WHO Drug Information

Contents

Biomedicines and Vaccines

Monoclonal antibodies: a special regulatory challenge?

Use of monoclonal antibodies is an important development in the search for new therapeutic agents. Monoclonal antibody (mAb) technology allows production of large amounts of pure antibodies which are potentially more effective than conventional drugs in targeting disease. However, although mAbs have revolutionized modern medicine, they show special peculiarities. Recent events in the United Kingdom and United States have been reported where subjects subsequently developed dramatic adverse reactions during clinical tests and also following use of a marketed product. As a consequence, the regulatory requirements and level of safety evaluation for high risk mAbs may need reconsideration.

Antibodies or immunoglobulins are physiological blood components produced by B cells and intended to bind to and neutralize foreign antigens and pathogens. Johann Wolfgang von Goethe in his famous tragedy "Faust" has rightly identified blood as "a very special juice". In today's view, this description would also cover cellular and molecular blood components, including immunoglobulins.

Most non-cellular blood components, such as immunoglobulins or clotting factors, are highly complex biological molecules both as regards structure and mechanism of action. Their clinical investigation requires special consideration and this article reviews use of mAbs in therapeutics, describes the peculiarities of this product class, and how — from a regulator's perspective — clinical trials should be considered with regard to approval and product dossier requirements .

Paul Ehrlich's magic bullet

Antibodies bind to a corresponding antigen in a highly specific manner, like a key in a lock. They recognize their antigen with the variable domain of the mAb— Fab part — and for some types mediate cytotoxicity with their Fc part, which binds and activates, complements and/or interacts with receptors on antigen-presenting cells.

Using these molecules to neutralize or even attack pathologic structures is not a new idea. In 1900, Paul Ehrlich proposed that certain compounds could be used to selectively target external pathogens or even tumours, representing "magic bullets" (1). However, the use of antibodies to target structures and use them as medicines was for a long time hampered by a lack of methods to generate viable B cell clones.

This became possible in 1975 through identification of hybridoma technology by Köhler and Milstein (2). This employs a fusion of murine B cells derived from the spleen of immunized donors to mouse myeloma cells. With this principle, the ability of the B cell to produce antibodies was combined with the infinite growth of a tumour cell within one cellular system while allowing for the production of specific antibodies. With this development, Paul Ehrlich's dream of a magic bullet became reality.

Evolution of monoclonal antibodies

The first monoclonal antibody products to be licensed were fully murine. An immune response against the murine mAb is mounted upon exposure in humans, and often led to a reduction of efficacy by neutralizing antibodies or to safety problems such as infusion reactions. In order to reduce immunogenicity (3), scientists initiated an evolutionary process, commencing with chimeric antibodies. The International Nonproprietary Name (INN) of these molecules commonly ends with the suffix "-ximab", representing the chimeric principle (fe.g., infliximab, Remicade®).

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As a next step, mAbs were humanized by insertion of human sequences (suffix: -zumab, e.g., trastuzumab, Herceptin®). Using the latest techniques, production of fully human mAbs has become possible and has reduced immunogenicity even further (suffix: -umab). The only fully human mAb licensed so far in Europe is adalimumab (Humira®), an antibody against human tumour necrosis factor alpha (TNF-alpha).

MAbs have also undergone an evolution from a functional point of view. While the classical approach of neutralizing infectious agents or attacking tumour cells with mAbs is still being used and represents a powerful tool, the trend is to develop more specific targets, such as immunomodulators binding to substructures of physiological molecules. A recent example is the anti-CD28 mAb TGN1412, directed against a distinct substructure of the human CD28 molecule, the C''D loop (4), exhibiting a distinct pharmacodynamic effect. This "supra-agonist" has gained sad attention due to serious adverse events during a first-in-man trial in the United Kingdom (5).

Additionally, compounds with different mechanisms of action have been developed, such as mAbs coupled to cytotoxic agents, radionuclides, or bispecific antibodies (combinations of different antigen specificities within one molecule). Since it has been shown that the strength of interaction with the Fc receptor on monocytic cells is also of high importance to efficacy, (6, 7), engineering to enhance (8) or lower Fc receptor interaction has also gained some interest in the pursuit of more efficacious and/or safe mAbs.

Currently licensed mAbs

Information on 15 currently licensed mAbs is available in scientific journals or from the European Public Assessment Reports on the European Medicines Agency (EMEA) website (9). Besides diagnostic antibodies like sulesomab (Leukoscan®), licensed mAbs exhibit three different basic mechanisms of action.

Firstly, antitumoural antibodies, like cetuximab (Erbitux®), trastuzumab (Herceptin®), alemtuzumab (MabCampath®), and rituximab (MabThera®), bind to tumour-associated antigens and most probably function through antibody- and/or cell-mediated cytotoxicity to tumour cells. Recently, a new principle has been added to the armamentarium — targeting of tumour vascularization by neutralization of human vascular endothelial growth factor (VEGF) by bevacizumab (Avastin®).

The second mechanism is the classical anti-infective principle. An example is palivizumab (Synagis®), which is directed against the antigenic site A on the fusion or F protein of respiratory syncytial virus (RSV).

The third, and quite popular, mechanism of action is modulation of the immune system by neutralizing cytokines or antagonistic targeting of membrane-bound activation molecules. Examples are:

- adalimumab (Humira®) and infliximab (Remicade®) which target soluble and membrane-bound TNF-alpha;
- efalizumab (Raptiva®) which binds to the CD11-a subunit of lymphocyte function-associated antigen 1 (LFA1) on leukocytes.
- basiliximab (Simulect®) and daclizumab (Zenapax®) which block T cell activation by interaction with a part of the interleukin-2 receptor (IL-2R), the CD25 antigen on T cells. In this way, both antibodies inhibit binding of the T cell activating cytokine interleukin-2 (IL-2).

Another licensed mAb, which cannot be subsumed to these three basic mechanisms, is abciximab (ReoPro®), a chimeric Fab fragment directed against the glycoprotein-(GP) IIb/IIIa-(αIIbβ3) receptor on human thrombocytes. This is indicated in cardiological indications like unstable angina pectoris or percutaneous coronary intervention.

Need for a holistic approach

Monoclonal antibodies are high molecular weight proteins with complex secondary and tertiary structures subject to post-translational modifications like glycosylation. Biotechnology-derived proteins often contain process- and product-related impurities and usually have low stability. As proteins, mAbs are immunogenic.

The manufacturing process is a complex and highly defined procedure, and fluctuations can

affect the final product considerably. Although small changes — such as those relating to pH in cell cultures, temperature, culture media suppliers — may not seem significant, they can have a high adverse impact. The manufacturing process including each and every step of manufacture is thus highly relevant and any change in this system will inevitably affect the final finished product. This underscores the need for mAbs to be considered on an individual basis. Neither can experience gained with these products be automatically extrapolated to the group in general.

Manufacturers will inevitably introduce changes in the process during pre-approval development. These can range from suppliers of raw materials to major changes in the cellular expression system. Such quality and manufacturing aspects can have a considerable impact on clinical performance. For example, product-related impurities like fragments and aggregates, or process-related impurities like residual host cell DNA and proteins, may not be removed sufficiently and can later lead to safety problems in clinical trials.

Furthermore, different "species" of mAbs showing microheterogeneity can have different potencies, potentially resulting in inconsistent efficacy in clinical testing when not constant between different batches. Immunogenicity in patients can reduce clinical efficacy by neutralizing antibodies that recognize the antigen-binding part of the mAb (anti-idiotypic antibodies). Antibodies against the mAb, as well as non-neutralizing antibodies, can impact on the pharmacokinetic profile, especially on clearance rate, which in turn can lead to altered pharmacodynamic or even clinical behaviour of the drug.

Quality attributes and defects can also influence preclinical outcomes like tissue cross-reactivity, toxicity profile, and immunotoxicity. Such preclinical findings may then trigger the need for implementation of additional safety endpoints in clinical trials. Thus, as a principle, the three different parts of the product dossier that characterize a medicinal product and that regulators have to assess for approval of clinical trial applications or marketing authorizations – quality, non-clinical and clinical data – are inherently interlinked, and should be evaluated as a whole: mAb assessment is thus an integrated, interdependent "threesome" process.

Monoclonal antibodies and clinical investigation

Quality requirements

In Europe, the EU Clinical Trial Directive 2001/20/EC requires European Regulatory Agencies to approve clinical trial applications on a national basis before a clinical trial can commence. The Investigational Medicinal Product Dossier (IMPD) makes up part of the documentation to be filed by the sponsor. For mAbs and other biotechnology products, data requirements to be submitted in the IMPD are high, even during early phase development. Quality documentation to be submitted includes:

- Structure (primary and higher-order structures, expression vectors, post-translational modifications like glycosylation patterns).
- Physicochemical characteristics and biological activity (potency).
- Detailed description of the manufacturing process.
- Changes in the manufacturing process during development.
- Data demonstrating that the change(s) do/did not have an adverse impact on the quality, safety and efficacy of the product (so-called "comparability exercise").
- In-process controls and product controls (impurities, aggregates, heterogeneity, fragments).
- Quality controls (material controls, production cell line, cell bank system etc.)
- Viral safety and safety for transmissible spongiform encephalopathy agents (TSEs).

Many IMPD quality requirements are stage-dependent; for example, validation of analytical tests that for later phases require evaluation of accuracy, precision, specificity, detection limit, linearity and range. Nevertheless, in general, quality data for early-phase clinical

trials have to conform with principles of good manufacturing practice (GMP) and are a central aspect of the dossier. From the perspective of the "threesome" principle already mentioned, these requirements make sense both for patients and sponsors.

For patients, high-quality products ensure maximum patient safety, at least from a quality perspective. For sponsors, the conduct of early clinical trials with GMP-assured material facilitates the final marketing authorization process. Thus, the better the physicochemical and biological characterization of a product at an early stage of development, the easier it is to demonstrate that data obtained from these early trials can be extrapolated and are relevant to the pivotal clinical trial data.

As already discussed, quality defects can have a profound impact on the clinical safety of mAbs. For some nonclinical or even clinical findings, it might become difficult to conclude whether a given event is a consequence of the mechanism of action, or a consequence of the quality profile of the drug. To avoid such misleading findings, a thorough characterization of the quality profile of a mAb is essential.

In Europe, the regulatory assessment of mAb product clinical trial applications is based on respective European Pharmacopoeia monographs for monoclonal antibodies (10) or products of recombinant DNA technology (11). These documents are considered binding, and deviations from them have to be thoroughly justified. Further, guidelines written for biotechnology products are taken as a benchmark for the assessment of such products. These are the respective quality guidelines issued by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) (12), expanded by regional regulatory guidelines. In the case of Europe, these would be guidelines issued by the European Medicines Agency's (EMEA) Committee for Medicinal Products for Human Use (CHMP) (13).

Non-clinical considerations and first-in-man trials

Biotechnology products may be highly species specific as regards their mechanism of action. Therefore, non-clinical testing of such products should only be performed in a "relevant species": one in which the test material is pharmacologically active due to the expression of the receptor or an epitope (14). Therefore, for a given mAb that is developed for human use, relevance of the species chosen to evaluate toxicity should be demonstrated.

The first step is normally comparison of the primary amino acid sequence of the human target structure or epitope with the corresponding sequence of the candidate species. However, sequence homology, even if it is 100% identical, is not sufficient to conclude on the relevance of the species. As a next step, species specific expression of the target epitope should be elucidated for example in immuno-histochemistry and the affinity of the mAb to its antigen has to be quantified by methods such as surface plasmon resonance technique and/or enzyme-linked immunosorbent assay (ELISA).

Once sequence and binding characteristics have been determined, the next step should be the characterization of downstream or pharmacodynamic effects, since binding itself does not necessarily mean that the mAb is pharmacodynamically active. One should bear in mind that interaction of the Fc-part of humanized mAbs with murine or primate Fc-receptors may result in artificial effects and misleading conclusions in terms of pharmacodynamics and toxicology. Thus, the choice of the relevant species and the interpretation of non-clinical results should not only focus on the binding of the mAb to its target via its Fab part, but also on the interaction with species Fc receptors via the Fc part of the mAb. Such non-clinical considerations are especially important for "high-risk" mAbs for which an enhanced non-clinical development should be undertaken before the transition to human studies.

For many mAbs, alternative approaches might be necessary in case no species proves to be "relevant". This can include data from human cell lines and/or ex-vivo data with human primary cell or tissue cultures. Other approaches can be transgenic animals, although in these animals the tissue distribution and attachment to the corresponding downstream signalling events might be different from

humans, and thus findings might be misleading. Important tools in this respect are "surrogate antibodies", which recognize a corresponding animal epitope in an animal species.

Based on the way they function physiologically, mAbs can cross-react with other epitopes that have similar structure as the desired target. Thus, an analysis should be undertaken to determine in which tissues the epitope itself is expressed and with what tissues the mAb cross-reacts ("tissue cross-reactivity" and "structure cross-reactivity"). The potential clinical sequelae that might be accompanied with mAb binding to non-target tissue should be considered, e.g. cardiotoxicity in the case of mAbs that show cross-reactivity with cardiac tissue sections. Adequate clinical endpoints should be implemented in order to detect potential clinical manifestations of such toxicity.

Another peculiarity of mAbs is that they can exhibit distinct effects based on the dose. In classical pharmacology it is assumed that for most products, lower doses of a drug will exhibit a smaller effect, and that effect size is proportional to the dose in the linear ascending part of the dose-response curve. For mAbs, this may be different. Examples have occurred where data suggest that lower doses might have different pharmacodynamic effects.

A recent example is the mAb TGN1412, which binds human CD28 as a "supra-agonist". TGN1412 was developed as a T cell activator with the aim of enhancing T cell mediated immunity in patients with chronic B cell leukaemia (B-CLL). These patients typically show a defect in immune function (15). However, published data also suggest that lower doses of TGN1412 might specifically target regulatory T cells (16) which have been described to be immunosuppressive. Therefore, the drug was also developed for the treatment of diseases where T cells are potential drivers of the disease, i.e. autoimmune diseases like rheumatoid arthritis and multiple sclerosis. Since different doses of mAbs might exhibit distinct pharmacodynamic effects, it is advisable to study lower doses of a newly developed mAb in non-clinical systems and include such considerations in the definition of the safety margin.

Within clinical trials, mAbs are often given in combination with other drugs, such as chemotherapy in the case of cytotoxic mAbs, or immunosuppressants in the case of immunomodulators. Moreover, patients are frequently pre-treated with other drugs before commencing the new product. Such concomitant or previous treatments might strongly influence the pharmacodynamic effect of a mAb, which in many cases requires a functional immune system. Thus, it is sometimes advisable to implement a non-clinical study which mimics the clinical situation as regards previous or concomitant therapy.

Transition from non-clinical testing in relevant species to the first human patient or even healthy volunteer is always a critical step. A recent incident with TGN1412 in the United Kingdom showed that, as with any other drug, clinical testing of mAbs can entail risks. TGN1412 non-clinical data submitted to the national competent authorities as part of the IMPD showed a 100% homology of the extracellular parts both of the human and cynomolgus monkey CD28 molecule. Data on the downstream effects were presented. Based on the non-clinical data, both the British Medicines and Healthcare Products Regulatory Agency (MHRA) in the United Kingdom and the Paul-Ehrlich-Institut in Germany approved the phase I trial protocol. The drug was tested simultaneously in six healthy volunteers at one centre. Subjects subsequently developed dramatic clinical adverse reactions reminiscent of a cytokine release syndrome and acute shock (5).

Many lessons can be learnt from this sad incident. Among them is the fact that non-clinical data are not 100% predictive of human experience even though they are of major importance to pre-empt potential toxicities. For example, if signs of cardiotoxicity are observed in a relevant species, even if not expected by the putative mechanism of action, clinical trials should then be amended with adequate cardiac monitoring endpoints. It is important to note that mAbs have not been shown to be high risk molecules per se, but that certain criteria might define high-risk mAbs that require particular precautions.

Such precautions could include enhanced non-clinical development before human

testing, including extensive elaboration of the starting dose and the safety margin to be applied, and a sequential inclusion of patients or volunteers — at least for the first dosages within dose cohorts. Such criteria could be, firstly, an entirely new mechanism of action, secondly, the targeting of an epitope that lacks appropriate animal models, and, thirdly, a new type of engineered format of the mAb molecule where no experience exists (17).

Pivotal trials: something special?

In principle, the clinical requirements for mAbs are no different than the general requirements in the regulatory framework and respective clinical guidelines issued by the ICH or regulatory authorities. However, as already discussed above, mAbs show peculiarities based on their complex molecular nature, the composition of the drug product, including process- and product-related impurities, and the way they function. Therefore, the study design will need to reflect these peculiarities.

Such measures might be deduced from theoretical considerations based on the putative mechanism of action. In addition, they should be derived from non-clinical observation. Also, seemingly unrelated findings in a relevant species could indeed be a particular safety signal occurring as a result of unknown pharmacodynamic effects. Other factors based on the “threesome” principle should be considered as already described.

Experience with natalizumab (Tysabri®) which is directed against alpha4-integrins on T cells, also shows how mAbs can act in an unwanted manner. Integrins are heterodimeric cell adhesion molecules with multiple roles in foetal development, immune reactions, leukocyte migration, haemostasis, and tumour biology (18). T cells circulating in the blood adhere to vascular endothelium by interaction of alpha-beta integrins on their surface (19). T cell migration into brain parenchymal tissue is mediated by a distinct subtype of these integrins, alpha4-beta1 integrin (20) which led to the idea of inhibiting T cell migration in diseases where T cells are considered key mediators, such as multiple sclerosis (MS), the most common inflammatory autoimmune disease of the central nervous system (21).

First clinical data from MS patients dosed with natalizumab for 6 months revealed a nearly complete inhibition of inflammation (22). This clinical benefit was reflected in pivotal phase III clinical trials demonstrating a significant reduction of relapse rate and delay in progression of disability as measured by Expanded Disability Status Score after 2 years of treatment (23). Based on one-year data demonstrating relapse rate reduction, the US Food and Drug Administration (FDA) granted accelerated approval of Tysabri® in November 2004 for the treatment of MS. However, in February 2005 the marketing authorization holder announced a voluntary suspension of marketing due to the occurrence of a serious unexpected adverse event, progressive multifocal leucoencephalopathy (PML).

PML is a rare, non-inflammatory demyelination of the CNS white matter (24), mediated by reactivation of a polyoma virus. PML is mainly seen in patients with severe immunosuppression. Under treatment with Tysabri®, this event evolved in two patients in long-term MS trials, both treated concomitantly with a beta-interferon (25, 26). One of the patients died, and one survived with severe disability. The most probable explanation on how PML could have occurred in the two patients is that the mAb potently suppresses migration of any T cell into the brain, including pathogenic autoreactive cells and circulating T cells.

As a consequence, reactivation of viruses might have become insufficiently controlled by lack of physiological T cell surveillance, and could have led to the development of PML. No other case of PML was found in the other patients, despite a retrospective case of a patient who had died of PML in a clinical trial of Crohn disease (27). Based on clinical efficacy in MS and medical need in these patients, EMEA’s Committee for Medicinal Products for Human Use (CHMP) issued a positive opinion in April 2006, recommending a marketing authorization for Tysabri® in a very restricted patient population with severe disease (28).

Clinical investigation of mAbs may need to be enhanced by more specific safety measures to detect and further characterize potential safety signals. Safety signals may not be that

prominent, but could still have significant impact on the benefit-risk of a mAb in the treatment of patients. Therefore, companies developing mAbs are well advised to proactively implement safety measures. The identification of a safety problem does not necessarily mean that a mAb is not suitable for the treatment of a particular disease. For natalizumab, a marketing authorization was finally granted based on a well-defined restriction of the patient population. Such safety measures might include risk management systems, educational programmes including algorithms for the detection of opportunistic infections, or patient alert cards.

The second lesson that can be learnt from the natalizumab case is that unwanted safety problems may occur only after longer-term treatment. Therefore, longer-term clinical safety data would be required for marketing authorization of drugs intended for non-life threatening diseases. This might also apply to mAbs that are not developed for chronic treatment, since an effect can last for a considerable time even after discontinuation. While long-term follow-up of patients withdrawing from trials might be difficult to organize, it is nevertheless an important tool to better characterize the safety profile of mAbs, and will also help the sponsor to better position the drug within the therapeutic cascade of a given disease.

Conclusion

MAbs are innovative molecules that show peculiarities both with regard to their biotechnological character and manufacture, and the way they function. As such, the entire development programme needs to take into account specific considerations focusing on a holistic approach and to unite quality, non-clinical and clinical expertise with a high safety standard in clinical trials. In many ways, mAbs have revolutionized modern medicine with their unprecedented efficacy. However, as recent experience shows, they can also demonstrate highly undesirable side effects. Specific measures can be implemented that nevertheless allow for a relatively safe administration of such drugs to specific patient populations.

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Improving world health through regulation of biologicals

On the occasion of the International Conference of Drug Regulatory Authorities (ICDRA) held in Seoul, Republic of Korea, 3-6 April 2006, a pre-meeting was organized on *Improving world health through regulation of biologicals*. Discussion centered on appropriate approaches and mechanisms for assuring the quality, safety and efficacy of biological medicines. Participants included representatives of national regulatory authorities, manufacturers and academics involved in the development of biological products, particularly from developing countries.

Development of biological medicines has been extremely rapid in recent years and the potential of such products for improving health care on a global scale is immense. However, there is an urgent need to match technological advances with appropriate mechanisms for assuring the quality of these products. This is particularly challenging for biologicals, since national authorities require specialized expertise and advice, and such resources may not always be readily available.

WHO has therefore developed long and medium term approaches to strengthening and building the capacity of national regulatory authorities, national control laboratories and biological manufacturers, and this has been successful in several countries. However, additional efforts are still required to develop, sustain and build strong and independent oversight and ensure international standards of compliance by manufacturers. Cost effective approaches — mutual recognition, sharing experiences, harmonization, networking, contracting external expertise, targeting critical functions, developing quality assurance systems, self assessment and development of institutional plans — need to be fully promoted to sustain these efforts.

A review of the relevant issues, sharing of up-to-date information, and exchanging country and success story experiences are important steps to achieving these goals. In order to reflect growing needs and challenges, the meeting was divided into the following sessions: *Biological medicines, Issues related to vaccine regulation, Issues related to the regulation of blood products*, and *Strengthening regulation of bioligicals*. Highlights from the various presentations made during the meeting are set out below while the full report can be accessed at http://www.who.int/biologicals.

Key outcomes of the meeting were:

1. Enhanced understanding of the challenges involving quality assurance of biological medicines, and possible solutions.

2. Increased recognition of the importance of appropriate regulatory oversight for biological medicines.

3. Constraints or concerns that need to be addressed to assure the quality of biological medicines.

Biological medicines

Regulation of biological medicines

Biologicals are increasingly sophisticated and complex. The past 25 years has seen an explosion in molecular biology and bio-production methods. This has opened new possibilities for disease diagnosis, treatment and prevention and for the role of biological medicines as major contributors to global health. The sector is undergoing a considerable period of growth with a range of biological products which includes hormones, animal-derived sera, vaccines, plasma products, blood and blood components, in vitro disgnositics, rDNA products (such as monoclonal antibodies), allergenic extracts, gene transfer products, cells, tissues and organs.

As can be seen, biologicals comprise a diverse group of products sharing common regulatory concerns of quality, safety and efficacy which require special attention and continuous vigilance. Biologicals differ from chemical drugs. They are highly complex in molecular terms and cannot be characterized by physicochemical means alone. Biologicals therefore need special regulatory attention and a science-based regulatory system before being allowed on the market.

To support regulatory systems in developing countries it is essential to strengthen international approaches to regulation and regulatory collaboration. WHO provides leadership, guidance and support for biologicals of assured quality.

Regulatory research

Regulatory research plays an essential role in supporting the development and accessibility of biologicals. Innovative product development can be facilitated by the establishment of clear and predictable regulatory pathways and guidelines based on science. Critical path adherence can improve, for example, characterization of products and safety outcomes, toxicological approaches, new assays, standards, biomarkers, multipathogen and rapid detection methodologies, enhanced clinical trial design, and storage conditions.

Regulatory research benefits public health by fostering more rapid availability of safer and more effective products. Public health challenges, such as rapid development of pandemic influenza vaccine, can benefit from regulatory and scientific tools and guidance which help to improve manufacturing capacity and speed of response.

Challenges of gene therapy medicinal products

Gene therapy represents a change in paradigm through manipulating the genome as a medicinal product. The benefits to individual patients are potentially profound. The first applications of gene therapy have now been reported. However, unintended non-target effects of the vector or of the inserted gene have occurred in some patients

Since the technology is highly complex, the theoretical risks of unintended effects extend not only to the patient under treatment but to the entire population. This type of product thus requires sophisticated regulatory oversight. The European Union has set up an Expert Working Group and has introduced legislation for gene therapy product definition and technical requirements.

Challenges of regulating cells and tissues

There is an increasing demand for cells and tissues fuelled by accelerated development of cellular or tissue engineered products. These can be derived from stem cells, musculoskeletal, ocular, or reproductive tissue.

Public expectations of safety are high and regulation should be in place for emerging technologies involving processing and manipulation of human cells and tissues. Different levels of regulatory activity are appropriate for different types of cell, tissue and cell based products — ranging from regulation of the facility for banking tissues through to full marketing authorization for tissues that are manipulated or combined with devices or other biologicals.

Cell therapies hold great promise but are not without challenges. Quality systems, traceability, development of rapid tests and suitable measures for quality, safety and efficacy are needed. Flexibility and new approaches to exercise independent batch release testing by authorities for these types of product is essential.

Biosimilars

Biosimilars are also known as biogenerics, follow-on-biologics, or similar biological medicinal products. These products are copies of biopharmaceuticals that can be made after the patent on the original product has expired.

Biopharmaceuticals have a well established role in controlling chronic diseases, in particular, and have sometimes been described as the key to the future of the healthcare industry. In many countries healthcare costs are increasing dramatically and generic biotechnology products could provide a solution.

An important challenge in regulating this sector is how to prove that the copies of

biopharmaceuticals are as safe and efficacious as the original product. At present, there is relatively little regulatory advice available and guidance from WHO would be extremely useful. As a priority objective, countries should commit to ensuring that there is appropriate independent regulatory oversight of biosimiliars.

Issues related to vaccine regulation

Global perspectives on vaccine safety

Vaccines are amongst the most useful means of disease prevention. However, as the incidence of a disease declines in a well vaccinated population, there is added focus on the adverse events associated with the vaccine and safety becomes a more prominent issue. Appropriate scientific and communication strategies are needed to pre-empt such concerns. The role of WHO is to provide scientific leadership and spearhead collaboration and access to technical expertise.

The role of vaccine safety monitoring is to collect data and provide a description of the risk factors and anticipated severity of reactions. Such risks, besides action of the vaccine, may involve adjuvants, vectors, additives and the devices used for administration. Finally, events should be assessed in relation to the context in which the reporting took place.

Currently there is inadequate monitoring of safety in some countries after the introduction of new vaccines. Post-marketing studies are essential both for further safety evaluation and to extend effectiveness assessments — particularly where a vaccine has been licensed on the basis of an immune correlate of protection.

Regulatory action in emerging diseases

Early in the course of the SARS outbreak, representatives from all sectors of the Chinese regulatory system were brought together in a newly formed response group which met weekly. Issues of importance in this emergency situation were identified as:

- Government support.
- Preparedness for pandemic vaccine development.
- Availability of expertise.
- Cooperation among the parties, including regulators, manufacturers, quality control laboratories, and investigators.

WHO was able to provide valuable input through organization of conferences and workshops. This international collaboration proved to be essential in the control of SARS. It soon became evident that international regulatory cooperation is needed, even if the disease is in one, or only a few countries, because of the possibilities of rapid international spread across borders and through international travel.

Outputs from this emergency situation were development of a diagnostic kit for SARS, specific immunoglobulin, and approval for a phase I study of inactivated vaccine.

Issues related to the regulation of blood products

Safety assessments and regulatory issues in blood products

Three principal complementary approaches are required to control potential viral contamination of blood products:

- selecting and testing source material for the absence of viruses;
- testing the capacity of the production processes to remove or inactivate viruses; and
- testing the product at appropriate stages of production for freedom from contaminating viruses.

This strategy requires that screening tests are also appropriately validated and controlled through independent evaluations performed by the regulators. In vitro diagnostics are important for the detection of the infectious agent, thereby preventing transmission of blood-borne pathogens and avoiding transmission chains. The principles of independent evaluation of in vitro diagnostic devices focus on verification of documents, laboratory control, and official batch (lot) release.

Potential viral contamination can be controlled or removed through complementary approaches focused on:

- selection of source material for the absence of viruses.
- testing capacity of production processes to remove viruses.
- testing the product at appropriate stages of production for freedom from contaminating viruses.

Rapid responses to emerging agents affecting blood product safety

Preparedness for emerging infections is the key to successful response. The infrastructure needed to address emerging infectious disease threats includes an effective surveillance system, capacity for epidemiological investigations, laboratory capability, risk assessment tools, communication mechanisms and control activities.

For example, in the US response to West Nile virus, appropriate risk communication with the public was found to be crucial, while cooperative interaction between government, blood organizations and device manufacturers led to the rapid development of experimental nucleic acid amplification tests that were widely used in blood screening. One such test has since been licensed.

Detailed knowledge of the epidemiology and biology of the infectious agent helps design optimally effective policy. An example was the introduction of individual donation testing for West Nile virus in high incidence areas of the USA to detect low level viraemic donations that would have been missed if only pooled donation testing was used.

In conclusion, multiple regulatory approaches are needed to ensure blood safety. Predominant is the value of collaboration between regulators, blood organizations and device manufacturers.

Role of post-marketing surveillance of blood products

Blood products include plasma-derived medicinal products as well as blood components for transfusion. In France, pharmacovigilance and haemovigilance constitute the tools for ensuring blood and blood product safety. However, to be effective it is necessary to have a well structured notification system which is well standardized and to apply the principles of traceability.

Traceability should work in at least two directions; when a recipient develops a disease it is important to know whether other patients exposed to the same batch(es) have experienced the same event. Also, when a donor is found, post donation, to have developed a condition that potentially could be transmitted through the donation, to recall (if necessary) the product and inform any other recipients of the potential risk. There may be three conditions affecting safety: microbiological contaminants and agents, degradation or loss of efficacy, and adverse drug reactions due to, for example, immunogenicity.

To ensure safe products the following key points need to be addressed:

- Quality control of the starting material.
- Quality management of the production/ supply chain, with adequate processes to remove or inactivate the contaminating agent.
- Viral safety management.
- Post-marketing surveillance.

Risk-based approach to biologicals and blood products regulation

Australia and New Zealand are committed to developing a joint regulatory authority, and this will result in harmonized regulatory measures for the two countries. A new framework for blood and other biological products will be introduced through the new agency.

Within this framework, organs harvested from cadaveric donors will, for the first time, be regulated under a risk-based tiered approach in both countries where the level of regulation (in terms of review and compliance assessment) is linked to the level of risk from biological involvement and therapy. Human cells that have been isolated, manipulated, preserved and reinfused carry the highest regulatory burden under the proposed new scheme.

As a result of regulatory harmonization provided by uniting the agencies, risk based regulation of these products will ensure appropriate levels of safety, quality and efficacy while nurturing innovation and facilitating access.

Strengthening regulation of biologicals

Strengthening regulation of biologicals in a producer country

Strengthening regulatory functions for biologicals in the Republic of Korea has followed WHO policy as follows:

- A published set of clear requirements for licensing;
- Surveillance of vaccine performance in the field;
- A lot release system ;
- Access to a laboratory;
- Regular GMP inspection of manufacturers; and
- Evaluation of clinical performance through authorized clinical trials.

Lot release of biologicals requires extensive laboratory facilities and resources, including the use of large numbers of animals.

In the Republic of Korea, inspection of manufacturing facilities for compliance with GMP is performed both for domestic companies and overseas. A government funded regulatory research programme has been developed and projects include the establishment of national biological reference materials calibrated against WHO or regional standards.

International collaboration is considered an important activity both through WHO and also through bilateral agreements supported by government and international development funds. A global training network set up by WHO consists of 13 training centres throughout the world. Within this network, the Korea Food and Drug Administration is involved in GMP and GCP evaluation activities.

A changing landscape

Export of biologicals by developing country manufacturers will help to address increasing health care costs. Currently, drug development and research is being undertaken by enterprises staffed by scientists trained in the developed world. However, developed country manufacturers are increasingly outsourcing biologicals production to developing countries.

Experience with products manufactured for local use builds confidence that can then be used to support entry onto the export market. In this context, a single harmonized regulatory standard should be applied to all products whether for local use or export.

Developing countries are exporting a variety of traditional biologicals (vaccines and blood products) and also recombinant biologicals and biosimiliar products. In this respect, WHO prequalification is a tremendous help in gaining acceptance for exported products, although at present the system is only applicable to products supplied through UN agencies. Confidence in national regulatory oversight is enhanced through external audits such as those provided by WHO assessments, or by the GMP inspectors from importing countries.

Government investment in an appropriate enabling environment for drug development should include support of the regulatory regime. Furthermore, effective systems are needed to share information on post-marketing data for products that have been exported.

Appropriate regulation of biologicals in an importing country

In South Africa, most registered biological medicines are imported, with the exception of blood products that are manufactured locally. Biologicals regulation represents a relatively small subset of resources within the regulatory authority.

A common set of problems for regulatory oversight of biologicals exists. Among these, is the small pool of experts available locally to provide support to the regulatory process. Also, the country has a unique set of health problems and policies which can only be addressed with local understanding of the issues. Because of the restricted numbers of local experts, these may also be involved in studies with sponsors. A significant problem therefore exists with conflict of interest when trying to populate expert committees to support the local regulatory process. Furthermore, powerful industry and international bodies can sometimes influence local regulators disproportionately.

Regional cooperation and mutual recognition is seen as a way forward to strengthening capacity and to maintaining proper control of the regulatory process.

New regulatory paradigms for biologicals and vaccines: an industry perspective

A viable research and development based pharmaceutical industry requires a regulatory environment that facilities access to safe and effective products in a timely manner.

Vaccines innovation is accelerating and a wide range of products are under development with novel technologies that bring new regulatory challenges. Also, companies are encouraged to invest in products that will be of relevance to developing country markets.

The environment is changing — with an industry that is working globally — and the following issues are recognized as strategically important.

- Challenges to global development of biologicals are increasing due to different national and local requirements and procedures which may lead to duplication of effort and wastage of animal and human resources.
- Strengthening of NRAs (national regulatory authorities) is essential and more authorities are expected to strive for excellence and leadership in biologicals regulation, but it is necessary to encourage harmonization across countries and regions as this happens.
- Predictability in the regulatory process across countries is a critical factor for the industry and the use of a common technical dossier is a good example of beneficial harmonization.
- Different categories of regulatory authorities exist worldwide and WHO guidance on the functions of NRAs in different circumstances is very helpful.
- A wider range of countries are conducting regulatory inspections, so that consideration should be given by inspectorates to communicating outcomes with each other, especially on a regional basis to maximize efficiency and use of regulatory resources.
- Other examples where regulatory collaboration and networking would be beneficial are clinical trials, lot release, and harmonization of regulatory requirements.
- Multiple regulatory harmonization initiatives are in progress globally, but few of the initiatives have full involvement of industry and there is a risk of parallel processes leading to de-harmonization rather than harmonization. To address this issue, increased dialogue between industry and regulators is required so that harmonization can proceed in a way that enhances access to information for developing country regulators.

Vaccine clinical trials and marketing applications

New vaccines or vaccine combinations are being developed that target diseases more prevalent in less developed countries. For any of these products to be first-licensed in developing countries, NRAs need to expand their expertise and proficiency in vaccine evaluation and develop new areas of competency.

Various approaches to achieve proficiency can be used, including exchange of experience with NRAs at a similar level of development. The WHO Developing Country Vaccine Regulators Network is an example of how this can be achieved at the global level. A regional initiative has also been established by WHO's Office for the Americas (PAHO) which focuses on capacity building activities and evaluation of a novel rotavirus vaccine. This initiative has now been extended to cooperative pharmacovigilance evaluation of the rotavirus vaccine after introduction into national immunization programmes.

Results of collaboration show that developing countries often have different questions or concerns compared to developed countries during the review process of a product. Incorporating a developing country perspective into future regulatory strategies for new products is an important lesson to be learnt from this experience.

Need for regional networks of regulators for blood products

A regulatory framework for blood and blood components was established in Cuba in 1994

and has resulted in the introduction of additional controls of viral markers at appropriate stages of the process.

WHO cooperation has been helpful to develop technical capacity in the country and in the region through workshops on quality assurance of plasma derived products and also on need for GMP in blood collection establishments. Workshops have been organized which have enabled countries to identify needs to strengthen blood and blood derivatives regulation through regional harmonization of guidelines for GMP in blood establishments, inspection procedures and training of GMP inspectors.

Access to animal derived sera for therapeutic use

Shortage of animal derived sera is an urgent public health issue. The world is at imminent risk of lacking effective treatment for rabies, envenomation and other serious treatable conditions because products from large scale manufacturers are no longer available and there is a decreasing number of small scale manufacturers.

WHO support to increase access to safe products includes strengthening GMP production of antisera and supporting the evaluation of viral validation studies for manufacturing steps. It is also proposed to establish a prequalification system for antisera products and develop guidance and training materials for proper management of these diseases.

National control laboratory testing of biologicals

Laboratory testing supports different regulatory functions, including licensing, clinical evaluation, lot release, and postmarketing surveillance. Lot release consists at a minimum of review of the summary lot production protocol but in producing countries this should be supplemented by selected laboratory tests.

Major needs for national control laboratories (NCLs) include method validation for new products and this is particularly difficult for imported vaccines if there are no international reference materials. Collaboration between the company and the NCL is particularly important for testing of biologicals. However, this link is sometimes weak, especially in developing countries.

The establishment of NCL networks has demonstrated benefits and is to be encouraged since such networks can overcome the constraints NCLs are currently facing.

Testing of antivenoms

Antivenoms against a group of related snakes found in three countries — Japan, Republic of Korea, and China — are produced on a small scale of around 3500 vials per year in each country. Antivenoms are produced by immunization of horses with crude venom extract and preparation of antisera.

Quality control tests include potency testing with bioassays for anti-toxin activity and anti-haemorrhagic activity. The three countries have formed an initiative to develop a regional working standard for use in these assays.

Biological reference preparations

Biological assays are comparative in nature and international biological reference preparations are essential to standardize measurements across countries and across time.

When candidate standards are evaluated during international collaborative studies, participating centres benefit through feedback on their own performance compared to other laboratories. Ensuring the participation of developing countries in the standard setting process is therefore a high consideration and assists in the promotion and implementation of international standards.

Safety and Efficacy Issues

Global progress in monitoring immunization adverse events

A WHO consultation on Global Monitoring of Adverse Events following Immunization was held from 9 to 10 January 2006 in Geneva. The meeting was held in response to greater political interest in patient safety and the importance of pharmacovigilance to public health programmes.

The overall objective of the meeting was to make recommendations on building a high-quality global monitoring system. Discussion focused on ways to:

- improve the quality and comprehensiveness of the reporting of adverse events by countries to the WHO Programme for International Drug Monitoring;
- strengthen communication and exchange mechanisms between national pharmacovigilance centres, national regulatory authorities and managers of immunization programmes and other surveillance departments at country level;
- improve the handling and analysis by the WHO Programme for International Drug Monitoring of adverse events following immunization for rapid signal identification and action.

Currently, only 35% of WHO's 192 Member States have an adequately functioning system for monitoring adverse events following immunization. WHO can provide direct technical support and advice for strengthening monitoring, building capacity for national regulatory authorities, providing training and technical documents as well as helping countries develop these documents. Specific initiatives designed to support global monitoring and investigative capacity as well as to communicate vaccine safety issues include the Vaccine Safety Net project, a proposal to establish a network of sentinel countries to monitor the effectiveness and safety of newly introduced vaccines, and collaboration with other partners and initiatives.

Key recommendations were agreed on improving reporting of immunization-related adverse events: resources and methods for reporting and analysis: and advocacy and collaboration.

Reference: WHO consultation on Global Monitoring of Adverse Events following Immunization, 9–10 January 2006. *Weekly Epidemiological Record*, 2006;**81**:261-5.

Intracranial haemorrhage in patients receiving tipranavir

Canada — The manufacturer of tipranavir (Aptivus®) has informed health care professions of important new safety information. Tipranavir co-administered with low-dose ritonavir is indicated for combination antiretroviral treatment of HIV-1 infected adult patients with evidence of viral replication who are treatment-experienced and have HIV-1 strains resistant to multiple protease inhibitors.

As of 7 June 2006, the manufacturer has received 14 reports of intracranial haemorrhage, including 8 fatalities, in 6840 HIV-1 infected patients receiving tipranavir in clinical trials. Many of the patients experiencing intracranial haemorrhage in the clinical trials had other medical conditions (CNS lesions, head trauma, neurosurgery, coagulopathy, hypertension or alcohol abuse) or were receiving concomitant medications, including anticoagulants and antiplatelet agents, that may have caused or contributed to these events.

Tipranavir has been observed to inhibit human platelet aggregation during in vitro experiments at levels consistent with concentrations observed in patients receiving tipranavir/ritonavir. No pattern of abnormal haematologic or coagulation parameters which might predict increased risk of intracranial haemorrhage has been observed in patients preceding the development of intracranial haemorrhage.

Tipranavir /ritonavir should therefore be used with caution in patients who may be at risk for increased bleeding from trauma, surgery or other medical conditions, or who are receiving medications known to increase the risk of bleeding, including antiplatelet agents or anticoagulants.

Reference: Letter dated 29 June 2006. http://ww.boehringer-ingelheim.ca

Infliximab: hepatosplenic T cell lymphoma

Canada — The manufacturers of infliximab (Remicade®) have informed health care professionals of important new safety information.

Infliximab is a chimeric IgG monoclonal antibody known as a biological response modifier that is directed against the cytokine tumour necrosis factor-α (TNFα**)**. It is indicated for the treatment of adults with rheumatoid arthritis, ankylosing spondylitis, Crohn disease, ulcerative colitis, psoriatic arthritis, and chronic plaque psoriasis. Infliximab is not authorized for paediatric use in Canada.

Six post-marketing cases of a rare type of lymphoma called hepatosplenic T cell lymphoma (HSTCL) have been reported in paediatric and young adult patients taking infliximab for Crohn disease. Exposure ranged from 1 or 2 infusions to over 4 years of maintenance therapy, and five of the six cases resulted in death. All cases reported concomitant or past use of other immunosuppressive agents, including azathioprine or 6-mercaptopurine. As a result, a causal relationship between infliximab and the development of HSTCL has not been clearly established. All reports originated from the United States, and one report was recently published in the literature.

This disease is a very rare form of non-Hodgkin lymphoma, which occurs most commonly in adolescent and young adult males, and there are only 150 cases published in the medical literature worldwide since the disease was first described in 1990. Both azathioprine and 6-mercaptopurine are known mutagens, and azathioprine has been classified as a human carcinogen.

In Canada, approximately 38 000 patients have received infliximab since its launch in 2001, with 16 000 patients having received the product for Crohn disease. In Canada there have been no reports of HSTCL.

Reference: Dear Health Care Professional Letter from Centocor, Inc. and Schering Canada, dated 24 July 2006, available at http://www.hc-sc.ca

Lamotrigine: increased risk of non–syndromic oral clefts

Canada — The manufacturer of lamotrigine (Lamictal®) has informed health care professionals of important new safety information.

Emerging data from the North American Antiepileptic Drug (NAAED) Pregnancy Registry suggest an association between lamotrigine and an increased risk of non-syndromic oral clefts over the reference population of the Active Malformations Surveillance Program at Brigham and Women's Hospital, Boston, USA (1). Recently published data from the Registry report three cases of isolated, non syndromic cleft palate and two cases of isolated, non syndromic cleft lip without cleft palate in infants.

To assist with the assessment of risk, analysis of data from additional pregnancy registries, with approximately 2200 additional lamotrigine monotherapy first trimester exposures has been conducted, and 4 additional non-syndromic cases of oral cleft have been identified.

Health-care professionals are reminded that patients should be advised to notify their physicians if they become pregnant or intend to become pregnant during therapy.

Reference: Dear Health Care Professional Letter dated 1 August 2006 from GSK at www.hc-sc.gc.ca

Bisphosphonates: osteonecrosis of the jaw

Australia — The Australian Adverse Drug Reactions Advisory Committee (ADRAC) has previously drawn attention to the problem of osteonecrosis of the jaw (maxilla or mandible) occurring in the context of treatment with

bisphosphonates (1) and further Australian cases have been published (2, 3). Up to June 2006 ADRAC has received 106 reports of this type, as shown below:

Zoledronate (IV)	69
Pamidronate (IV)	33
Alendronate (oral)	19
Risedronate (oral)	2
Clodronate (IV and oral)	1
Ibandronate (IV)	1

A recent review of 368 published case reports of osteonecrosis of the jaw found that 94% involved patients with multiple myeloma or bony metastases who were receiving intravenous bisphosphonates (4). A small proportion, however, involved patients receiving oral bisphosphonates for treatment of osteoporosis. This review also found that 60% of cases were preceded by a dental surgical procedure, usually dental extraction. The mechanism of osteonecrosis of the jaw is unknown. Bisphosphonates may impair bone vascularity or immune mechanisms which may be of particular importance in the jaw because of the bacterial flora of the mouth and repeated bacterial exposure with chewing. Bisphosphonate-induced reduction of bone turnover may cause adynamic bone and impair healing of the socket after tooth extraction (4).

Prevention is of the utmost importance (4). Accordingly, any patient being considered for bisphosphonate treatment should be informed of the symptoms of osteonecrosis of the jaw and, if they occur, to bring these to the attention of their dental practitioner. Health professionals should be aware of the presenting clinical features of this condition, which include altered local sensation (hyperaesthesia or numbness), maxillofacial pain, "toothache", denture sore spots, loose teeth, exposed bone in the oral cavity, impaired healing, recurrent or persistent soft tissue infection in the oral cavity, and marked oral odour. The onset can be from months to years after commencing bisphosphonate therapy. The risk of osteonecrosis is significantly increased after dental extraction (4).

Extracted from Australian Adverse Drug Reactions Bulletin, Volume 25, Number 4, August 2006

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Enoxaparin dosage in chronic kidney disease

Australia — Although low molecular weight heparins (LMWH) are a convenient and effective alternative to unfractionated heparins, it is important to remember that LMWH, such as enoxaparin, also have associated risks. LMWH have a longer half life than unfractionated heparins, their anticoagulant effect is not routinely monitored, and their effects are harder to reverse in cases of bleeding. The clearance of enoxaparin is decreased in chronic kidney disease, hence the dose of enoxaparin should be reduced in this situation (1).

In 2005–2006, the Australian Adverse Drug Reactions Advisory Committee (ADRAC) received 10 reports of death associated with haemorrhage after the use of enoxaparin, bringing the total to 46 since 1997. In three of the reports received in 2005, patients with chronic kidney disease received inappropriate doses. Two of the reports also implicated an incorrect dose for the weight of the patient. Other risk factors include use of other anticoagulants, age (neonates, children, and the elderly), pregnancy and extremes of body weight (2, 3).

Before commencement of LMWH therapy, the patient's renal function should be assessed. In patients with severe chronic kidney disease (GFR < 30 mL/min), requiring therapeutic anticoagulant doses, the dose of enoxaparin should be reduced from 1 mg/kg twice daily or

1.5 mg/kg once daily to 1 mg/kg once daily (1). An alternative is to use unfractionated heparin with dose monitoring by aPTT. Similarly, in patients with unstable or deteriorating renal function, unfractionated heparin is preferred (2). Where there is a high bleeding risk, such as in the post-operative period, unfractionated heparin is preferred, since rapid and complete reversal of anticoagulation can be achieved. If there is a high probability of proceeding to surgery in the next 5 days (including for coronary angioplasty), unfractionated heparin with the usual aPTT monitoring is advised.

Extracted from Australian Adverse Drug Reactions Bulletin, Volume 25, Number 4, August 2006

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Terbinafine and life–threatening blood dyscrasias

Australia — Oral terbinafine (Lamisil)® is indicated for severe ringworm unresponsive to topical treatment and onychomycosis in adults. Prescribers should be aware that there are three serious, albeit rare, reactions associated with oral terbinafine — white blood cell disorders, severe skin reactions and severe hepatotoxicity. These reactions have not been reported with topical forms of terbinafine (Lamisil® cream or gel).

The Australian Adverse Drug Reactions Advisory Committee (ADRAC) reminded health professionals of the association between oral terbinafine and blood dyscrasias in October 2004 (1). ADRAC has now received 16 reports of white blood cell dyscrasias with oral terbinafine, including agranulocytosis (7), neutropenia (7) and pancytopenia (2) from a total of 663 reports.

Patients taking terbinafine for longer than a month should be advised to be alert for any symptoms of possible infection/neutropenia, such as fever, sore throat or mouth ulcers. Total white blood cell count and neutrophil count should be checked if symptoms develop since a delay in diagnosis is likely to be associated with an increase in morbidity and mortality.

Extracted from Australian Adverse Drug Reactions Bulletin, Volume 25, Number 4, August 2006

Reference: ADRAC. Terbinafine and blood dyscrasias. *Aust Adv Drug React Bull* 2004;**23**:19.

Adverse reactions in children: why report?

Canada — Like other patients using health products, children are at risk of adverse reactions (ARs). In 2005, 7.3% of the domestic AR reports received by Health Canada described ARs associated with health products in patients 18 years and younger (excluded were reports in which age was not indicated). ARs reported in adults do not always predict ARs in children (1). Several factors help explain why a child's risk of an AR differs from that of an adult when taking the same health product. Some ARs are specific to the paediatric population because of the growth and development that children undergo (e.g., enamel dysplasia with tetracyclines, Gray syndrome with chloramphenicol), whereas other ARs occur in adults as well but are more common in children (e.g., dystonia with metoclopramide) (2–6).

Many health products used in paediatrics have not been developed and assessed specifically for this population and are prescribed to children outside the authorized indications listed in the product monographs (commonly referred to as off-label use) (2, 4, 5). Furthermore, clinical trials, which usually enrol adults, may not be a reliable measure in revealing the risk of ARs in the paediatric population.

Scientific evaluations of ARs in children are further complicated by the fact that there are fewer paediatric than adult patients in the general population (7). In addition, there are age-specific subgroups in the paediatric population that often require separate investigations; (7) during childhood physiologic changes take place that may have an impact on the pharmacokinetic processes and pharmacodynamic effects of a compound (2).

All of the above can result in a relative scarcity of prospectively generated safety information for health products prescribed to children (5, 7).

Therefore, voluntary reporting (4) can contribute to the identification of which types of health products are more likely to cause ARs in children (6). Spontaneous reporting systems may also uncover other types of health-product-related safety issues, such as drug abuse, unsafe drug use and the outcome of accidental drug exposure (Table 1: examples 6, 9 and 13).

The safe use of health products in children is a responsibility shared by various stakeholders, such as health care professionals, research communities, manufacturers, regulatory agencies, and parents and caregivers. Parents and caregivers need to be informed of the benefits as well as potential safety issues related to health products and be encouraged to report any observations to their health care providers to enable better monitoring for possible ARs. The prevention of ARs is highly dependent on communication by health care professionals (8).

Extracted from Canadian Adverse Reactions Newsletter. Volume 16, Issue 3, July 2006

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Table 1: Examples of paediatric safety issues reported in the Canadian Adverse Reaction Newsletter (CARN) from 1991 to 2006

1	Iodoquinol: suspected association with hypertensive encephalopathy and seizures July 2006;16(3)
2	Extended-release methylphenidate (Concerta) withdrawal: suspected association with priapism July 2006;16(3)
3	Isotretinoin (Accutane): myocardial infarction, cerebrovascular and thromboembolic disorders April 2006;16(2)
4	Overnight orthokeratology and Acanthamoeba keratitis April 2006;16(2)
5	Intrathecal baclofen (Lioresal): suspected adverse incidents associated with implantable drug pump system October 2005;15(4)
6	Transdermal fentanyl (Duragesic): abuse in adolescents July 2005;15(3)
7	Ibuprofen: Stevens-Johnson syndrome July 2005;15(3)
8	Ceftriaxone (Rocephin) and immune hemolytic anemia in children January 2005;15(1)
9	Transdermal fentanyl (Duragesic): respiratory arrest in adolescents October 2004;14(4)
10	Sterol and sterolin-containing products: hematologic adverse reactions April 2004;14(2)
11	Fluticasone and adrenal suppression October 2003;13(4)
12	Ibuprofen pediatric oral liquid: gastrointestinal bleeding January 2002;12(1)
13	Brimonidone (Alphagan) ophthalmic drops: accidental ingestion October 2001;11(4)
14	Pemoline (Cylert): market withdrawal January 2000;10(1)
15	Isotretinoin and depression January 1999;9(1)
16	Cefaclor-associated serum sickness-like reaction October 1996;6(4)

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Hepatitis B reactivation and anti–TNF–alpha agents

Singapore — Three anti-tumour necrosis factor alpha (anti-TNFα) agents are registered in Singapore — etanercept (Enbrel®) adalimumab (Humira®) and infliximab (Remicade®). These products are indicated for the treatment of rheumatoid arthritis, with Remicade® having additional indications for Crohn disease and ankylosing spondylitis.

Anti-TNFα agents exert their actions by binding to human TNF, which are proinflammatory and immunoregulatory cytokines. When TNF are overexpressed, they mediate chronic inflammation.

Rare cases of hepatitis B virus (HBV) reactivation have been reported in patients receiving anti-TNFα therapy. From 2003 to date, there are at least seven published cases of HBV reactivation associated with the use of these products (1–6). These seven patients were positive for HBV surface antigen prior to anti-TNFα treatment and the clinically active HBV infection occurred following a latency period ranging from 1–18 months after initiation of anti-TNFα therapy (mainly with infliximab). With the exception of one fatal case, the HBV conditions were controlled with discontinuation.

The Health Sciences Agency (HSA) has not received any local report pertaining to HBV reactivation associated with the use of these products.

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Dolasetron mesylate and serious cardiovascular reactions

Canada — The label for dolasetron mesylate products has carried warnings about QTc prolongation and the description of serious cardiovascular adverse reactions since approval in 1997. Although dolasetron has never been indicated for use in children in Canada, Health Canada is aware of the off-label use of this product in the paediatric population. Health Canada is also aware of the off-label use of dolasetron in adults for the treatment of post-operative nausea and vomiting. Dolasetron is only indicated for the prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including high dose cisplatin, in adults.

Health Canada is requesting all manufacturers of drugs in this class to conduct thorough analyses of their safety databases. Following review of these data, Health Canada will take action as appropriate. At this time, health care providers are requested to strictly adhere to the dosing recommendations in the product monographs of these drugs.

Reference: Health Canada Advisory dated 23 June 2006, available at http://www.hc-sc.gc.ca

Valproic acid and pancreatitis in a child

Malaysia — The Malaysia Adverse Drug Reactions Advisory Committee (MADRAC) has received a report of a 3 year-old girl who who was suspected to have developed pancreatitis as a result of the use of sodium valproate which was prescribed to manage her epilepsy.

The child presented with vomiting, abdominal tenderness and poor oral intake which was attributed to loss of appetite. The child had been taking sodium valproate syrup 100 mg twice daily but the exact duration was unknown. On admission, the laboratory findings were suggestive of acute pancreatitis and a

laprotomy was done which confirmed the diagnosis. Sodium valproate was stopped and the patient was switched to clonazepam syrup and subsequently recovered.

Valproic Acid has been used extensively as one of the primary anticonvulsants for generalized seizures in children for the past 25 years. It has been stated that drug induced pancreatitis is thought to account for 2–5% of cases of acute pancreatitis with as many as 13% of paediatric cases of acute pancreatitis being drug induced (1, 2).

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Safety updates

Singapore — The Health Sciences Agency (HSA) has approved the following package insert changes as aa result of safety updates from January to March 2006. They are also listed at http://www.hsa.gov.sg/cda/labelchanges. Please note that there might be some lag time in the availability of the package insert which reflects the latest change(s).

1. Calcitriol (Calcijex®)
Under "Precautions", it is stated that use of vitamin D analogs & cardiac glycosides may result in cardiac arrhythmias. Its effects may be reduced in patients taking barbiturates or anticonvulsants. Corticosteroids may counter the effects of vitamin D analogs. Rare cases of hypersensitivity reactions including anaphylaxis and localized redness or pain at injection site have been reported.

2. Clarithromycin (Klacid®)
Contraindicated with concomitant use of ergotamine or dihydroergotamine. Under warnings, clarithromycin should only be used in pregnancy after risk/benefit assessment. Pseudomonas colitis is possible with clarithromycin/macrolide therapy. It is cautioned that cross-resistance between clarithromycin and other macrolide drugs is possible. Some new drug interactions include that with HMG-CoA reductase therapy, cisapride, pimozide, quinidine, disopyramide, colchicine and ritonavir.

New ADRs include hypoglycaemia in patients on oral hypoglycaemic agents or insulin, leucopenia and thrombocytopenia, ventricular tachycardia, Torsades de Pointes, pancreatitis, convulsions and interstitial nephritis.

3. Ciclosporin (Gengraf®)
New drug interactions documented with colchicine, quinopristin/dalfopristin, amiodarone, orlistat & St John's Wort. Ciclosporin potentially enhances the toxic effects of colchicine especially in patients with renal dysfunction. Close monitoring is required in patients concurrently taking digoxin or colchicine. Myotoxicity has been reported with concomitant administration with HMG-CoA reductase inhibitors.

4. Daunorubicin (Daunorubicin®)
Contraindicated in pregnancy. New safety information added to the sections on cardiac toxicity and bone marrow depression. Significant hepatic or renal impairment can enhance the toxicity of recommended doses of daunorubicin. A rise in blood urea or uric acid can also occur with rapid destruction of leukaemia cells. Monitoring is thus required. Drug interaction includes vaccines and live virus.

5. Fluticasone (Flixotide®)
Very rare cases of increased blood glucose levels reported. Ritonavir (a CYP3A4 inhibitor) can greatly increase fluticasone propionate plasma concentrations resulting in markedly reduced cortisol concentrations, Cushing syndrome and adrenal suppression. Caution should be exercised when CYP3A4 inhibitors e.g. ketoconazole are coadministered with fluticasone.

New ADR terms include respiratory symptoms, anaphylactic reactions, Cushing's syndrome, adrenal suppression, hyperglycaemia, behavioural changes, hyperactivity and irritability n children.

6. Lidocaine, Prilocaine (Emla Cream®)
Patients with G6PD deficiency or congenital or idiopathic methaemoglobinaemia are more susceptible to drug induced methaemoglobinaemia; and if eye contact occurs, loss of

protective reflexes may allow corneal irritation and potential abrasion. Patients treated with anti-arrhythmic drugs class III (e.g. amiodarone) should be under close surveillance and ECG monitoring as cardiac effects may be additive. The results of intracutaneous injections of live vaccines (e.g. BCG) should be monitored as lidocaine and prilocaine have bacteriocidal and antiviral properties in concentrations above 0.5–2%. Caution should be exercised when using Emla® in pregnant women.

7. Nimesulide (Nidol®)
Maximum dose is reduced to 100 mg twice daily. Some new contraindications include patients with a history of hepatotoxic reactions to nimesulide, cerebrovascular bleeding, severe coagulation disorders, severe heart failure, children under 12 years, third trimester of pregnancy and lactation. Avoid concomitant administration of hepatotoxic drugs and alcohol abuse. New drug interactions include valproic acid, lithium, methotrexate and ciclosporin.

8. Propafenone (Rytmonorm®)
Drugs that inhibit CYP2D6, CYP1A2 and CYP3A4 e.g. ketoconazole might lead to increased levels of propafenone. Propafenone should be used with caution in nursing mothers.

New ADRs include hepatitis, anorexia, syncope, hepatocellular injury, jaundice and lupus syndrome. New precautions added were: (1) Each patient should be evaluated electrographically and clinically prior to and during propafenone therapy to determine if the therapy is warranted; (2) Propafenone may worsen myasthenia gravis; (3) Propafenone may affect both the pacing and sensing thresholds of artificial pacemakers; (4) there is a predisposition of patients taking this class of drugs with significant structural heart disease to serious adverse events.

9. Ritonavir (Norvir®)
Pancreatitis has been observed in patients receiving ritonavir, including those who developed hypertriglyceridaemia especially patients with advanced HIV. New onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus and hyperglycaemia have been reported in HIV-infected patients receiving protease inhibitor therapy. In some cases, diabetic ketoacidosis occurred and in others, hyperglycaemia persisted despite removal of protease inhibitor.

Some new drug interactions include ritonavir with erectile dysfunction agents, herbal products and HMG-CoA reductase inhibitors. Cardiac and neurologic events have been reported when ritonavir has been coadministered with disopyramide, mexiletine, nefazodone, or fluoxetine. Some new ADR terms include myocardial infarction and menorrhagia.

10. Verapamil (Isoptin®)
New contraindications include congestive heart failure, atrial fibrillation/flutter and concomitant Wolff-Parkinson-White syndrome. Use with caution in patients with first degree AV block, hypotension, bradycardia and severely impaired liver function.

New ADRs include abdominal discomfort/pain, impotence and galactorrhoea. New drug interactions include quinidine, lithium, prazosin, midazolam, neuromuscular blockers, acetylsalicylic acid, ethanol, simvastatin/lovastatin and grapefruit juice.

11. Vinorelbine (Navelbine®)
Contraindicated in patients with neutrophil counts <1500/mm^3 or with current or recent severe infection. New precautions: (1) dose limiting neutropenia where treatment should be delayed till recovery if neutrophil count <1500/mm3 and platelet count <75000/mm3. (2) In severe liver impairment, dose should be reduced by 33% and haematological parameters closely monitored. (3) Combination of Navelbine® with other bone marrow toxic drugs (e.g. cisplatin) may exacerbate myelosuppressive adverse effects. A new list of ADRs has been added. Navelbine® should not be used in pregnant or lactating patients.

12. Fluoxetine (Prozac Dispersible®)
A new contraindication states that if fluoxetine has been prescribed chronically and/or at a high dose, a longer interval of discontinuation (>5 weeks) should be considered when switching to MAOI. Serious and fatal cases of serotonin syndrome have been reported in patients treated with fluoxetine and MAOI in close temporal proximity. It is warned that there is a possibility of suicide in depression

which may persist till significant remission occurs. Cases of suicidal ideation and behaviours have been reported during fluoxetine/antidepressant therapy or early after treatment discontinuation. Close supervision of high-risk patients is recommended.

Concomitant Ibuprofen and acetylsalicylic acid

United States of America — Healthcare professionals should be aware of interaction between low dose acetylsalicylic acid/aspririn (81 mg per day) and Ibuprofen which might render acetylsalicylic acid less effective when used for its anti-platelet cardioprotective effect.

Existing data using platelet function tests suggest there is a pharmacodynamic interaction between 400 mg ibuprofen and low dose aspirin when they are dosed concomitantly. The Food and Drug Administration (FDA) is unaware of data addressing whether taking less than 400 mg of ibuprofen interferes with the antiplatelet effect of low dose aspirin. For single doses of ibuprofen, the pharmacodynamic interaction can be minimized if ibuprofen is given at least 8 hours before or at least 30 minutes after immediate release aspirin (81mg; not enteric coated). The timing of dosing of ibuprofen and low-dose aspirin is important for preserving the cardioprotective effect of aspirin.

Recommendations for concomitant use:
Health care providers should counsel patients about the appropriate timing of ibuprofen dosing if the patients are also taking aspirin for cardioprotective effects.

With occasional use of ibuprofen, there is likely to be minimal risk from any attenuation of the antiplatelet effect of low dose aspirin. Patients taking immediate release low-dose aspirin (not enteric coated) and ibuprofen 400 mg should take the ibuprofen at least 30 minutes after aspirin ingestion, or at least 8 hours before aspirin ingestion to avoid any potential interaction.

Other nonselective OTC NSAIDs should be viewed as having potential to interfere with the antiplatelet effect of low-dose aspirin unless proven otherwise.

Analgesics that do not interfere with the antiplatelet effect of low dose aspirin should be considered for populations at high risk for cardiovascular events.

***Source**: Food and Drug Administration . Science Paper, 8 September 2006. http://fda.gov/cder/news*

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

Topics of Current Interest

Expert Committee on Drug Dependence: recommendations

WHO's Expert Committee on Drug Dependence (ECDD) provides advice to the United Nations Commission on Narcotic Drugs concerning substances controlled under the Single Convention on Narcotic Drugs (1961) and the Convention on Psychotropic Substances (1971). These treaties serve as a basis for decisions at national level on control schedules for medicines like morphine and benzodiazepines, or substances like cocaine, amfetamine and cannabis.

The ECDD held its 34th meeting in Geneva from 28–31 March 2006. On the agenda were a number of issues relating to the critical review of substances, including buprenorphine, butorphanol, dronabinol, ketamine, khat (*Catha edulis* Forsk.), oripavine and zopiclone, while tramadol and gammahydroxybutyric acid (GHB) were on the agenda for pre-review. Buprenorphine and oripavine were also being considered subsequent to a previous review by the Thirty-third ECDD. The following recommendations were proposed.

Dronabinol should be moved from Schedule II to Schedule III of the UN Convention on Psychotropic Substances. The Committee recommended this because dronabinol has medical usefulness that is likely to increase. It is currently used against nausea and vomiting but is under research for a number of other conditions including multiple sclerosis and neuropathic pain. Moving to Schedule III will ensure that lighter control measures apply and access for legitimate purposes will be improved.

Oripavine should be brought under the most restrictive schedule of the Single Convention on Narcotic Drugs (Schedule I) since it is used in the chemical synthesis of other opioids.

No recommendations were made to the scheduling of **buprenorphine,** which is included in the WHO Model List of Essential Medicines. The Committee was concerned that a change in scheduling (from the Convention on Psychotropic Substances to the more stringent Single Convention on Narcotic Drugs) would have a negative impact on medical availability. Tighter requirements could limit the effectiveness of treatment programmes where patients are also available for administration of medication and diagnosis for infections or diseases. Buprenorphine administered as sublingual tablets also usefully replaces injections and, besides playing a major role in the effective treatment of opioid dependence, limits transmission of HIV/AIDS and other blood borne infections among injecting drug users by reducing use of contaminated needles.

It was decided not to recommend the scheduling of **butorphanol** and **tramadol** (both analgesics), **zopiclone** (a hypnotic and anxiolytic) or **khat** *(Catha edulis* Forsk*),* a plant chewed in some countries for its pleasant effects. A decision on **ketamine** was deferred until the next ECDD meeting**.** Ketamine is an anaesthetic included in the WHO Model List of Essential Medicines that is useful in situations where there is little infrastructure or resources. A critical review showed limited health effects caused by abuse except in East-Asian countries, where abuse reports are increasing. In this respect, the ECDD requested access to the information provided to the Commission on Narcotic Drugs in its 49th session, in 2006.

The Committee also decided not to critically review **tramadol** (a weak-acting opioid analgesic) at this time. Although its use has increased substantially over the past few years, levels of abuse have remained stable. The Committee decided that its next meeting would focus on the recreational drugs **gammahydroxybutyric acid** (GHB), **gammabutyrolactone** (GBL) and **1,4-butanediol** (1,4-BD).

Over 80% of the world's population does not have proper access to opioid analgesics for

medical use and the ECDD urges Member States to cooperate with WHO in improving the situation. The ECDD will discuss the impact of scheduling on medical accessibility of controlled substances and prevention of abuse at its next meeting.

The ECDD Report will be published as soon as possible. In the meantime, the report will become available on the WHO Medicines website at: http://www.who.int/medicines

Lack of essential medicines for children

The first international Expert Consultation on Paediatric Essential Medicines, organized by WHO and UNICEF, 9–10 August 2006, has delivered a plan to boost access to essential medicines for children. Ten million children die every year, many of them from diarrhoea, HIV/AIDS, malaria, respiratory tract infection or pneumonia. Although effective medications exist for these illnesses, there is a little knowledge on use, safety and efficacy in children, and there is a real lack of properly designed paediatric formulations.

During two days of intensive discussion, representatives of more than 20 developed and developing countries, and nongovernmental organizations, regulatory agencies, UNICEF and WHO prioritized a long-needed approach to overall paediatric care. The main objective is to dramatically expand access to child-focused formulations, including fixed-dose combinations which are crucial for easier administration and improved adherence.

The plan also calls for the extension of treatment guidelines to address the entire range of infant and child care needs including respiratory infections, neonatal care, palliative care for end stage AIDS, HIV/TB co-infection and opportunistic infections. This should be supported by improved electronic access to independent information such as the WHO Formulary.

The WHO Expert Consultation warned that without a model of best practice guidelines, paediatric formulations and support at national level for local care centres, children — who in many countries make up half of the population — will continue to be considered as therapeutic orphans. The expert consultation was unanimous in its support for urgent, specific action addressing cost issues and ensuring correct medicine formulations.

UNICEF is particularly concerned that children's access to medicines is very low in many resource limited settings. Furthermore, there is a lack of availability of several paediatric formulations. Based on the work of this new project and WHO clinical recommendations, UNICEF Supply Division will be strengthening and expanding dialogue with industry on access to paediatric formulations for HIV/AIDS.

High priority will also be placed on ensuring a holistic approach to child care and treatment, including addressing quality of life issues such as producing painless remedies over injections, better tasting medications and investigating new mini tablet presentations. Emphasis also needs to be placed on considering the stability requirements linked to distribution and use whenever new product formulations are made. For example, chewable or soluble powders are preferred over syrups as they do not require refrigeration and are less bulky to transport. In addition, WHO will consider several children's medicines for inclusion in the WHO Essential Medicines List to be updated in March 2007.

Reference: WHO Press Release, PR42. dated 14 August 2006. Available at http://www.who.int/mediacentre/news/

Access to new medicines by developing countries

In May 2006, the World Health Assembly adopted a resolution that could change the concept of drug research and development and offer greater access to medicines. This urges Member States to make research and development of medicines a public interest priority and to work with WHO and other international bodies to support research and development of essential medicines to treat the most common illnesses in poor countries.

The resolution was adopted in response to a call from developing countries and nongovernmental organizations to redirect the tendency of pharmaceutical companies to concentrate

research and development efforts on seeking solutions to diseases which are commercially attractive.

The Assembly resolution also paves the way for a debate on intellectual property rights for medicines and patenting mechanisms regulated by agreements of the World Intellectual Property Organization (WIPO) and the World Trade Organization (WTO). WHO is attempting to reconcile the creation of new medicines with the need for them to be immediately accessible to those in need. Under the present intellectual property regulations, patents may protect the sale of drugs for as long as 35 years, putting those medicines out of the reach of poor people because of their high price.

The World Health Assembly also addressed a proposal for creation of a framework to define priorities in public health and to support research and development. An intergovernmental working group should draw up a strategy and action plan to guide future work on innovation and public health. This would include exploring new ways of financing the development of new products so as to ensure that all countries have access to innovations.

Reference: World Health Organization. http://www.who.int/medicines

Counterfeit taskforce launched

The World Health Organization (WHO) has launch a Taskforce to fight a thriving multimillion-dollar illegal trade in counterfeit drugs, vaccines and other medical products. The International Medical Products Anti-Counterfeiting Taskforce (IMPACT) aims to put a stop to the deadly trade in fake drugs, which are a threat to thousands of people every year.

People need to become more aware of the growing market in counterfeit medicines and the public health risks associated with this illegal practice. IMPACT will encourage the public, distributors, pharmacists and hospital staff to inform the authorities about their suspicions regarding the authenticity of a drug or vaccine. In a parallel move, IMPACT will help governments eliminate corruption in those authorities charged with enforcing laws against drug counterfeiting. Drug manufacturers will be encouraged to make their products more difficult to fake.

Key members of IMPACT will be national drug regulatory authorities and law enforcement agencies. WHO will also seek the involvement of other international organizations, non-governmental organizations, pharmaceutical manufacturing and wholesaling industry associations, patient advocacy groups and health-care professionals. IMPACT will meet for the first time in mid-November 2006 in Germany to decide on concrete projects, deliverables and deadlines.

The idea of setting up this Taskforce was approved at a meeting in Rome in February but it is the latest initiative in a long campaign. For almost 20 years, WHO has been fighting drug counterfeiting since it became a major threat in the 1980s. The problem was first noticed by the pharmaceutical industry. They saw that their own products were being copied: an estimated 1 in 4 packets of medicine sold in street markets in developing countries could be fake.

In mainland southeast Asia, artesunate, a vital antimalarial drug, is commonly faked. An international study conducted by Nick White and colleagues and published in *Tropical Medicine and International Health* in 2004 found that 53% of artesunate tablet packs sold in the region did not contain artesunate.

Although it is difficult to obtain precise figures, the Food and Drug Administration in the United States of America estimates that worldwide sales of fake drugs exceed US$ 3.5 billion per year, according to a paper published in the journal *PLoS Medicine* in April 2005. The US Center for Medicines in the Public Interest predicts that counterfeit drug sales could reach US$ 75 billion globally in 2010 if action is not taken to curb the trade.

Counterfeit drugs are found everywhere, but sub-Saharan Africa is particularly affected. The dismantling of the health-care system in many African countries has created the vacuum into which counterfeiters have been able to slip. In Africa, drugs are sold through the informal economy in large open-air markets. People may realize the risk they are taking, but they have no alternative. Hospitals

cannot buy directly from the pharmaceutical companies for many reasons, including cost and the small quantities they need. So they buy drugs from local suppliers who sometimes are not even licensed by the local authorities.

After assessing current national laws on drug counterfeiting, IMPACT will focus on effective measures and advise governments on how controls might be implemented. Closer cooperation between police, customs services and health-care providers is also required. Enforcement officers would like to be able to identify fake drugs on the spot. But sometimes it is impossible to do so without laboratory analysis. Drugs also need to be readily traceable from the point of manufacture to the point of sale.

Reference: World Health Organization, Press Release, 2006.

Fake artesunate warning sheet

Fourteen different types of counterfeit artesunate tablets have been identified in South-East Asia labelled as made by Guilin Pharmaceutical Co. Ltd. A warning sheet that lists the types containing small amounts of artesunate, and a new Type 13 and Type 14 which bears a Myanmar registration number is available on www.tropicalmedicine.ox.ac.uk/News.htm. This sheet is meant for health professionals and drug regulatory authorities. A CD of the Word® file containing scans of the holograms and stickers, to use the pictures elsewhere, or to translate the sheet into another language is available from Paul Newton at paul@tropmedres.ac.

Much stronger action by governments and international organisations is needed and we hope that this information will prompt vigorous action to combat this under-recognized and serious public health problem.

Reference: www.tropicalmedicine.ox.ac.uk/News.htm.

Resolution on counterfeiting

The European Parliament has adopted a non-binding resolution calling on the creation of an international convention to fight counterfeiting of medicines. The European Union (EU) is urged to play a key role in the creation of a specific criminal offence of counterfeiting in the legislation of every country. Currently, no EU anti-counterfeit measures exist specifically for medicines, but the European Medicines Agency (EMEA) supports anti-counterfeiting activities in co-operation with the European Commission and national medicines agencies.

The resolution, adopted by a show of hands on 7 September 2006, regrets that the "EU became involved at a late stage in the international fight against counterfeiting when more open borders and new technologies (Internet) were likely to exacerbate the problem of piracy". It therefore urges a strengthening of the regulatory and quality-control capacity for medicinal products and medical equipment put on the market in countries with inadequate resources and to improve access to affordable medicines.

Counterfeit drugs are deliberately and fraudulently mislabelled with respect to identity and source, without necessarily having the effectiveness of the branded, clinically tested originals. Counterfeit medicines can have dangerous consequences to health due to unexpected side effects, allergic reactions or worsening of the patient's medical condition due to wrong ingredients or absence of active ingredients. The resolution states:

The European Parliament,

- having regard to the statement on the fight against counterfeiting by the Heads of State and Government of the G8 at the St Petersburg Summit on 15 and 16 July 2006,
- having regard to the Declaration of Rome adopted at the WHO international conference of 18 February 2006,
- having regard to the Commission's initiatives on enforcing intellectual property rights and its action plan against counterfeiting and piracy adopted in October 2005,
- having regard to the judgment of the Court of Justice in 2005 (C-176/03) which has strengthened the European Community's capacity to impose penal sanctions for counterfeiting,
- having regard to the WHO resolution on public health, innovation, essential health research and intellectual property rights' adopted on 29 May 2006,

• having regard to Rule 108(5) of its Rules of Procedure,

A. whereas the counterfeiting of medicines can have extremely serious consequences and may well endanger the health and life of millions of people,

B. whereas, according to the WHO, a counterfeit medicine is one which is deliberately and fraudulently mislabelled with respect to identity and/or source. Counterfeiting can apply to both branded and generic products and counterfeit products may include products with the correct ingredients or with the wrong ingredients, without active ingredients, with insufficient active ingredients or with fake packaging,

C. whereas counterfeit medicines are primarily circulating in developing countries and are used to treat fatal conditions such as malaria, tuberculosis and HIV/AIDS,

D. whereas WHO estimates that the counterfeiting of medicines now affects 10% of the world market, and the Food and Drug Administration puts the figure at more than 10%; up to 70% of anti-malaria drugs circulating in Cameroun are counterfeit, a figure confirmed for six other African countries by the WHO in 2003; 25% of all medicines used in developing countries are apparently counterfeit (50% in Pakistan and Nigeria),

E. whereas, according to WHO, 200 000 of the one million deaths a year from malaria are attributable to medicines wrongly administered or the administration of counterfeit medicines,

F. whereas the counterfeiting of medicines is rife in all continents but mainly in Africa, Asia, Latin America and Russia,

G. whereas the most common factors identified by the WHO as encouraging the appearance of counterfeit medicines are: the lack of legislation prohibiting counterfeiting of medicines, weak penal sanctions, weak or absent national drug regulatory authorities, shortages/erratic supply of medicines, lack of control of drugs for export, trade involving several intermediaries, corruption and conflict of interest,

H. whereas this trafficking in fake medicines is also a consequence of the lack of political awareness and commitment, weak regulatory systems, inadequate enforcement capacity and, especially in developing countries, the lack of public access to genuine medicines supervised by the public authorities,

I. regretting that the European Union became involved at a late stage in the international fight against counterfeiting when more open borders and new technologies (Internet) were likely to exacerbate the problem of piracy,

1. Considers that the European Community should equip itself as a matter of urgency with the means to combat effectively illicit practices in the area of piracy and the counterfeiting of medicines;

2. Calls on the Commission to go beyond its communication Strategy to enforce intellectual property rights in third countries; in particular, urges the European Union to take adequate measures to combat the scourge of counterfeiting of medicines in its territory;

3. Calls on the EU to take steps to strengthen the regulatory and quality-control capacity for medicinal products and medical equipment put on the market in countries with inadequate resources and to improve access to affordable medicines;

4. Urges the European Union to play a key role in promoting an international convention to create a specific criminal offence of counterfeiting or the receiving and distribution of counterfeit medicines in the legislation of every country;

5. Calls for greater cooperation at both national and international level between the various authorities involved in anti-counterfeiting measures;

6. Emphasises the importance of preventive measures in action programmes, more specifically, the establishment of structures, cooperation, awareness campaigns, preferably carried out by the public authorities, and finally the political will to carry through such measures successfully;

7. Instructs its President to forward this resolution to the Council, the Commission, the heads of government of the Member States, the UN Secretary-General and the Director-General of WHO.

Reference: Euractiv, Health and Pharma, 7 September 2006. http://www.euractiv.cm and European parliament at http://www.europarl.europa.eu

Regulatory Action and News

Influenza virus vaccines for 2006–2007 northern hemisphere

World Health Organization — It is recommended that vaccines to be used in the northern hemisphere 2006–2007 contain the following:

- an A/New Caledonia/20/99(H1N1)-like virus;
- an A/Wisconsin/67/2005 (H3N2)-like virus. Candidate vaccine viruses include: A/Wisconsin/67/2005 (H3N2) and A/Hiroshima/52/2005;
- a B/Malaysia/2506/2004-like virus. Candidate vaccine viruses include: B/Malaysia/2506/2004 virus and B/Ohio/1/2005

As in previous years, national control authorities should approve the specific vaccine viruses used in each country. National public health authorities are responsible for making recommendations regarding the use of the vaccine.

Reagents for use in laboratory standardization of inactivated vaccine may be obtained from:

- Immunology (Vaccines), Therapeutic Goods Administration Laboratories, 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 1707 641050, e-mail: enquiries@nibsc.ac.uk, web site: http://www.nibsc.ac.uk);
- Division of Viral Products, Center for Biologics Evaluation and Research, Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20892, United States (fax: +1 301 402 5128).

Requests for reference strains for antigenic analysis should be addressed to:

- WHO Collaborating Centre for Reference and Research on Influenza, 45 Poplar Road, Parkville, Victoria 3052, Australia (fax: +61 3 9389 1881, website: http://www.influenzacentre.org).
- 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, website: http://www.nih.go.jp/niid/indexe.html);.
- 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 2334, website: http://www.cdc.gov/flu/).
- WHO Collaborating Centre for Reference and Research on Influenza, National Institute for Medical Research, The Ridgeway, Mill Hill, London NW7 1AA, England (fax: +44 2089 064 477).

Reference: World Health Organization. http://www.who.int/influenza .

Trastuzumab approved for primary breast cancer

New Zealand — Trastuzumab (Herceptin®) has been provisionally approved for the treatment of some women with early stage breast cancer by Medsafe, the Medicines and Medical Devices Safety Authority. Medsafe is the first medicines regulatory authority to assess and approve Herceptin® as a treatment for primary breast cancer. Provisional consent limits the use of trastuzumab to treating women with early breast cancer who test positive for the HER2 gene once they have had surgery and completed adjuvant chemotherapy.

Due to concerns that use of trastuzumab may be associated with heart damage, the provi-

sional consent also limits the treatment to those women who have a normal heart function before treatment starts and requires women to have echocardiograms every three months during treatment.

As part of the approval process, the Medicines Assessment Advisory Committee considered an interim analysis of clinical trial results including the pivotal HERA study, and other published data. The HERA study found that after 12 months, the recurrence of HER2 breast cancer was reduced by 9% after treatment with Herceptin®. The Committee concluded that treatment with trastuzumab significantly reduced the recurrence rate of breast cancer compared to women who received no additional treatment.

Another study includes a small number of women who have been followed up. This study has reported that treatment with trastuzumab in addition to standard adjuvant chemotherapy reduced the recurrence of HER2 breast cancer by 18%.

In addition to demonstrating benefits, research also demonstrated that use of trastuzumab was associated with significant side effects. most concern was the finding that up to 3% of women developed severe heart failure while being treated with Herceptin®.

Reference: Herceptin® (trastuzumab) provisionally approved. MedSafe Media Release, 23 March 2006.

Emergency contraception over-the-counter

United States of America — The Food and Drug Administration (FDA) has announced approval of Plan B®, a contraceptive containing 0.75 mg levonorgestrel, as an over-the-counter (OTC) option for women aged 18 and older. Like other birth control pills, Plan B® will remain available as a prescription-only product for women age 17 and under.

This action concludes an extensive process that included obtaining expert advice from a joint meeting of two FDA advisory committees and providing an opportunity for public comment on issues regarding the scientific and policy questions associated with the application to switch Plan B® to OTC use. The marketing application raised novel issues regarding simultaneously marketing of both prescription and non-prescription Plan B® for emergency contraception, but for different populations, in a single package.

Reference: *FDA News*, P06-118. 24 August 2006. http://www.fda.gov/cder/drug/infopage/planB/default.htm.

Ocular *Fusarium* infections: ReNu MoistureLoc® voluntary withdrawal

United Kingdom — An increase in ocular *Fusarium* infections has occurred in Hong Kong, Singapore and the USA. A root cause for these infections has not been found, but a disproportionate number of those infected used ReNu MoistureLoc®. Investigations into this product have not revealed any issues relating to product contamination, sterility or other production related factors. However, the manufacturer has been unable to exclude the possibility that the problem may be related in some way to formulation of the product and has decided to withdraw the product worldwide.

Fusarium keratitis is a relatively rare source of eye infection, but a serious one. *Fusarium* typically enters the eye through some sort of trauma or injury to the cornea, resulting in an inflammation. If diagnosed and treated late, significant loss of vision can result, sometimes leading to the need for a corneal transplant.

This is a precautionary measure taken by the manufacturer. The Medicines and Healthcare products Regulatory Agency (MHRA) has received no reports of *Fusarium* eye infection in the UK related to the product.

Reference: Medicines and Healthcare products Regulatory Agency (MHRA) at www.mhra.gov.uk

Saquinavir: withdrawal of soft gel capsule Fortovase®

European Union — On 20 August 1998 the European Commission issued a marketing authorization for the medicinal product saquinavir (Fortovase®), soft gel capsules, intended for the treatment of HIV-1infected

adult patients. Fortovase® should only be given in combination with ritonavir and other antiretroviral medicinal products. On 17 May 2006, the European Commission was notified by the marketing authorization holder (MAH) of their decision to voluntarily withdraw the marketing authorisation for Fortovase® for commercial reasons.

Therapeutic alternatives are available throughout the European Union, including Invirase®, 200 mg hard capsule and 500 mg film-coated tablet formulations of saquinavir as a mesylate salt.

The European Public Assessment Report has now been removed from the EMEA website. The MAH for Fortovase® will continue to be responsible for any remaining product on the market until the expiry date (January 2007) of the latest released batch in the European Union.

Reference: European Medicines Agency (EMEA), Public Statement, EMEA/304680/2006, 4 August 2006. http://www.emea.eu.int

Latest list of prequalified products and manufacturers

World Health Organization — The objective of the Prequalification Programme, is to assess the acceptability in principle of HIV/AIDS, tuberculosis and malaria medicines and diagnostics for procurement by UN Agencies.

The assessment procedure identifies products and suppliers meeting WHO standards. The two main components of the assessment process are dossier evaluation and manufacturing site inspections.

This list indicates products found to be acceptable by WHO, as manufacture, at the specified manufacturing sites. Inclusion in the list does not, however, imply any approval by WHO of the products and manufacturing sites in question (which is the sole prerogative of national authorities).

Products listed with the note “US FDA” have been added to the list of products prequalified by WHO based on scientific assessment and inspections conducted by the US FDA and exchange of relevant information between the US FDA and WHO and the product meets all of the US FDA’s safety, efficacy, and manufacturing quality standards required for marketing in the USA. Equally, products listed with the note “HCnda” have been added to the list of products prequalified by WHO based on scientific assessment and inspections conducted by Health Canada.

The full list of products, manufacturing sites, and quality control laboratories prequalified by WHO, including a description of the Prequalification Programme itself can be found on the WHO website at http://www.who.int/medicines or http://mednet3.who.int/prequal

Prequalified HIV/AIDS drugs during August 2006

Approved/ prequalifed by	INN/generic name	Dosage form	Manufacturer and site
WHO	stavudine	30 mg capsules	Strides Arcolab Ltd Bangalore India
H. Canada	zidovudine/ lamivudine/ nevirapine	300 mg/ tablets 150 mg/ 200 mg	Apotex Inc. Toronto Canada
US FDA	lamivudine/ zidovudine + abacavir	150 mg/ tablets 300 mg + 300 mg	Aurobindo Pharma Ltd Hyderabad, India

Clopidogrel: new medical use

United States of America — The Food and Drug Administration (FDA) has approved the use of clopidogrel bisulfate (Plavix ®) for patients who have had a type of heart attack called acute ST-segment elevation myocardial infarction (STEMI) and are not going to have angioplasty.

Clopidogrel prevents subsequent blockage in the already-damaged heart vessel, which could lead to more heart attacks, stroke, and possibly death.

FDA approved clopidogrel in November 1997 to decrease platelet function in people who suffer from acute coronary syndrome (ACS).

Two studies support the effectiveness of clopidogrel in treating STEMI heart attack patients. A large trial, the Clopidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT) study, has been supported by the results of the Clopidogrel as Adjunctive Reperfusion Therapy (CLARITY) study.

Serious side effects of clopidogrel include bleeding and, rarely, low white blood cell counts or thrombotic thrombocytopenic purpura.

Reference: *FDA News*, P06-115. 17 August 2006

Dronedarone: withdrawal of marketing authorization

European Union — The European Medicines Agency (EMEA) has been formally notified of the manufacturer's decision to withdraw the application for a centralized marketing authorization for the medicinal product dronedarone hydrochloride (Multaq®). The requested indication was rhythm and rate control in patients with atrial fibrillation or atrial flutter (abnormalities of the heartbeat), to maintain normal sinus rhythm or to decrease ventricular rate.

At the time of withdrawal, the application was under review by the Agency's Committee for Medicinal Products for Human Use (CHMP). In its letter, the company stated that the withdrawal of Multaq® was due to the fact that the additional clinical data requested by the CHMP cannot be provided within the timeframe of the current procedure.

Reference: European Medicines Agency (EMEA), Press Release, Doc. Ref. EMEA/354409/2006, 8 September 2006.

Recent Publications, Information and Events

MSF issues ninth antiretroviral price list

Untangling the Web of Price Reductions: a Pricing Guide for the Purchase of ARVs for Developing Countries was first published by Medecins Sans Frontieres (MSF) in October 2001 in response to the lack of transparent and reliable information about prices of pharmaceutical products on the international market — a factor which significantly hampers access to essential medicines in developing countries.

The purpose of the document is to provide information on prices and suppliers that will help purchasers make informed decisions when buying antiretrovirals (ARVs). The report is a pricing guide and does not include detailed information about the quality of the products listed. Since the first edition, prices of some first-line ARVs have fallen significantly due to competition between multiple producers. However, MSF finds that there are still common problems affecting the availability of the most needed essential medicines:

1. In the absence of competition from multiple producers, companies may charge prohibitive prices (this is particularly the case for the most recent ARVs, including those recommended in the 2006 WHO treatment guidelines for both first and second-line);

2. Most originator companies establish a country premium, thereby excluding patients in some developing countries;

3. Even if companies announce discounted prices for their products in some eligible developing countries, the products are in fact not always available or affordable; and

4. Paediatric HIV/AIDS is neglected by most pharmaceutical companies.

Reference: Full report available at http://www.accessmed-msf.org/documents/

Progress in HIV / AIDS medicines access

The World Health Organization (WHO) continues its work in pharmaceuticals and technologies to promote access to safe, effective medicines and equipment of assured quality for the treatment, diagnosis and monitoring of HIV/AIDS. The Health Technology and Pharmaceuticals (HTP) cluster at WHO has taken concrete steps to widen the choice and availability of quality assured HIV treatment related products for procurement or bulk purchasing in developing countries. In addition, work has begun on children's medicines for HIV/AIDS and other priority diseases and a data base is being developed to gather information on the patent status of priority medicines.

Reference: World Health Organization.Progress since Bangkok 2004 for HIV / AIDS and HIV Progress Report, Press Release, 10 June 2006 at http://www.who.int

Antiretroviral treatment failure and patient support

A new report was presented by the World Health Organization at the Toronto International AIDS Conference held in August 2006. It shows that access to antiretrovirals is only part of the treatment equation. Without targeted patient support, the report finds, patients may not take their medicines regularly and frequently enough, thereby nullifying the therapeutic benefits of treatment.

From Access to Adherence: the Challenges of Antiretroviral Treatment, exposes the tough realities faced daily by people living with HIV and AIDS in Botswana, Tanzania and Uganda. The report identifies reasons for adherence failure and provides a series of practical recommendations to improve the situation.

The optimal adherence rate for antiretroviral therapy is 95%, as recommended by WHO.

Lack of adherence to therapy has serious public health consequences, such as treatment failure, the spread of drug resistance and the waste of resources. The report finds that individuals trying to take all of their medicines are often trapped in a vicious circle of social, economic and workplace obstacles hampering their adherence to treatment.

Out of a sample 514 patients interviewed in Botswana, 23% were taking less than the critical 95% of dosage. In Tanzania, 79% of the 207 patients interviewed were below the critical level.

Reasons found for adherence failure were: alcohol or substance abuse; work-related problems such as not getting time off to go to the clinic or stigma in the workplace; long travel time to clinics and a long wait before attention; stigma and discrimination in the community and at home. In Uganda, it is common for people to stop their medication because they cannot afford the food they need to eat when taking the drugs; distance to health facilities and the costs related to lifelong treatment were also cited by study participants.

The report's research teams propose specific priorities for immediate implementation:

- Enforcement of legislation to protect the rights of workers to access to treatment without fear of discrimination.
- Training and supporting community counsellors who operate from home.
- Waiving registration and consultation fees at health clinics for those on antiretroviral therapy.
- Providing food support for antiretroviral users, particularly at the beginning of treatment, when appetite increases.
- Examining the possibility of a transport voucher scheme for people who cannot afford to go and pick up their medicines.

Reference: World Health Organization. *From Access to Adherence*. Available at http://www.who.int/medicines

Nanotechnology-based medicinal products

The scope of *Nanotechnology-based medicinal products for Human Use* reflects current thinking and initiatives taken by the European Medicines Agency (EMEA) following recent developments in development of nanotechnology-based medicinal products. Nanotechnology is an emerging scientific research field with wide applicability and, in the context of medical science, is expected to contribute in developing a more proactive paradigm for the diagnosis and therapy of disease. Medicinal products containing nanoparticles have already been authorized both in EU and the USA under existing regulatory frameworks.

Although nanosizing does not necessarily imply novelty, it is expected that nanotechnology will yield innovative products. Such products could span the regulatory boundaries between medicinal products and medical devices, challenging current criteria for classification and evaluation. Appropriate expertise will need to be mobilized for the evaluation of the quality, safety, efficacy and risk management of nanomedicinal products and the need for new or updated guidelines will be reviewed in the light of accumulated experience.

EMEA has created the Innovation Task Force (ITF) to ensure EMEA-wide coordination of scientific and regulatory competence in the field of emerging therapies and technologies, including nanotechnologies, and to provide a forum for early dialogue with applicants on regulatory, scientific or other issues that may arise from the development (1).

In the absence of specific guidance, applicants are encouraged to contact the EMEA during the early stages of development of their products (2).

References

1. EMEA Innovation Task Force. http://www.emea.eu.int/htms/human/itf/itfintro.htm

2. Scientific Advice procedure. http://www.emea.eu.int/pdfs/human/sciadvice/426001en.pdf.

3. Reflection paper on nanotechnology-based medicinal products for human use. EMEA/CHMP/79769/2006, 29 June 2006. http://www.emea.eu.int/htms/human/itf/itfguide.htm

Public health, innovation and intellectual property rights

In May 2003, WHO Member States agreed to set up a body to consider the relationship between intellectual property rights and innovation and their impact on public health. A Commission was established in February 2004 and has now published its report: *Public Health, Innovation and Intellectual Property Rights*. The Commission endeavoured to bring together a large spectrum of different experiences, opinions and scientific dsciplines through a process of consultation and research.

In recent years, there has been a rapid increase globally in technological and economic potential, implying an enhanced ability to overcome problems related to poverty and poor health. The impact of these trends on global health is complex. At the same time, there has been a reversal of life expectancy in many countries due to the burden of HIV, tuberculosis and malaria.

Whereas there is an innovation cycle in developed countries which broadly works to provide the health care required by their inhabitants, this is far from being the case in developing countries. Also, and in spite of progress made in the last decade, the basis for continued progress in the development of new products needed by developing countries remains fragile. To assure their sustainability and guarantee that medicines, vaccines and diagnositcs reach the people who are in need, much more effort is required. Chapter 6 of the report points to the various problems which need to be addressed and sets out its recommendations.

Reference: World Health Organization. *Public health, innovation and intellectual property rights. Report of the Commission Intellectual Property Rights, Innovation and Public Health*. April 2006. http://www.who.int