intestines. It is used as a short-term treatment of gastro-oesophageal reflux disease in patients who have not responded to other therapies, and to treat diabetic gastro-paresis. It is recommended that treatment not exceed three months.

**Reference:** *FDA News*, 26 February 2009 at <http://www.fda.gov>

## Metabolic effects of antipsychotics

**New Zealand** — Although schizophrenia itself is associated with several adverse metabolic effects it is now clear that all antipsychotics, and in particular some atypical antipsychotics, are associated with adverse effects on weight, blood glucose, and lipid concentrations. All of these adverse effects have long-term consequences in terms of life expectancy.

While the effects of antipsychotics on weight gain may be responsible for the increased risk of diabetes and hyperlipidaemia, a direct effect on glucose metabolism may also occur.

Not all atypical antipsychotics are associated with the same level of risk. Clozapine and olanzapine are considered to cause adverse metabolic effects more

frequently than other agents. Prescribers are advised to monitor all patients taking antipsychotics for adverse metabolic effects.

## References

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3. *Prescriber Update* 2009;**30**(2):12 at <http://www.medsafe.govt.nz/profs/PUarticles.asp>

## Cefaclor and serum sickness-like reactions in children

**Australia** — The association between cefaclor and serum sickness-like reactions (SSLR), particularly in children, has long been recognized (1). These reactions are characterized by a variety of rashes, which include urticaria or erythema multiforme, with or without angioedema, accompanied by arthritis/arthralgia, with or without fever.

The reactions are rare but occur more often after a second or subsequent course of treatment. Onset time is often a few days after cefaclor is commenced and signs and symptoms typically subside a few days after the drug is ceased. However, onset may also be delayed and occur 7–21 days after stopping cefaclor. Children are more susceptible than adults.

The TGA continues to receive about 10 reports per year of cefaclor-related SSLR in children. If cefaclor must be prescribed to a child, the parents/caregivers should be advised to remain alert for the development of new or worsening symptoms that might indicate a hypersensitivity reaction to the drug and to contact their doctor immediately if there are concerns.

*Extracted from the Australian Adverse Drug Reactions Bulletin, Volume 28, Number 2, April 2009 at <http://www.tga.gov.au/adr/aadrb/aadr0904.htm>*

**Reference:** ADRAC. Cefaclor in the young patient: arthritis and arthralgia <<http://www.tga.gov.au/adr/aadrb/aadr9508.htm#cefaclor>>. *Aust Adv Drug React Bull* 1995; **14** (3).

## Toremifene: prolongation of QTc interval

### United Kingdom/European Union —

The manufacturer of toremifene (Fareston®) has informed healthcare professionals of new information on prolongation of the QTc interval related to toremifene. The approved therapeutic indication for toremifene 60 mg/day is the first line treatment of hormone dependent metastatic breast cancer in postmenopausal patients.

Both in preclinical investigations and in humans, changes in cardiac electrophysiology have been observed following exposure to toremifene, in the form of QT prolongation. Consequently:

- Toremifene is therefore contraindicated in patients with:

Congenital or documented acquired QT prolongation; electrolyte disturbances, particularly in uncorrected hypokalaemia; clinically relevant bradycardia; clinically relevant heart failure with reduced left-ventricular ejection fraction; previous history of symptomatic arrhythmias.

- Toremifene should not be used concurrently with other drugs that prolong the QT interval.
- Toremifene should be used with caution in patients with ongoing proarrhythmic conditions (especially elderly patients) such as acute myocardial ischaemia or QT prolongation as this may lead to an increased risk for ventricular arrhythmias (including Torsade de Pointes) and cardiac arrest.

- If signs or symptoms that may be associated with cardiac arrhythmia occur during treatment with toremifene, treatment should be stopped and an ECG should be performed.

Currently, toremifene 20 mg/day and 80 mg/day are being studied in prostate cancer indications.

**Reference:** Communication from Orion Pharma UK at <http://www.mhra.gov.uk/Safetyinformation/>

## Atomoxetine: risk of psychotic or manic symptoms

**United Kingdom —** Atomoxetine (Strattera®) is a selective noradrenaline reuptake inhibitor, authorized since 2004 for use in the treatment of attention-deficit/hyperactivity disorder (ADHD) as part of a comprehensive treatment regimen. Continued case reports of possible nervous-system and psychiatric adverse effects prompted a review of data from all sources resulting in updated information on the risk of new-onset or worsening of serious psychiatric disorders, including psychotic reactions, hallucinations, mania, and agitation.

Product information for prescribers has been updated to reflect more fully the emerging safety information. Atomoxetine is associated with treatment-emergent psychotic or manic symptoms in children and adolescents without a history of such disorders. If such symptoms occur, consideration should be given to a possible causal role of atomoxetine and discontinuation of treatment.

Advice for healthcare professionals:

- At normal doses, atomoxetine can be associated with emergent psychotic or manic symptoms (e.g., hallucinations, delusional thinking, mania, or agitation) in children and adolescents without a history of psychotic illness or mania.

- If such symptoms occur, consideration should be given to a possible causal role of atomoxetine and discontinuation of treatment.
- It remains possible that atomoxetine might exacerbate pre-existing psychotic or manic symptoms

**Reference:** Medicines and Healthcare Products Regulatory Agency, Drug Safety Update, Volume 2, Issue 8 March 2009 at <http://www.mhra.gov.uk/Safetyinformation/>

## Lignocaine with chlorhexidine gel: anaphylaxis

**United Kingdom** — Lignocaine 2% gel with chlorhexidine 0.05% is an anaesthetic/antiseptic/disinfectant combination used as a lubricant for urology procedures and examination, and as symptomatic treatment of painful urethritis.

Since 1990, the TGA has received 19 reports of suspected adverse reactions to lignocaine with chlorhexidine gel. Eleven of these were of anaphylaxis. Some were life threatening, but there have been no fatalities.

The MHRA warns of the potential for anaphylaxis or other hypersensitivity reactions with both lignocaine and chlorhexidine. Users of local anaesthetic preparations should check which products contain chlorhexidine and are reminded of the risk of severe allergic reactions to medicines, even when applied topically.

**Reference:** Medicines and Healthcare Products Regulatory Agency, <http://www.mhra.gov.uk/Safetyinformation/>

## Moxifloxacin safety update

**Singapore** — Moxifloxacin (Avelox® and Vigamox®) is a broad-spectrum antibacterial that is available locally.

In February 2008, the manufacturer informed healthcare professionals of very rare liver injuries and serious skin reactions associated with moxifloxacin. This was in response to a worldwide review of serious, including fatal cases of hepatotoxicity and bullous skin reactions such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) reported for moxifloxacin.

To date, HSA has received 22 local spontaneous adverse drug reaction reports associated with oral moxifloxacin. Patient exposure to moxifloxacin to date is estimated to be 230 577, according to local figures provided by the manufacturer. In the interpretation of the above figures, there is a need to consider the significant degree of under-reporting of adverse reactions as is the case with all spontaneous adverse drug reaction reporting programmes.

### References

1. *EMEA Press Release*. European Medicines Agency recommends restricting the use of oral moxifloxacin-containing medicines. <http://www.emea.europa.eu/pdfs/human/press/>
2. Direct Healthcare Professional Communication regarding moxifloxacin (Avelox®) and serious hepatic and bullous skin reactions. <http://www.mhra.gov.uk/>
3. *HSA Safety News*, 19 Mar 2009 at <http://www.hsa.gov.sg>

## Codeine toxicity in breastfed infants

**Singapore** — Codeine is found in many prescription and non-prescription pain relievers and cough syrups. Once ingested, codeine is metabolised by cytochrome P450 2D6 (CYP2D6) to its active metabolite, morphine, which relieves pain or cough. Limited evidence suggests that individuals with a specific CYP2D6 genotype (otherwise known as ultra-rapid metabolisers) may convert codeine to

morphine more rapidly and completely than other people. In nursing mothers, this metabolism can result in higher than expected levels of morphine in serum and breast milk, putting nursing infants at increased risk for morphine overdose.

Regardless of ethnic variation in the prevalence of ultra-rapid metabolisers, it is important to bear in mind that polymorphism of CYP2D6 is clinically important.

When prescribing codeine to a nursing mother, physicians should choose the lowest effective dose for the shortest period of time.

### References

1. *FDA Alert*. Use of codeine products in nursing mothers. <http://www.fda.gov/cder/drug/infopage/codeine/default.htm>
2. *Lancet* 2006, Vol 368:704, August 2006
3. *FDA Public Health Advisory*. Use of codeine by some breastfeeding mothers may lead to life-threatening side effects in nursing babies. <http://www.fda.gov/cder/drug/advisory/codeine.htm>
4. *FDA News*. FDA warning on codeine use by nursing mothers. <http://www.fda.gov/bbs/topics/NEWS/2007/NEW01685.html>
5. *Health Canada Advisory*. Use of Codeine Products by nursing mothers. [http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/\\_2008/2008\\_164-eng.php](http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2008/2008_164-eng.php)
6. *HSA Safety News*, 19 Mar 2009 at <http://www.hsa.gov.sg>

## Atypical antipsychotics: risk of stroke

**United Kingdom** — In 2004, the Committee on Safety of Medicines advised of a clear increase in the risk of stroke with the use of the atypical antipsychotics risperidone or olanzapine in elderly people with dementia (approximately

three-times increased risk compared with placebo), and that the magnitude of risk outweighed any likely benefit of treating dementia-related behavioural problems with these drugs. A year later a Europe wide review concluded that this risk could not be excluded for other antipsychotics (atypical or typical), and the product information for all antipsychotics was updated to include a class warning.

In 2005, an analysis of 17 placebo-controlled trials found that atypical antipsychotics are associated with increased mortality when used in elderly people with dementia (about 1–2% increased risk compared with no treatment) (1). For risperidone, there is an additional increase in the risk when coprescribed with furosemide.

Subsequently in November 2008, a European assessment of published observational data concluded that a similar increased risk of death could not be excluded for the typical (conventional) antipsychotics (2, 3).

In the case of persistent aggression in moderate to severe Alzheimer disease, where the patient puts themselves or others at risk of harm, short-term treatment with risperidone may be indicated if the behaviour has not responded to nonpharmacological means. A new analysis of three randomized control trials (4–6) conducted in behavioural problems in the elderly showed a clear benefit for the short-term use of risperidone when aggression only was considered. The balance of risks and benefits for risperidone use to treat behavioural disturbances in dementia is only considered to be positive within its narrow licensed indication: i.e., short-term use for persistent aggression in Alzheimer-type dementia.

Advice for healthcare professionals:

- There is a clear increased risk of stroke and a small increased risk of death when antipsychotics (typical or atypical) are used in elderly people with dementia.
- The balance of risks and benefits associated with risperidone treatment should be carefully assessed for every patient, taking into consideration the known increased mortality rate associated with antipsychotic treatment in the elderly. Prescribers should carefully consider the risk of cerebrovascular events before treating with risperidone any patient who has a previous history of stroke or transient ischaemic attack. Consideration should also be given to other risk factors for cerebrovascular disease including hypertension, diabetes, smoking, and atrial fibrillation.

#### References

1. Deaths with antipsychotics in elderly patients with behavioural disturbances. *FDA Public Health Advisory*, 11 April 2005. <http://www.fda.gov/cder/drug/advisory/>
2. Schneeweiss S et al. *CAMJ* 2007; **176**: 627–32.
3. Gill SS et al. *Ann Intern Med* 2007; **146**: 775–86. See also statement from the European Medicines Agency at [http://www.emea.europa.eu/pdfs/human/opiniongen/Conventional\\_Antipsychotics\\_Article5.3-CHMP\\_Opinion.pdf](http://www.emea.europa.eu/pdfs/human/opiniongen/Conventional_Antipsychotics_Article5.3-CHMP_Opinion.pdf), accompanying report and question-and-answer document at [http://www.emea.europa.eu/pdfs/human/opiniongen/Conventional\\_%20Antipsychotics\\_Article5.3-Appendix1-CHMPAR.pdf](http://www.emea.europa.eu/pdfs/human/opiniongen/Conventional_%20Antipsychotics_Article5.3-Appendix1-CHMPAR.pdf) and [http://www.emea.europa.eu/pdfs/human/opiniongen/Conventional\\_antipsychotics\\_Article\\_5.3-Q&A.pdf](http://www.emea.europa.eu/pdfs/human/opiniongen/Conventional_antipsychotics_Article_5.3-Q&A.pdf)
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5. De Deyn PP et al. *Neurology* 1999; **53**: 946–55.
6. Brodaty H et al. *J Clin Psychiatry* 2003; **64**: 134–43. See also [http://www.emea.europa.eu/pdfs/human/referral/Risperdalrisperdal\\_bi\\_en.pdf](http://www.emea.europa.eu/pdfs/human/referral/Risperdalrisperdal_bi_en.pdf) and [http://www.emea.europa.eu/pdfs/human/referral/Risperdalrisperdal\\_annexI\\_IV\\_en.pdf](http://www.emea.europa.eu/pdfs/human/referral/Risperdalrisperdal_annexI_IV_en.pdf), p 48.
7. Medicines and Healthcare Products Regulatory Agency, Drug Safety Update, Volume 2, Issue 8 March 2009 at <http://www.mhra.gov.uk/Safetyinformation/>

## Bisphosphonates: atypical stress fractures

**United Kingdom** — Individual bisphosphonates have different indications and are used for prophylaxis and treatment of osteoporosis, treatment of Paget disease; and as part of some cancer regimens, particularly for metastatic bone cancer and multiple myeloma.

Recent evidence from published literature suggests that long-term use of alendronic acid may be associated with an increased risk of atypical stress fractures (1–3). A Europe wide review of bisphosphonates and atypical stress fractures has analysed preclinical data, clinical-trial data, postmarketing spontaneous reports of adverse drug reactions, published literature, and information from other drug regulatory authorities.

Atypical stress fractures of the proximal femoral shaft have been reported in patients treated long-term with alendronic acid. Patients who develop stress fractures should discontinue alendronic acid and receive no further bisphosphonate treatment unless the benefits for the individual clearly outweigh the risk of harm. An increased risk of atypical stress fractures with other bisphosphonates cannot be excluded

Limited data are available for the other bisphosphonates in support of a causal association with atypical stress fractures. This might reflect their lower usage and

the limited long-term data that exist for other bisphosphonates. The possibility that they may be associated with an increased risk of atypical stress fractures cannot be excluded.

#### References

1. Kwek EB et al. *Injury* 2008; **39**: 224–31.
2. Lenart BA et al. *N Engl J Med* 2008; **358**: 12.
3. Neviasser AS et al. *J Orthop Trauma* 2008; **22**: 346–50.
4. Medicines and Healthcare Products Regulatory Agency, Drug Safety Update, Volume 2, Issue 8 March 2009 at <http://www.mhra.gov.uk/Safetyinformation/>

### Effects of MRI on implantable drug pumps

**United Kingdom** — In December 2008, a medical device alert was issued about MRI scanning of patients with implanted Medtronic SynchroMed® drug pumps. These pumps provide baclofen and morphine therapy but they do not behave as expected when exposed to the magnetic field of an MRI scan. Product labelling states that MRI temporarily stops the pump rotor and suspends drug infusion during MRI exposure. The pump should resume normal function when removed from the MRI field. However, MHRA are aware of risks, including delays in drug infusion, after MRI of patients implanted with these devices (1).

Healthcare professionals are advised to ensure that departmental procedures are in place for MRI scanning of patients with Medtronic SynchroMed® implantable drug pumps.

#### References

1. MHRA Safety Warnings. [http://www.mhra.gov.uk/Publications/Safety\\_warnings/MedicalDeviceAlerts/CON033658](http://www.mhra.gov.uk/Publications/Safety_warnings/MedicalDeviceAlerts/CON033658).

2. Medicines and Healthcare Products Regulatory Agency, Drug Safety Update, Volume 2, Issue 8 March 2009 at <http://www.mhra.gov.uk/Safetyinformation/>

### Sodium valproate and fetal malformations

**Australia** — Sodium valproate is well known to cause fetal malformations and is classified as a Pregnancy Category D drug (drugs that have caused, are suspected to have caused or may be expected to cause an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects) (1). Teratogenic risk appears to be dose-dependent and increases markedly at doses greater than 1100 mg/day in the first trimester (2).

Sodium valproate is mainly used to treat epilepsy but it is increasingly being prescribed to treat psychiatric disorders.

Since 1980, the Therapeutic Goods Administration (TGA) has received 72 reports of babies born with malformations from mothers taking sodium valproate during pregnancy, including 18 of spina bifida, four of myelomeningocele and 13 of multiple malformations mainly involving the CNS. In most of these cases, sodium valproate was being used to treat epilepsy, but two recent reports describe fetal spina bifida and myelomeningocele in babies born to mothers taking sodium valproate for bipolar disorder.

One of the cases reported has been described in correspondence to the *Australian and New Zealand Journal of Psychiatry* (3) and serves to remind that sodium valproate must be used with caution after careful consideration of the risk-benefit profile in women of child-bearing potential.

Women of child-bearing age prescribed sodium valproate for any indication

should be informed about the potential risks of the drug, including teratogenesis, and should be strongly advised, and periodically reminded, to maintain adequate contraception while taking this drug. Routine folic acid supplementation is recommended but efficacy in the prevention of sodium valproate-related malformation is unproven (4).

*Extracted from the Australian Adverse Drug Reactions Bulletin, Volume 28, Number 2, April 2009 at <http://www.tga.gov.au/adr/aadrb/aadr0904.htm>*

### References

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2. Whitehall J & Smith J. Valproate and babies. *Aust NZ J Psychiatry* 2008; **42**: 837.
3. Vajda FJ, O'Brien TJ, Hitchcock A, Graham J, Cook M, Lander C, Eadie MJ. Critical relationship between sodium valproate dose and human teratogenicity: results of the Australian register of anti-epileptic drugs in pregnancy. *J Clin Neurosci* 2004; **11**: 854-83.
4. Lagrange AH. Folic acid supplementation for women with epilepsy who might become pregnant. *Nature Clin Pract* 2009; **5**: 16-17.

## Abacavir: determining risk of heart attack

**European Union** — The European Medicines Agency (EMA) has looked at data from the D:A:D (Data collection of Adverse effects of anti-HIV Drugs) study, which suggest an increased risk of heart attack (myocardial infarction) associated with the use of abacavir-containing medicines.

The Agency's Committee for Medicinal Products for Human Use (CHMP) concluded at its March 2008 meeting that the available data do not allow a definitive conclusion on the association between

the use of abacavir and an increased risk of myocardial infarction to be drawn. At present no changes to the prescribing information for abacavir-containing medicines are required but further information is needed to determine the risk of myocardial infarction.

Abacavir is a nucleoside reverse transcriptase inhibitor (NRTI) indicated in antiretroviral combination therapy for the treatment of human immunodeficiency virus (HIV) infection. In the European Union, it is available as Ziagen®, in combination with lamivudine as Kivexa®, and in combination with lamivudine and zidovudine as Trizivir®.

**Reference:** *EMA Press Release*, Doc. Ref. EMEA/142888/2008, 2 April 2008. <http://www.emea.europa.eu>

## Carbamazepine: serious adverse skin reactions

**Singapore** — Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are life-threatening adverse skin reactions with mortality rates of up to five and 40% respectively. Drugs are most often implicated as the suspected cause of SJS and TEN in adults and elderly persons.

Carbamazepine, indicated for the treatment of epilepsy, neuropathic pain and bipolar disorder, is known to be associated with an increased risk of adverse cutaneous skin reactions, including SJS and TEN. This risk has been observed in the local population through relatively higher numbers of SJS and TEN reported in association with the drug over the years. More recently, studies have been published which demonstrate a plausible genetic association with SJS and TEN among Asian patients, in particular, Han Chinese and Thais.

Between 2003 and 2008, the Health Sciences Agency (HSA) received 290

reports of drug-induced SJS and TEN. Other drugs such as allopurinol, phenytoin and cotrimoxazole were also reported to be associated with a higher number of SJS/TEN reports received respectively .

### **Association observed with HLA-B\*1502 allele**

Recently, carbamazepine-induced SJS and TEN have been found to be associated with the HLA-B\*1502 allele among Han Chinese (in Taiwan and Hong Kong) and Thais (1–3).

A European study from the RegiSCAR group (4) found that out of the 12 patients with carbamazepine-induced SJS/TEN, all four who were positive for the HLA-B\*1502 allele were of Asian origin. It further suggested that the genetic link may be specific to patients with Asian ancestry such as the Han Chinese.

An analysis of worldwide post-marketing cases reported to the World Health Organization (WHO) also pointed to a much higher reporting rate of SJS/TEN, about 10 times higher in some Asian countries (5).

### **Pharmacogenetics initiative by HSA**

In an effort to understand the relevance of genetic association with adverse drug reactions among the diverse ethnic groups (Chinese, Malays and Indians) in the local population, HSA is embarking on a pharmacogenetics-based pharmacovigilance programme together with scientific collaborators from the various public institution hospitals and research institutes (6).

### **References**

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2. *Pharmacogenet Genomics* 2006, **16**(4):297-306.
3. *Epilepsia* 2007, **48**(5):1015-1018.
4. *Pharmacogenomics J* 2006, **6**(4), 265-268.

5. <http://www.fda.gov/cder/drug/InfoSheets/HCP/carbamazepineHCP.htm>

6. HSA Safety News, 19 Mar 2009 at <http://www.hsa.gov.sg>

### **Electronic adverse reaction reporting tool**

**New Zealand** — An electronic adverse reaction reporting tool has been launched designed to facilitate the reporting of adverse drug reactions to the Centre for Adverse Reactions Monitoring (CARM). It uses an online reporting form pre-populated with patient details from the GP practice software.

The World Health Organization (WHO) rates New Zealand as having the highest number of reports submitted per capita compared to other countries in their programme. Reports from New Zealand are also rated as being of the highest quality. Despite this, international research indicates that at best, only 1 in 10 adverse reactions are being reported in New Zealand.

In addition, research conducted in New Zealand examined the data stored in the patient management systems of 30 general practices. Of the 725 entries in the medical warnings files that recorded an adverse reaction or allergy to at least one medicine, only 21 were reported to CARM.

Known barriers to reporting include the absence of a prompt to initiate reporting, considering that the reaction is already well known, and finally the time required to manually fill in adverse reaction forms. The adverse reaction reporting tool has been developed to help overcome these barriers.

When the tool is opened it automatically pre-populates the patient's medical history, medicine history, and gives the

reporter the option of including laboratory test results. If a vaccine is a suspected medicine, the tool pre-populates the batch number, the date of administration, and how the vaccine was given. Once a description of the reaction is entered, one click on the mouse sends an electronic report to CARM.

**Reference:** *Prescriber Update* 2009;**30**(2):9 at <http://www.medsafe.govt.nz/profs/PUarticles.asp>

## Intensive monitoring of varenicline

**New Zealand** — Varenicline (Champix®) is the newest smoking cessation medicine available in New Zealand and has been monitored by the Intensive Medicines Monitoring Programme (IMMP) since its introduction in 2007. The IMMP has recently analysed results for 3389 patients who were dispensed a prescription for varenicline in the first year (1 April 2007 to 31 March 2008) of marketing in New Zealand.

In this interim analysis the IMMP identified a total of 293 reports (for 284 patients) with a total of 538 adverse events occurring while the patient was taking varenicline. These events have been identified from follow-up questionnaires sent to doctors in June 2008 and spontaneous reports submitted to the New

Zealand Pharmacovigilance Centre (NZPhvC). The most frequently reported adverse events were psychiatric effects, with a total of 169 events (31% of all events). The most common psychiatric adverse events reported were depression (22 events), insomnia (22), sleep disturbance (13), fatigue (12), vivid/strange dreams (10), nightmares (10), and anxiety (9). There have also been four reports of depersonalisation, four reports of mood swings, four of panic attacks, and two of hypomania/ mood elevation.

The IMMP has identified six reports of symptoms following cessation of varenicline which appear to be withdrawal effects.

Prescribers are reminded that patients may also experience psychiatric symptoms such as depression and irritability for many reasons including nicotine withdrawal.

### References

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2. Pzifer Inc.(2009).Data sheet for Champix accessed 30 March 2009 at: [www.medsafe.govt.nz/profs/datasheets](http://www.medsafe.govt.nz/profs/datasheets).
3. *Prescriber Update* 2009;**30**(2):9 at <http://www.medsafe.govt.nz/profs/PUarticles.asp>

# Regulatory Action and News

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## Influenza virus vaccines: 2009–2010 season

**World Health Organization** — It is recommended that vaccines for use in the 2009–2010 influenza season (northern hemisphere winter) contain the following:

- an A/Brisbane/59/2007 (H1N1)-like virus [A/Brisbane/59/2007 is a current vaccine virus; A/South Dakota/6/2007 (an A/Brisbane/59/2007-like virus) is a current vaccine virus used in live attenuated vaccines.]
- an A/Brisbane/10/2007 (H3N2)-like virus [A/Brisbane/10/2007 and A/Uruguay/716/2007 (an A/Brisbane/10/2007-like virus) are current vaccine viruses].
- a B/Brisbane/60/2008-like virus. [B/Brisbane/33/2008 is a B/Brisbane/60/2008-like virus].

Vaccine viruses (including reassortants) and reagents for use in the laboratory standardization of inactivated vaccine may be obtained from:

Immunobiology Section, Office of Laboratory and Scientific Services, Therapeutic Goods Administration, P.O. Box 100, Woden, ACT 2606, Australia (fax: +61 2 6232 8564, web site: <http://www.tga.gov.au>); Division of Virology, National Institute for Biological Standards and Control, Blanche Lane, South Mimms, Potters Bar, Hertfordshire, EN6 3QG England (fax: +44 1707641050, e-mail: [enquiries@nibsc.ac.uk](mailto:enquiries@nibsc.ac.uk), web site: [http://www.nibsc.ac.uk/fl\\_u\\_site/index.html](http://www.nibsc.ac.uk/fl_u_site/index.html)); or Division of Product Quality, Center for Biologics Evaluation and Research, Food and Drug Administration, 1401 Rockville Pike, Rockville, MD, 20892, United States (fax: +1 301 480 9748).

Requests for reference strains for antigenic analysis should be addressed to the WHO Collaborating Centre for Reference and Research on Influenza, 10 Wreckyn Street, North Melbourne, VIC 3051, Australia (fax: +61 3 9342 3939, website: <http://www.influenzacentre.org>); the WHO Collaborating Centre for Reference and Research on Influenza, National Institute of Infectious Diseases, Gakuen 4-7-1, Musashi-Murayama, Tokyo 208-0011, Japan (fax: +81 42 561 0812 or +81 42 565 2498, web site: <http://www.nih.go.jp/niid/index.html>); the WHO Collaborating Center for Surveillance, Epidemiology and Control of Influenza, Centers for Disease Control and Prevention, 1600 Clifton Road, Mail Stop G16, Atlanta, GA 30333, United States (fax: +1 404 639 0080, web site: [http://www.cdc.gov/fl\\_u/](http://www.cdc.gov/fl_u/)); or the WHO Collaborating Centre for Reference and Research on Influenza, National Institute for Medical Research, The Ridgeway, Mill Hill, London NW7 1AA, England (fax: +44 208 906 4477, email [whocc@nimr.mrc.ac.uk](mailto:whocc@nimr.mrc.ac.uk), web site: <http://www.nimr.mrc.ac.uk/wic/>.)

**Reference:** Weekly Epidemiological Record, Vol. 84(9) 65–76, 2009 at <http://www.who.int/publications>

## Sale of efalizumab suspended

**Singapore** — The Health Sciences Authority (HSA) has requested the product licence holder to suspend sales of efalizumab (Raptiva®) in Singapore with effect from 26 February 2009 due to the emergence of new safety issues associated with the product.

Raptiva® is available locally as a prescription medicine. It contains the active

ingredient, efalizumab, an immunomodulating, humanized monoclonal antibody, licensed for the treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates of phototherapy or systemic therapy.

HSA's Pharmacovigilance Advisory Committee has assessed data which included recent adverse reports of progressive multifocal leukoencephalopathy (PML) and the limited place in therapy of efalizumab in the local setting and concluded that the risk versus benefit of efalizumab is no longer favourable.

The review took into consideration the risks of potentially fatal PML associated with efalizumab countered with the fact that it is not a first-line therapy, that it is used in a potentially serious but non-life threatening condition, and the availability of other treatment options for plaque psoriasis. Besides PML, efalizumab is also associated with serious adverse effects such as Guillain-Barre and Miller-Fisher syndromes, encephalitis, encephalopathy, meningitis, sepsis and opportunistic infections.

PML is a rare neuromuscular disease caused by opportunistic infections that usually leads to severe disability or death. There is no reliable way of knowing which patients will develop PML or when the disease is likely to occur. To date, there are four worldwide reports of PML (three virologically confirmed and one suspected) associated with the product in patients who had been continuously treated with Raptiva® for three or more years. Two of the three confirmed cases resulted in the patient's death. Locally, the HSA has not received any adverse drug reaction reports associated with Raptiva®.

**Reference:** *HSA Alert*, Sales of efalizumab (Raptiva®) suspended. 27 February 2009. [http://www.hsa.gov.sg/publish/hsaportal/en/health\\_products\\_regulation/safetyinformation/product\\_safety\\_alerts.html](http://www.hsa.gov.sg/publish/hsaportal/en/health_products_regulation/safetyinformation/product_safety_alerts.html)

## Efalizumab: voluntary withdrawal

**United States of America** — The manufacturer of the psoriasis drug efalizumab (Raptiva®), has announced that it has begun a voluntary, phased withdrawal of the product from the US market. The company is taking action because of a potential risk of progressive multifocal leukoencephalopathy (PML), a rare, serious, progressive neurologic disease caused by a virus that affects the central nervous system. By 8 June 2009, efalizumab will no longer be available in the United States.

Prescribers are asked not to initiate efalizumab treatment for any new patients and immediately begin discussing with patients currently using efalizumab on how to transition to alternative therapies.

The risk that an individual patient taking Raptiva® will develop PML is rare and is generally associated with long-term use. Generally, PML occurs in people whose immune systems have been severely weakened and often leads to an irreversible decline in neurologic function and death. There is no known effective treatment for PML.

**Reference:** *FDA Statement*, 8 April 2009 at [www.fda.gov/medwatch/](http://www.fda.gov/medwatch/) and [www.gene.com/gene/products](http://www.gene.com/gene/products).

## Oseltamivir: extension of shelf life

**European Union** — The European Medicines Agency (EMA) has recommended that the shelf life of oseltamivir (Tamiflu®) capsules should be extended from five to seven years. Once formally approved by the European Commission, this will apply to all newly manufactured oseltamivir capsules.

In view of the recent outbreak of the novel influenza A/H1N1 virus, the European

Medicines Agency has also reviewed ways to use oseltamivir capsules in case of a shortage. The Agency's Committee for Medicinal Products for Human Use (CHMP) recommended that oseltamivir capsules that are already on the market may be used for up to two more years after their current five-year expiry date during a declared pandemic. Patients who have oseltamivir capsules that have recently expired should not dispose of them because they might be needed during a novel influenza A/H1N1 pandemic. These recommendations will only apply if a pandemic has been declared by the World Health Organization (WHO).

**Reference:** *Press Release*, Doc. Ref. EMEA/284971/2009, 8 May 2009 at <http://www.emea.europa.eu/>

## Antiviral medicines in an influenza pandemic

**European Union** — The European Medicines Agency (EMA) has given guidance on the use of oseltamivir (Tamiflu®) in children under one year of age and use of oseltamivir (Tamiflu®) and zanamivir (Relenza®) in pregnant and breastfeeding women in the case of a declared influenza A/H1N1 pandemic by the World Health Organization (WHO).

### **Children under the age of one**

The Agency's Committee for Medicinal Products for Human Use (CHMP) has concluded that during an officially declared influenza A/H1N1 pandemic the benefits of oseltamivir outweigh its risks in the treatment of children under the age of one. Because there is less evidence to support the use of oseltamivir for the prevention of influenza, doctors should carefully consider the benefits and risks for each patient.

During a pandemic, if oseltamivir is prescribed to children under the age of one, the recommended dosage is 2 to 3 mg per kg body weight.

### **Pregnant and breastfeeding women**

Following a review of the available data for oseltamivir and zanamivir, the CHMP concluded that the benefits of using these medicines in pregnant or breastfeeding women outweigh the risks in case of an influenza A/H1N1 pandemic.

**Reference:** *Press Release*, Doc. Ref. EMEA/285148/2009, 8 May 2009 at <http://www.emea.europa.eu/>

## European Union and Health Canada: confidentiality arrangement

**Canada/European Union** — The European Medicines Agency, the European Commission and Health Canada, the Canadian regulatory authority for medicines, have agreed on an implementation plan for their confidentiality arrangement.

The implementation plan details the process for both regular and ad-hoc exchanges of information, and describes the process for monitoring the progress of the implementation plan. It also foresees an exchange programme for staff to promote mutual learning and sharing of regulatory experience.

The confidentiality arrangement, signed in December 2007, allows the parties to share non-public information on all human and veterinary medicines — already authorized or still under review — that fall within the scope of the agreement. It also allows the exchange of information on legislation under development or draft regulatory guidance documents.

The implementation plan with Health Canada follows largely the plan in place for implementation of the confidentiality arrangements with the United States Food and Drug Administration (FDA). The regulatory agencies will explore potential joint implementation activities with the FDA to avoid duplication of efforts.

**Reference:** Press Release, Doc. Ref. EMEA/220316/2009, 8 April 2009 at <http://www.emea.europa.eu/>

## **Ixabepilone: withdrawal of application for marketing authorization**

**European Union** — The European Medicines Agency (EMA) has been formally notified by the product licence holder of its decision to withdraw the application for a centralized marketing authorization for ixabepilone (Ixempra®), 2 mg/ml powder and solvent for concentrate for solution for infusion. Ixabepilone was expected to be used to treat locally advanced or metastatic breast cancer after failure of previous cytotoxic chemotherapy treatments. It was to be used in combination with capecitabine.

The application for the marketing authorization for Ixempra was submitted to the Agency on 24 September 2007. On 20 November 2008, the Agency's Committee for Medicinal Products for Human Use (CHMP) adopted a negative opinion, recommending the refusal of the marketing authorization. Following this, the company requested a re-examination of the opinion, which was under review by the CHMP at the time of the withdrawal.

**Reference:** EMA Press Release, Doc. Ref. EMEA/177056/2009, 19 March 2009. <http://www.emea.europa.eu>

## **Peginterferon alfa-2b: withdrawal of application for marketing authorization**

**European Union** — The European Medicines Agency (EMA) has been formally notified by the product licence holder of its decision to withdraw the application for a centralized marketing authorization for the medicine peginterferon alfa-2b (Cylatron®), 200 micrograms /0.5 ml, 300 micrograms /0.5 ml and 600 micrograms/0.5 ml.

Peginterferon alfa-2b was expected to be used for the adjuvant treatment of patients with stage III melanoma as evidenced by microscopic, non-palpable nodal involvement.

In its official letter, the company stated that the withdrawal of the application was based on the CHMP's view that the data provided were not sufficient to allow the Committee to conclude on a positive benefit-risk balance for Cylatron® at that time.

**Reference:** Press Release, 16 March 2009 Doc. Ref. EMEA/158824/2009 at <http://www.emea.europa.eu/>

## **Levodopa/carbidopa/entacapone: withdrawal of application for extension of indication**

**European Union** — The European Medicines Agency (EMA) has been formally notified by the product licence holder of its decision to withdraw its application for an extension of indication for the centrally authorized medicine levodopa/carbidopa/entacapone (Stalevo®) film-coated tablets.

Stalevo® was first authorized in the European Union on 17 October 2003. It is currently authorized for use in patients with Parkinson disease, who are being treated with a combination of levodopa and an inhibitor of dopa decarboxylase but are having 'fluctuations' (a wearing-off of the medicine's effects and re-emergence of symptoms) towards the end of the period between two doses of their medication, which cannot be stabilized with the standard combination alone.

In its official letter, the company stated that the withdrawal of the application was based on feedback from the evaluation of the application that indicated that the data provided were insufficient to support

approval for this indication. In addition, the company also stated that it is unable to provide additional clinical data to the CHMP within the permitted timeframe.

Stalevo® continues to be authorized for the currently approved indication.

**Reference:** Press Release, 10 March 2009  
Doc. Ref. EMEA/147137/2009 at <http://www.emea.europa.eu/>

# Medicines Strategy and Policies

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## Good Governance for Medicines Programme

Corruption is the single greatest obstacle to social and economic development in countries worldwide, undermining democracy and creating unstable governments. With an annual global expenditure estimated at more than US\$ 4.4 trillion, the health sector is a very real target for corruption and other unethical practices.

Corruption in the pharmaceutical sector can take various forms. Whether it is bribery of a government official, falsification of efficacy and safety data, theft in the distribution chain or recruitment of personnel based on favouritism, its impact on public health and government financial resources can no longer be ignored.

Although hard data on global financial losses due to corruption in the pharmaceutical sector are lacking, related figures indicate that losses are potentially very high. For example, Transparency International estimates that, on average, 10 to 25 % of public procurement spending, including in the health sector, is lost due to corruption. Such abuse can aggravate the global inequalities in access to essential medicines and can be detrimental to a country's ability to improve the health of its population.

The Good Governance for Medicines (GGM) programme began in late 2004, in line with the World Health Organization's (WHO) Global Medicines Strategy. Its goal is to reduce corruption in the pharmaceutical sector by the application of transparent, accountable administrative procedures and by promoting ethical practices. Through this initiative, WHO's objective is to support countries in maintaining efficient health-care systems.

## GGM Activities Report

WHO has defined a model process and a long-term strategy for implementing the Good Governance for Medicines (GGM) programme in countries, based on the following three-phase approach.

**Phase I: National assessment of transparency and potential vulnerability to corruption of key pharmaceutical system functions.** Independent national assessors conduct the assessment, and on completion a report with the findings and recommendations for action is produced, providing a baseline to monitor the country's progress over time.

**Phase II: Development of a National GGM Framework.** This involves a nationwide consultation process among key stakeholders. Countries validate the results of the assessment and define the basic components necessary for promoting good governance practices in the management of their national pharmaceutical system.

**Phase III: Implementation of the National GGM Framework.** This phase aims to promote the framework among key pharmaceutical actors and to translate its recommendations into action through a set of strategic activities increasing

## Basic components of the GGM Framework

Values-based strategy	Discipline-based strategy
<ul style="list-style-type: none"> <li>• Framework of moral values &amp; ethical principles:               <ul style="list-style-type: none"> <li>-Justice/fairness</li> <li>-Truth</li> <li>-Service to common good</li> <li>- Trusteeship</li> </ul> </li> <li>• Code of conduct</li> <li>• Programme for socialization of ethical framework &amp; code of conduct</li> <li>• Promotion of moral leadership</li> </ul>	<ul style="list-style-type: none"> <li>• Established anti-corruption legislation</li> <li>• Whistle-blowing mechanisms</li> <li>• Sanctions on reprehensible acts</li> <li>• Established regulations and administrative procedures</li> <li>• Collaboration between anticorruption agencies, CSOs and private sector</li> <li>• Management, coordination and evaluation of GGM programme (Steering Committee &amp; Task Force)</li> </ul>

awareness, strengthening integrity systems and building capabilities for leadership.

### **GGM technical package**

WHO has developed a complete technical package to guide countries in each of the three phases of GGM implementation.

### ***Measuring transparency in the public pharmaceutical sector***

The GGM transparency assessment instrument for Phase I measures the level of transparency in eight key functions of medicines regulatory and procurement systems, and provides both quantitative and qualitative information. Assessors collect information through semi-structured interviews of key informants who represent different stakeholders, such as government, the private sector, academia and nongovernmental organizations. The information collected is then converted to a 0 to 10 scale to provide a score of vulnerability to corruption for each function, from minimally to extremely vulnerable. The basic assumption is that the more transparent any system is, the less vulnerable to corruption it will be. A first

draft of the instrument was developed in 2004 and was regularly refined in light of the experience gained by countries. The English version of the instrument was finalized during a global expert consultation in February 2008. The Arabic, French and Spanish translations will be available shortly to facilitate the future expansion of the GGM programme in other countries.

### ***GGM framework for good governance in the pharmaceutical sector***

This GGM framework serves as a Phase II model for the development of national GGM frameworks. At the crux of the argument presented in this document is that to achieve significant impact efforts to address corruption must include the application of two basic strategies:

- Discipline-based strategy – establishing anti-corruption laws, pharmacy practice laws and regulation, foreseeing adequate sanctions for violations of the law.
- Values-based strategy – building institutional integrity through the promotion of moral values and ethical principles.

**Guide for promoting the framework for good governance in the pharmaceutical sector**

There are no "quick fixes" for tackling corruption and promoting good governance in the pharmaceutical sector. A long-term strategy is needed that actively continues after a country officially adopts its national GGM framework. Phase III consists of translating the GGM framework into action. The guide for Phase III recommends a set of strategic activities to socialize the GGM framework, to (i) promote awareness among health professionals and the general public on the potential for corruption and its impact on health system functioning and (ii) build national capacity for sustaining good governance in the pharmaceutical system.

A consultation process for the revision of the guide has started, and after further testing in countries the revised version will be completed in 2009.

**Progress in countries**

The GGM programme started in 2004 in four Asian countries: Lao People's Democratic Republic, Malaysia, the Philippines and Thailand. Since then the success of the programme has exceeded expectations. The number of countries adopting the GGM programme globally has increased significantly and the programme currently operates in 26 countries across the six WHO regions (5).

WHO has developed a training package for each of the three phases and these are provided to countries before the start of each phase. WHO has also established a monitoring and reporting system, whereby countries report their activities to WHO on a bi-annual basis.

**Countries in Phase 1**

Implementation of the GGM programme starts after receiving clearance from the Ministry of Health (MoH). Independent

national assessors are selected to conduct the transparency assessment. WHO provides technical training workshops for the assessors on the use of the assessment methodology and accompanying tools.

To date, results indicate that in the majority of countries promotion, selection and inspection are the functions that are the most vulnerable to corruption. Comparison of the findings between countries showed some common trends, in both the strengths and weaknesses. For example, most countries have transparent and competitive procurement procedures, with a post-tender mechanism to monitor suppliers' performance.

In the selection function, most countries had a national essential medicines list, with transparent procedures for the selection process. The common weaknesses related to the lack of conflict of interest guidelines, the absence of a responsible unit within the medicines regulatory authorities for monitoring medicines promotion or the lack of publicly available terms of reference for the committee responsible for overseeing medicines registration or selection, describing its role and responsibilities.

WHO encourages countries to publish the results of the national transparency assessment, although this takes time as the results need to be validated by national stakeholders and officially approved by the government before publication. By the end of 2008, WHO had published results from 11 countries.

**Countries in Phase II**

Assessing the level of transparency and potential vulnerability to corruption is not an end in itself but rather the beginning of a long process intended to generate good governance in the pharmaceutical sector. WHO recommends that countries hold a national workshop with key stakehold-

## GGM leadership and network

### **Global Advisory Group**

WHO's GGM programme is now guided by its Global Advisory Group (GAG) that provides overall strategy and policy guidance. It is comprised of a wide range of stakeholders, including international and bilateral organizations (World Bank, DFID), civil society (Transparency International, Procurement Watch), academia, national anti-corruption agencies, ministries of health and the private sector. It meets once or twice a year.

### **Global Stakeholders Group**

A meeting of the Global Stakeholders Group (GSG) was held in Bangkok, 3 to 5 December 2007 with the objective of providing a platform to exchange experiences in curbing corruption and promoting good governance in the pharmaceutical sector, as well as an opportunity to network with stakeholders. Seventy participants from 25 countries, including country officials involved with the implementation of GGM in their countries as well as a wide range of key stakeholders, attended this two and a half day meeting. The theme selected "Transparency for change" aimed to mobilize a "call for action" for all participants to meet the challenges ahead, and ultimately to help make quality essential medicines accessible and affordable to all. WHO plans to hold GSG meetings every two years.

### **GGM human resources**

WHO's priority in the coming years is to create a global team of "GGM human resources" who will be responsible for training and working closely with GGM country teams, especially from Phase II onwards. This will be essential for the sustainability of GGM programmes in countries. The global team will be multilingual (Arabic, English, French and Spanish) and its members will be selected on a specific set of criteria, such as familiarity with the GGM concepts, and availability to participate actively in GGM activities. WHO will develop a "training of trainers" package and provide training for this group in 2009.

ers shortly after the assessment is completed. The objective of such a workshop is to validate the results of the transparency assessment and consult on the key components that need to be included in the national GGM framework document. The workshop is the first key element of Phase II.

A national GGM team is then nominated by the MoH, which is responsible for (i) the development and finalization of the framework document in consultation with all key stakeholders and (ii) the overall management, coordination and evaluation of the GGM programme in each country. In some countries, it has been

decided to have a Steering Committee, headed by high-level officials to set the strategic directions for the GGM programme and to guide the country team.

Once officially adopted, this document authorizes country teams to implement and promote good governance in the pharmaceutical sector.

### **Countries in Phase III**

GGM frameworks are effective only if translated into action. Too often good policy documents are developed but not widely used. The aim of Phase III is to ensure that concrete actions are implemented and anti-corruption efforts remain

sustainable. By the end of 2008, the following four countries were in Phase III and planned activities included:

- *Bolivia*. Training of the national GGM team, briefing sessions for government officials, production of advocacy materials.
- *Mongolia*. Changing procedures in regulation and supply systems to make them more transparent, moving towards a web-based registration and licensing system, adoption of a code of conduct for pharmacists and development of a conflict of interest form.
- *Philippines*. Launching of a GGM national award for Local Government Units to decentralize GGM practices to the provinces.
- *Thailand*. Introducing the GGM concept into university curricula and producing advocacy materials.

To ensure the sustainability of the GGM programme, training the national GGM team and continuing to work closely with it will be essential. In January 2009 a Phase III training workshop was held for the first time in Amman for Jordan's national team. It focused on anti-corruption and pharmaceutical sector legal frameworks, implementation of the recommendations included in the transparency assessment (Phase I) and moral leadership capabilities. WHO's focus in the coming years will be to build capacity in countries, through a combination of Phase III training and coaching.

### **Lessons learnt and the way forward**

Interest in the GGM programme has been higher than anticipated at global and country levels, for a number of reasons. The preventive and constructive approach, namely measuring vulnerability to corruption and strengthening pharmaceu-

tical systems by increasing transparency has appealed to governments. Also, the GGM programme is addressing real concerns and a deep-rooted issue, which is increasingly and openly acknowledged by colleagues in ministries of health, academia, civil society organizations and the private sector. There appears to be an increased consciousness that as long as corruption is not addressed, development work will not be successful. This has led senior colleagues in countries to become involved in the national GGM teams. Momentum for change is increasing.

High-level commitment has proved to be beneficial, not only for giving this sensitive programme the profile it ought to have, but also for ensuring its sustainability. Experience has also shown that partnering with national anti-corruption or good governance bodies is extremely valuable, together with constant communication and staff training. It is important to acknowledge that some countries need more time than others, depending on their political situation and the availability of human resources to carry out GGM activities.

"Cross-fertilization" between participating countries has proved to be probably the best learning platform and WHO will continue its role as a hub in sharing information and experiences gained in countries, ensuring systematic evaluation and reflection on how best to increase transparency and build capacity to promote good governance in the pharmaceutical sector.

In the next few years WHO will focus on consolidating the GGM programme in countries and is committed to continuing to provide technical support in this challenging and rewarding area of work.

*More information and a list of key GGM publications is available at <http://www.who.int/medicines/ggm> or contact [ggminfo@who.int](mailto:ggminfo@who.int)*

# Recent Publications, Information and Events

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## **ASEAN: mutual recognition arrangement for GMP**

The Association of Southeast Asian Nations (ASEAN) has moved a step closer to the realization of its vision of an integrated regional health care sector through the reduction of technical barriers to trade in pharmaceutical products.

On 10 April 2009, the ASEAN signed a Sectoral Mutual Recognition Arrangement (MRA) for good manufacturing practice (GMP) inspection of manufacturers of medicinal products (IRMMP) that would ensure the safety, quality, efficacy and lower prices of drugs being sold in the region.

The 14th ASEAN Summit and Related Summits report has stated that divergences in national product standards often act as impediments to trade in goods. In order to promote deeper economic integration between economies towards the realization of the ASEAN Economic Community by 2015 the harmonization of product standards, and mutual recognition of test reports and certification is necessary.

Inspection reports of manufacturers of medical products seeking good manufacturing practice certifications and/or inspection by authorized agencies will serve as the basis in determining compliance with regulatory requirements. These include the issuance of licences for pharmaceuticals.

The Sectoral Mutual Recognition Arrangement will be fully implemented by all ASEAN member countries by 1 January 2011. Pharmaceuticals must also demonstrate proper compliance with the

Pharmaceutical Inspection Cooperation Scheme (PIC/S) Guide for Medicinal Products.

**Reference:** *ASEAN Press Release*, 11 April 2009 <http://www.gov.ph/news/?i=24164>

## **Losing artemisinin?**

**World Health Organization** — For many months there have been reports from Cambodia of cases of malaria showing resistance to what is now the mainstay of malaria treatment – artemisinin combination therapy (ACT) (1, 2)

A programme has now been launched seeking to contain the spread of artemisinin resistance (3). It must be hoped that these efforts will achieve some success. The loss of this drug would be calamitous for malaria control globally.

Since it was first established that artemisinin could be an effective replacement for the older malaria treatments, massive investments have been made with the aim of making ACT drugs accessible to those who need them (4)

The sale of substandard ACTs containing inadequate levels of the active drug and the use of artemisinin as a monotherapy both promote the development of resistance. It is essential that these practices should be halted.

## **References**

1. <http://www.tropika.net/svc/review/Chinnock20080509Revartemisin> last year.
2. <http://blog.tropika.net/tropika/2008/11/03/artemisin-is-resistance-appearing-in-cambodia/>

3. <http://www.tropika.net/svc/news/20090302/Chinnock-20090302-News-Artemisinin-resistance>

4. <http://blog.tropika.net/tropika/2009/03/04/malaria-a-breakthrough-in-artemisinin-production/>

5. News on UNICEF/UNDP/WorldBank/WHO-TDR <http://www.who.int/tdr/topmenu/news/>

## International drug price indicator guide

Management Sciences for Health has announced the availability of the 2008 edition of the *International Drug Price Indicator Guide*. The Guide provides a spectrum of prices from 25 sources, including pharmaceutical suppliers, international development organizations, and government agencies. The Guide assists supply officers to determine the

probable cost of pharmaceutical products for their programmes, allows users to compare current prices paid to prices available on the international market, or assess the potential financial impact of changes to a medicines list, and helps to support rational medicine use education.

This edition of the Guide was produced in collaboration with the World Health Organization. Development and publication was supported by the UK Department for International Development (DFID) and the Medicines Transparency Alliance (MeTA).

**Reference:** Center for Pharmaceutical Management, Management Sciences for Health at <http://www.msh.org/resource-center/ebookstore>