WHO Drug Information

Contents

(Continued ...)

Contents *(... continued)*

International Harmonization

ICDRA: medicines agencies decide future action

The Thirteenth International Conference of Drug Regulatory Authorities (ICDRA) held in Berne, Switzerland, from 16 to 19 September 2008 has once again provided drug regulators with a unique opportunity to meet and discuss the particular challenges of medicines regulation.

On this occasion, the ICDRA was hosted by the Swiss Agency for Therapeutic Products, Swissmedic, in collaboration with the World Health Organization (WHO). The event was highly appreciated for its continuing role in fostering a regulatory forum where matters of urgency and international relevance can be openly debated among regulatory officials from developed and developing countries. The ICDRA was attended by over 300 participants from 96 countries and led to adoption of recommendations which regulators consider important in assuring the quality, safety and efficacy of medical products. The recommendations are set out below and on the following pages.

Building mutual trust as a key to access

Regulatory approval of medicines — evaluation, registration, and marketing authorization — is based on scientific assessment. The approval process needs considerable resources and capacity if it is to be carried out properly. This plenary session set out to show how mutual trust constitutes a capacity building factor and leads to improved access to medicines. Potential public health gains can be harnessed from a harmonized understanding of what is needed to ensure the quality, safety and efficacy of medicines.

This session addressed the many questions faced by regulators in difficult, resource constrained environments, including:

- How can regulators best contribute to public health with the resources they have?
- Should regulators assess and inspect every innovative product that is proposed for their market?
- Can and should all regulators assess and inspect generic medicines?
- Does repetitive assessment and inspection provide added value?
- How can confidence be built into scientific assessments carried out by other parties?

Moderator
Canada: Meena Ballantyne

Presentations
WHO Intergovernmental Working Group on Public Health, Innovation and Intellectual Property: Implications for regulators. Mandisa Hela, South Africa.

How to benefit from other regulators' work. A New Zealand view point . Stewart Jessamine, New Zealand.

Building trust, enhancing competence among African medicines regulatory authorities: a WHO initiative. Jonathan Martey, Ghana.

Recommendations

WHO should:

1. Promote, in a targeted and prioritized way, adoption and implementation of the WHO Model Registration Package as minimum information requirements for product registration.

2. Produce a guidance and draft regulation for managing confidentiality issues among regulatory authorities.

3. Undertake joint assessments of selected applications, using the WHO Model Registration Package.

4. Foster the development of regional, collaborative post-market surveillance and pharmacovigilance systems to monitor the quality, safety and efficacy of health products.

5. Explore the potential development of an interagency e-governance working group to harmonize electronic requirements to assist in the development of regulatory management systems and the sharing of information in accordance with established WHO international regulatory norms and standards.

6. In partnership with well-resourced regulatory authorities:

- establish formal mechanisms for the exchange and use of regulatory information among all authorities to strengthen capacity and to maximize efficiencies, and
- facilitate cooperation between small and medium well-resourced regulatory authorities to develop systems for the abbreviated assessment, approval and monitoring of health products.

Regulatory systems in a changing environment

Regulators are facing a rapidly changing environment including demographics and burden of disease, scientific progress, globalization of manufacturing and clinical research, difficulties in availability of new and old drugs, and difficulties for individual agencies to meet challenges on their own.

Moderator

European Union: Thomas Lönngren

Presentations

Changing environments and small regulatory authorities. Ngawang Dema, Bhutan.

Implications of rapid socioeconomic changes to the regulatory affairs. Cuong Truong Quoc, Viet Nam.

The changing environment and regulatory systems. Björn Beermann, Sweden.

Regulatory paradigms for change: A Singapore perspective. John Lim, Singapore.

Regulatory systems: a Dutch viewpoint. Aginus Kalis, Netherlands.

Recommendations

Member States should:

1. Facilitate and speed up global regulatory cooperation.

2. Support and stimulate their regulatory authorities to work with regional and global partners.

WHO should:

1. Continue to support and create new activities that stimulate cooperation and build trust among regulatory agencies.

Crisis management: safeguarding health

In the course of their work, staff working in regulatory authorities may often experience crises with medicinal products. Some of these crises can lead to loss of public confidence and can be deeply damaging to the reputation and effectiveness of the regulation of medicines.

This session explored ways in which the International Health Regulations can be used as a mechanism for information-sharing during a medicinal product crisis. The Regulations stipulate that it is mandatory to notify WHO of 'all events which may constitute a public health emergency of international concern' and cover serious international safety events due to medicinal products.

The case study of nelfinavir, which has been suspended due to contamination with a harmful substance, was presented. This case represents a complex example of an international problem involving multiple stakeholders and areas for improvement in the communications area. Experience in two different countries where the product had been withdrawn completely from the market and where the product had been reinstated into the treatment programmes were discussed. Finally, a few examples were discussed on how vaccine crises are handled. There are no substantial differences between a medicine crisis and a vaccine crisis.

It was agreed that there should always be a crisis management plan in place. This should consist of a process through which organizations, in collaboration with external stakeholders, prevent or effectively manage crises. Key elements are systematic and planned operation and involvement of all stakeholders is essential in order to provide an efficient, rapid and effective response.

Moderators
Republic of Korea: Inkyu Kim
WHO: Bruce Plotkin

Presentations
Mechanisms for information sharing and public health response under the International Health Regulations (IHR). B. Plotkin, WHO.

Communication during a crisis: nelfinavir case study. Emer Cooke, EMEA, European Union.

Nelfinavir: Where are we now? Experience in Barbados. Maryam Hinds, Barbados.

Nelfinavir: Where are we now? Experience in Ghana. Delese Darko, Ghana

Responding to vaccine safety events. Karen Midthun, USA.

Recommendations

Member States should:

1. Have in place a standard operating procedure (SOP) for communication in times of crisis. Main initial communication difficulties which are linked to uncertainty of toxicity implications could be avoided by use of such SOPs.

2. Consider that many reports may be required to generate a signal, depending on the seriousness of the event and the quality of the information.

3. Through national health authorities, continue encouraging spontaneous reporting and vigilance systems and introduce crisis management systems.

4. Play an important role in monitoring, analysing, and communication of vaccines safety.

5. Undertake passive and active surveillance after licensure including observational studies needed to detect and evaluate medicine and vaccine safety concerns.

WHO and Member States should:

1. Work further to integrate and coordinate information and other requirements in the International Health Regulations (IHR) (2005) with functions and activities of medicines regulatory authorities and related networks. Such integration could include establishing links between medicines regulatory authorities and their respective national IHR focal points, including potential access to the WHO IHR Event Information Site.

Current topics

Moderators
European Union/Council of Europe: Susan Keitel
Armenia: Emil Gabrielyan

Good Governance for Medicines
In late 2004, WHO implemented the Good Governance for Medicines (GGM) programme in an attempt to curb corruption in the pharmaceutical sector. Its goal is to increase transparency and promote ethical practices in national medicines regulatory authorities and supply management systems.

The GGM programme started with four countries in the WHO South-East Asia Region and has now extended to 27 countries in all WHO regions. WHO has now a technical package to guide countries in implementing the GGM programme and facilitates sharing of accumulated experiences within countries.

The programme is based on a three-phase model process:

Phase I: National assessment of transparency and vulnerability to corruption in six functions of the medicines chain supply (from registration to distribution).

Phase II: Development of a national GGM framework and its official adoption by the Ministry of Health.

Phase III: Implementation of a national GGM programme.

Presentation
WHO Good Governance for Medicines Programme: the Zambian experience. Esnat Mwape, Zambia.

Recommendation

1. Develop, implement and monitor a Good Governance for Medicines implementation framework, including:

- Establishment and implementation of codes of conduct.
- Enforcement of anticorruption laws.
- Provision of transparency and access to information.
- Protection of whistleblowers.
- Improvement of inter-institutional collaboration and cooperation.
- Provision of guidelines to define and underpin public-private partnerships.

Variations

Presentation
New proposal for the EU Variation Regulation – point of view of an EU National Competent Authority. Christa Wirthumer-Hoche, Austria.

Recommendation

1. Create a robust and efficient variation system as it is vital for the quality of a medicine throughout its life-cycle.

Radiopharmaceuticals

Presentation
Challenges in regulating radiopharmaceuticals: view of the International Consultancy Group affiliated to IAE. Kadariah Mohamed Ali, Malaysia.

Recommendations

1. Encourage better regulatory oversight.

2. Establish a prequalification system for radiopharmaceuticals.

3. Establish an international common platform (website and electronic database) for harmonized dossiers to prequalify radiopharmaceuticals.

4. Establish detailed mechanisms.

Involvement of consumers in medicines surveillance reporting

Presentation
Involving consumers in medicines surveillance reporting. Tan Lie Sie, Malaysia, and Cynthia Lim, Philippines.

Recommendation

1. Increase efforts to include consumers in medicines surveillance reporting by fostering consumer awareness, informing and educating the public and by promoting the programme to consumers.

WHO Stability Testing Guideline

Presentation
Revision of WHO stability testing guidelines. Tamás Paál, Hungary.

Recommendations

1. Finalize the revision of the guideline and apply it in Member States.

2. Provide information about the national long-term conditions to WHO.

3. WHO to make the data available on its web site.

WHO Certification Scheme

Presentation
WHO Certification Scheme for finished pharmaceutical products, where are we today? Margareth Sigonda, Tanzania.

Recommendations

1. Review reports of recent meetings held at WHO.

2. Give feedback to WHO for further discussion.

Adverse reactions

Presentation
Adverse reactions related to change of formulation: thyroxine case. Stewart Jessamine, New Zealand.

Regulatory aspects of paediatric medicines

This session was linked to the two day pre-ICDRA meeting “Better Medicines for Children: the way forward”. The meeting was unique in inviting, for the first time, regulators, industry, clinicians, civil society and academics to meet and identify challenges and seek solutions to ensuring better access to medicines for children. The pre-ICDRA meeting was attended by more than 240 participants from 75 countries. [A summary of the main themes to emerge from the meeting is presented on page 282.]

Moderator
European Union: Agnès Saint-Raymond

Presentations
Recent legislative changes regarding paediatric medicines in the European Union. Agnès Saint-Raymond, European Union.

Clinical trials in neonates – challenges for all stakeholders? Irja Lutsar, Estonia.

Paediatric medicines: a viewpoint from an African regulator. Richard Rukwata, Zimbabwe.

Report from the pre-ICDRA meeting "Better medicines for children – the way forward". Agnès Saint-Raymond, European Union.

Recommendations from pre-conference vaccines and biologicals track. David Wood, WHO.

Recommendations

Member States should:

Assist WHO to form an ICDRA paediatric working group to:

1. Ensure global collaboration.

• Agree on global regulatory standards.

• Streamlining paediatric clinical trials.

2. Implement efficient registration of children's medicines.

• Put children medicines as top priority.

• Fast track strategies: e.g., hybrid applications, mutual recognition, cooperative review, waivers, etc.

3. Develop consolidated views/advice on dosage forms and delivery devices.

• Guideline on dosage forms.

• Manipulations, extemporaneous formulations.

• Increase knowledge on paediatric excipients.

4. Devise mechanisms for ensuring transparency and exchange of information on trials, licensing, and children's medicines (dose, adverse effects).

5. Improve information on safety of medicines used in children and building infrastructure for pharmacovigilance.

Other parties

For industry: continue integrating paediatric dosage forms and delivery devices early in development of new medicines.

For industry: continue integrating paediatric needs, including developing countries needs in the development of new vaccines.

For the generic industry: develop missing dosage forms of off-patent medicines (including necessary fixed-dose combinations).

To health professionals: engage actively in sound, ethical research with children, with the aim of avoiding duplication of research.

WHO should:

1. Convene a global paediatric working group of regulators.

2. Work with civil society to mobilize and empower consumers, parents, patients' groups and health professionals to advocate for better medicines for children.

3. Develop strategies for addressing high priority needs with achievable results including: zinc for diarrhoea, *Pneumoniae* treatment, neonatal sepsis, HIV, TB, malaria treatments, and analgesics.

4. Establish a drug development helpline to support new essential medicines for children.

Vaccines and biologicals:

1. National regulatory authorities (NRAs) should prioritize evaluation of vaccines for diseases of most importance to child survival.

Member States and WHO:

1. Networking among NRAs for the joint evaluation and oversight of clinical trials of new vaccines is proving an effective process in Africa. NRAs are requested to continue to develop this type of collaboration and WHO is requested to facilitate the long-term sustainability of this and other vaccine regulatory networking initiatives.

2. Post-marketing effectiveness data is an important aspect of vaccine evaluation. WHO is requested to support capacity building and NRAs are requested to strengthen collaboration with public health agencies in this area.

3. Vaccine pharmacovigilance is a regulatory function that needs to be strengthened. NRAs are requested to prioritize capacity building for this function and WHO is requested to support this activity through setting standard definitions, development of guidelines, training, and development of networks.

4. NRAs are requested to expedite national-level approval of WHO prequalified vaccines. To facilitate this, WHO is requested to provide more detailed information about the quality, safety and efficacy of prequalified vaccines.

5. Forty per cent of venomous snake bite victims are children. There is a shortage of appropriate antivenoms globally. Improving the quality, quantity and distribution of antivenoms is essential. NRAs are requested to implement new WHO guidance on the quality, safety and efficacy of antivenoms and WHO is requested to develop a prequalification programme for antivenoms

Development of regulation for herbal medicines

Currently, around 110 countries regulate herbal medicines in response to a dramatically increased use globally and demand for more vigorous requirements to ensure quality, safety and efficacy. A number of countries also review and strengthen existing regulations for herbal medicines in a continued effort to improve their use and efficacy. Regulation of herbal medicines varies from country to country, reflecting national circumstances and legislative frameworks. A global network of regulatory agencies responsible for regulation of herbal medicines, the "International regulatory cooperation for herbal medicines (IRCH)" was established in 2006 under the coordination of WHO and currently has 19 members.

Moderators
Singapore: Shen Kuan Yee

Lao PDR: Somthavy Changvisommid

Presentations
Regulatory Framework: overview of the regulation of herbal medicines in Switzerland. Karoline Mathys, Swissmedic, Switzerland.

Regulatory Framework: overview of the regulation of herbal medicines in Brazil Bruno Rios, ANVISA, Brazil.

Overview of the regulation of herbal medicines in Benin in supporting primary health care needs. Regina Badet, Department of Traditional Medicine and pharmacopoeia, Ministry of Health, Benin.

Overview: revising the regulatory framework of herbal medicines in China. Zhang Wei, State Food and Drug Administration, China.

Promotion of regulatory cooperation: perspectives from IRCH. Shen Kuan Yee, Deputy Director, Centre for Drug Adminis-

tration, Health Products Regulation Group, Health Sciences Authority, Singapore.

Recommendations

Member States should:

1. Promote and improve use of traditional medicine (TM) as an important therapeutic tool within health-care systems.

2. Provide well balanced prescribing information concerning TM including potential interactions with conventional medicines.

3. Promote research and use of TM as an important therapeutic tool.

4. Raise awareness of cases of adulteration of TM with undeclared plants or conventional medicines, or synthetic substances.

5. Countries with resources should support developing countries to achieve access to better technology tools for evaluation of the therapeutic potential of plants.

WHO should:

1. Provide policy and technical support to countries to facilitate integration of traditional medicine into the health-care system.

2. Support developing countries to access modern technologies to facilitate production and manufacturing of herbal medicines.

3. Support and coordinate North-South cooperation to improve access to better technology to evaluate the therapeutic potential of plants.

4. Continue to support sub-regional group countries in developing monographs on commonly used medicinal plants through cooperation and in building national research capacity for traditional medicines.

5. Provide technical guidance to countries on how to avoid interactions between conventional and herbal medicines.

6. Continue to play a coordinating role in International Regulatory Cooperation on Herbal Medicines (IRCH) functions by promoting the network to involve other countries while encouraging member countries of IRCH to incorporate their national lists of registered herbal products into the IRCH library and to share this with IRCH non-member countries.

7. In cooperation with other relevant international organizations, promote introduction of intellectual property rights ("patent protection") for all newly registered herbal products.

Safety and pandemic preparedness

Pandemics and epidemics are public health emergencies that put sudden and intense stress on all institutions involved. Regulatory authorities will be faced with several issues that need to be dealt with rapidly, efficiently and possibly with limited resources as pandemics are likely to disrupt many aspects of public life.

Medicines, vaccines and blood products will have to be made available at short notice for large populations. This includes large scale quality control and intense monitoring of therapeutic agents that might not have been previously administered outside clinical development settings.

In the case of an avian influenza pandemic the safety of vaccines administered during the pre-pandemic phase needs to be evaluated very rapidly.

Adequate storage of therapeutic agents and safe and rapid distribution channels are further challenges to be taken on.

Moderators
Switzerland: Pia Carduff-Janosa

Indonesia: Lucky Slamet

Presentations
Medicines and associated regulatory issues relevant in the pandemic context. Philip Bryan, United Kingdom.

Vaccines and associated regulatory issues relevant in the pandemic context. Elwyn Griffiths, Canada.

PaniFlow tool for monitoring drug/vaccine adverse events during a pandemic. Andres Schneider, Switzerland.

Blood supply and blood products: regulatory issues in the pandemic context. M. Heiden, Germany.

Convalescent plasmas during a pandemic. Jay Epstein, USA.

Recommendations

WHO should:

1. Establish, facilitate and intensify international collaboration in safety surveillance of pandemic vaccines and antivirals.

2. Request the WHO Collaborating Centre for International Drug Monitoring/ Uppsala Monitoring Centre, to provide free access to PaniFlow (a simplified online reporting form for primary reporters) for all countries who wish to use it, and to develop and implement a tool for rapid signal detection on pooled data and keep all countries informed on findings in a timely manner.

3. In recognition of the potential value and availability of convalescent plasma as a therapeutic in pandemic flu and its likely empirical use, WHO should:

- Develop guidance on best practices for collection and use of convalescent plasma in a flu pandemic
- Promote pre-pandemic research on convalescent plasma
- Encourage rapid sharing of scientific and technical knowledge from both pre-pandemic and pandemic experience

National regulatory authorities (NRAs) should:

1. Develop and share business continuity plans to enable essential functions to be performed during the pandemic.

2. Develop and share regulatory plans to enable rapid access to medicines, including vaccines, that may need to be imported to respond to the pandemic. This should include emergency use provisions; information sharing agreements between NRAs and batch release procedures for vaccines to be implemented in the pandemic context.

3. NRAs are encouraged to actively participate in already existing networks (such as the pandemic influenza vaccine regulatory network, blood regulators network).

Regulatory approaches to proving interchangeability

Experience has demonstrated that prescribers and other health-care professionals as well as patients are reluctant to change to generics unless there is a clear reason to do so and this reluctance is a major hurdle for the introduction of generics. Demonstrating qualitative and quantitative equality with the originator is therefore important for the introduction of generics and subsequent drop in medicines prices and health-care costs.

In light of knowledge gained in the last forty years on pharmaceuticals, scientific evidence supports the need for regulating the interchangeability of medicinal products. Many national competent authorities have issued guidelines on bioquequivalence studies and on the type of medicinal product that can be exempted from *in vivo* bioequivalence studies.

Interchangeability of medicinal products is regulated in most EU Member Countries, Japan, USA and other countries. The regulation of interchangeability of medicinal products requires a strong team within each drug regulatory authority. Surveillance of performance and outcomes also requires expertise and resources.

Moderators
Saudi Arabia: Salah Bawazir

Spain: Carlos Lens

Presentations
Proof of interchangeability of pharmaceutical products and assurance of their quality in Ukraine. Olga Baula, Ukraine.

Implementation of bioequivalence requirements: lessons learned. Rodrigo Christofoletti, Brazil.

Interchangeability and registration of multisource (generic) products in Japan. Daisuke Koga, Japan.

WHO biowaiver guideline in regulatory practice. Kamal Iddir, Tunisia.

Recommendations

Member States should:

1. Ensure that drug laws and regulatory frameworks contain the required provisions to ensure submission of bioequivalence data to regulators.

2. Promote generic prescribing based on assurance that all mulltisource (generic) products are therapeutically equivalent.

3. Allocate more resources to medicines regulatory authorities (MRAs) for training of assessors for evaluation of interchangeability of multisource (generic) products.

4. Enable MRAs to certify the contract research organizations (CROs) conducting bioequivalence studies

WHO should:

1. Promote mutual trust and international cooperation mechanisms in order to recognize MRA inspections of CROs that have been conducted based on internationally acceptable standards.

Strategies to fight counterfeit medicines

Counterfeiting of medicines, including the entire range of activities from manufacturing to providing such products to patients, is a vile and serious criminal offence that puts human lives at risk and undermines the credibility of health systems. Because of its direct impact on health, counterfeiting of medicines should be combated and punished accordingly.

Combating counterfeit medicines requires the coordinated effort of all the different public and private stakeholders that are affected and are competent to address the different aspects of the problem.

Counterfeiting medicines is widespread and has escalated to such an extent that effective coordination and cooperation at the international level is essential for regional and national strategies to be more effective.

The above principles have been the basis for the establishment of the International Medical Products Anti-Counterfeiting Taskforce (IMPACT). The Taskforce has identified five areas where action is needed in order to combat counterfeit medical products effectively. Accordingly,

five working groups have been created, covering: legislative and regulatory infrastructure, regulatory implementation, enforcement, technology, and communication.

Moderators
Nigeria: Dora Akunyili

Brazil: Bruno Rios

Presentations
National Experience in combating counterfeit medical products:

Justina Molzon, USA.
Eishah A. Rahman, Malaysia
Domenico Di Giorgio, Italy
Danny Lee-Frost, United Kingdom

Recommendations

1. Medicines regulatory agencies (MRAs) should be more proactive in providing other NRAs and the general public with appropriate information on the scope of the problem of counterfeit medical products at the national level.

2. MRAs should ensure that all concerned governmental institutions are aware of the scope of the problems related to counterfeit medical products and of the activities that are undertaken to address these at national and international level.

3. MRAs should develop and adopt multipronged anti-counterfeiting strategies addressing at least: (a) ensuring proper regulatory oversight, (b) securing the supply chain, (c) increasing and applying penalties, (d) increasing public and health professional vigilance and awareness, (e) developing and applying effective authentication and detection technologies, and (f) improving coordination with all concerned stakeholders at the national and international level.

4. MRAs should clearly define the responsibilities of manufacturers and operators of the supply chain at all steps of the pharmaceutical supply system.

5. In developing track and trace methodologies used to secure the supply chain, MRAs should take into account the need to ensure international compatibility in order to improve their effectiveness in tracking products that move across borders, whenever applicable.

6. WHO and MRAs should promote the development of collaborative networks based on the principle of Single Points of Contact (SPOC).

7. WHO should further assist MRAs to strengthen their capacity to detect and combat counterfeit medical products and to exchange information at the international level.

8. WHO should further promote a harmonized definition of a counterfeit medical product that is based on the 1992 definition of counterfeit medicine, that focuses on the protection of public health, and takes into account the need to safeguard legitimate generic medicines.

9. WHO should develop and implement initiatives aimed at disseminating awareness and triggering political will to combat counterfeit medical products.

Emerging regulatory issues concerning biosimilars and biologicals

Draft WHO guidance states that, in contrast to a generics approach, the dossier for a similar biological product will need to contain information on the non-clinical and clinical data in addition to the quality data. However, the proposed guidance considers that a non-clinical and clinical package could be abbreviated; the extent of abbreviation will depend on the level of similarity to the

well established reference product with a proven record of quality, efficacy and safety.

Experience gained by using a "biosimilar approach" in the EU was considered in the development of the WHO guidelines and one abbreviated regulatory pathway is proposed. However, during review of the document, a need for an alternative was identified and an additional abbreviated pathway is under development.

Moderators
European Union/EMEA: Nick Gates
Republic of Korea: Chung Keel Lee

Presentations
Regulation of copies of therapeutic biological medicinal products: WHO guidelines. Elwyn Griffiths, Canada.

Regulatory considerations in Thailand. Prapassorn Thanaphollert, Thailand.

WHO guidelines: abbreviated licensing pathways for biological products. Martina Weise, Germany.

Panel discussion: Experience with existing regulatory pathways for copies of therapeutic biological medicinal products.

Elwyn Griffiths, Canada.
Prapassorn Thanaphollert, Thailand.
Martina Weise, Germany.

Recommendations

WHO should:

1. Develop guidance for regulatory evaluation of similar biological products that includes clarification of the scientific basis for the reduction, wherever possible, of non-clinical and clinical data requirements for such products.

2. Assist regulators in implementing globally agreed regulatory principles into national regulations and, where appropriate and feasible, develop support mechanisms such as regional centres of excellence in regulatory evaluation of similar biological products.

Member States should:

1. Strengthen NRA functions for the evaluation, pharmacovigilance and overall regulation of biotherapeutics.

Emerging diseases: regulating blood products

This session recognized the need worldwide for blood product regulation to ensure availability of safe blood and blood products in the face of known and emerging threats, including emerging infectious diseases.

Moderators
USA: Jay Epstein

Indonesia: Lucky Slamet

Presentations
Emerging Diseases, blood safety and supply: Chikungunya virus outbreak in 2005/2006. Isabelle Sainte Marie, France.

Dengue outbreaks in Latin America. Clarice Lobo, Brazil.

Assessment criteria for blood regulatory systems: effectiveness in risk management. Christian Schaerer, Switzerland.

Plasma Quality: How does it matter? Rainer Seitz, Germany.

Assessment criteria for blood regulatory systems: effectiveness in risk management. Jay Epstein, USA (presenting for Peter Ganz, Canada).

Recommendations

WHO should:

1. Take steps to further develop and strengthen national and regional blood

regulatory authorities and promote cooperation among them.

2. Provide well-harmonized "Assessment Criteria for Blood Regulatory Systems" building on work of the Blood Regulators Network

3. Take full account of existing assessment tools in use by NRAs by:

- Convening a consultation of NRAs to review the draft assessment tool, and
- Ensuring coordination with related WHO guidance documents.

4. Prioritize development of guidelines on good manufacturing practices (GMP) for Blood Establishments.

5. Promote introduction of WHO recommended plasma standards by NRAs.

Regulators contribution to access

Moderator
Hungary : Tamás Paál

Presentations
Availability of human medicinal products in Europe – how big is the problem and what can we do? View from the regulator. Kristin Raudsepp, Estonia.

Can regulators facilitate access? A viewpoint from China. Zhang Wei, China.

Panel Discussion

Recommendations

Member States should:

1. Involve regulators in the formulation of policies and measures assuring patient access to medicines. Regulators should, in addition to their traditional roles, take responsibility for facilitating availability of medicines.

2. Formulate policies and, as far as possible, legislation to enable priority medicines availability according to local health care needs.

3. Direct drug regulatory authorities to reveal medicine availability problems by giving priority to new applications for products answering locally unmet health needs.

WHO should:

1. Provide a forum to discuss and facilitate both availability and affordability of medicines in all Member States.

Update on harmonization initiatives

Moderators
Tanzania: Margareth Sigonda

Canada: Mike Ward

Presentations
Development of ICH Global Cooperation Group: a non-ICH regional harmonization and country perspective. Yuppadee Javroongrit, Thailand.

Harmonization of drug regulation in East Africa: the way forward. Apollo Muhairwe, Uganda.

Harmonization of regulatory requirements: a view point from an APEC country. Mike Ward, Canada.

Update on Pan American Network for Drug Regulatory Harmonization. James Fitzgerald, PAHO/WHO.

Recommendations

1. WHO should encourage and facilitate Member States' use of the assessment tool for drug regulatory authorities as an important step in promoting effective

regulatory strategies and harmonization efforts.

2. WHO should promote the principle of interconnectivity by information sharing and cooperation *between* harmonization initiatives and enabling organizations to build synergies, leverage capacity and sustain efforts.

3. WHO and Member States should promote effective mechanisms of harmonization through the establishment or strengthening of secretariats or coordination points, steering committees and procedures respecting expert working groups, governance and transparency.

4. WHO should facilitate the adoption by Member States of a common format for marketing applications as a means of promoting a common regulatory language that supports the sharing of information, good review practices and access to medicines.

5. The topic of harmonization should be a standing agenda item at each ICDRA.

Role of regulators in clinical trial approval

Moderator
Australia: Rohan Hammett

Presentations
Registration of clinical trials in the national registry or authorization by the national DRA – what should come first? Surinder Singh, India.

Roles and responsibilities of national regulators and the ethics committees: ways for better cooperation and communication. Lucky Slamet, Indonesia.

Interactions between manufacturing and trial host country regulators. Pieter Neels, Belgium.

Recommendations

Member States should:

1. Promote national mechanisms for communication and collaboration between ethics committees and regulatory agencies regarding the oversight of clinical trials.

2. Provide mechanisms that allow experts from well resourced regulatory agencies to assist in capacity building of regulation of clinical trials in less resourced regulatory authorities. This may include expert support from regulators of the manufacturing country to regulators of the trial host country.

3. Promote a risk-based approach to regulatory oversight of clinical trials.

WHO should:

1. Promote regulation of clinical trials by supporting countries to establish robust legal and regulatory frameworks and systems to register and publish ongoing trials to achieve transparency.

2. Facilitate the establishment of confidentiality provisions that will allow communications and cooperation between regulatory agencies from manufacturing and trial host countries.

Building regulatory capacity: best practices for the future

Moderators
India: Debasish Panda

Japan: Takayuki Okubo

Presentations
Building regulatory capacity. Debasish Panda, India.

NRA assessment/benchmark system and institutional development plan (IDP). Rafael Perez Christia, Cuba.

Building regulatory capacity in a regulatory network: experience from twinning projects and EU worksharing. Dagmar Stará, Slovak Republic.

Recommendations

WHO should:

1. Systematically inform ministries of health of outcomes of NRA assessments.

2. Evaluate ways for improving benchmarking activities within the assessments.

3. Strengthen NRAs in regulatory self-assessment approaches.

Member States and NRAs should:

1. Use WHO tools for conducting self evaluation as an adequate way for improving regulatory performance.

2. Provide staff to support the WHO assessment process and take advantage of the experience resulting from this process.

GMP inspections: impact of information sharing and risk management

Increasingly, strategies are discussed on how best to cope with the increasing need for inspections by national and regional bodies. This topic was also discussed during several WHO consultations and meetings of the WHO Expert Committee on Specifications for Pharmaceutical Preparations, which suggested that this would be a good subject for discussion at the 13th ICDRA.

Moderators
USA: Justina Molzon

South Africa: Joey Gouws

Presentations
Risk management of GMP inspections: Australian approach. Tony Gould, Australia.

Coping with increasing need for inspections: ASEAN initiatives. Abida Haq, Malaysia.

What is EMEA's approach in GMP inspections? Emer Cooke, European Union.

Recommendations

Member States should:

1. Work towards ensuring quality, efficacy and safety of drugs while making efforts to contain escalating costs of drug prices by minimizing duplication of inspection activities through:

• Better networking.

• Improved information sharing.

• Enhanced collaboration.

• Increased mutual trust/confidence.

2. Promote efficient use of inspectorate resources through use of a risk management approach in GMP inspections, especially for overseas manufacturers, by taking advantage of information available from other drug regulatory authorities.

3. Collaborate with WHO Member States and the WHO Medicines Prequalification Programme to share information about dates, purpose of inspection and major outcomes.

Manufacturers should:

1. Actively collaborate in information sharing among national, regional and international bodies involved in inspections.

2. Increase availability of non-confidential information on the web sites of interested authorities and on protected sites access-ed by national authorities.

WHO should:

1. Promote and enable networking and information sharing among national, regional and other relevant authorities involved in inspections.

ICH–Q11 appears on the horizon: development and manufacture of drug substances

The US Food and Drug Administration (FDA) and the Pharmaceutical Research and Manufacturers of America (PhRMA) hosted an ICH Quality satellite round table in Rockville, Maryland, USA 27– 28 September 2007. The objectives of the meeting were:

- To discuss the technical and regional differences and similarities in describing the development and manufacturing of drug substances in the common technical document (CTD).
- To determine how best to apply the principles of ICH Q8, Q9 and Q10 guidelines for both small and large molecules.
- To integrate these principles into developing future quality guidances.

The conclusion of the meeting was that the quality by design (QbD) approach, including the design space, is applicable to both chemical and biotechnological (1) active pharmaceutical ingredients (APIs), although opportunities and challenges are different in the two groups of pharmaceutical substances.

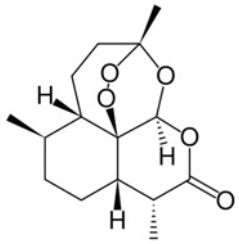
The business plan was approved by the ICH Steering Committee (ICH SC) in Yokohama in October 2007 and the Final Concept Paper *Q11: Development and Manufacture of Drug Substances* (chemical entities and biotechnological / biological entities) was endorsed by the ICH Steering Committee in April 2008. A six-party expert working group (EWG) was established, including observers from the European Free Trade Association (EFTA), Health Canada and WHO. The EWG follows the process used by the CTD-Q EWG where biotechnological / biological and chemical experts work together.

The concept paper (2) summarizes the goals of the guideline, as follows:

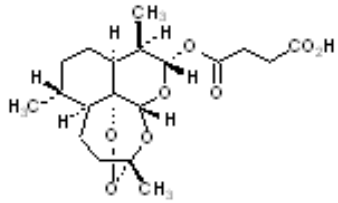
- Harmonize and encourage the submission of relevant documents regarding the manufacturing process information and its justification.
- Outline the science-based concepts relevant to the design of a robust manufacturing process that reliably delivers a quality drug substance.
- Provide examples as appropriate of acceptable approaches for demonstrating process and product understanding.
- Facilitate the regulatory evaluation process for authorities.

Article submiited by János Pogány, Budapest. Comments to: pogany.janos@chello.hu

Organic active pharmaceutical ingredients (APIs) may be manufactured by isolation from herbal, animal or human sources, for example: The structure synthesized from *Artemisia annua* has been modified by chemical synthesis to obtain a molecule with improved pharmacological and pharmaceutical properties.



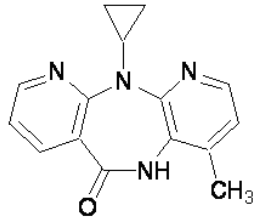
Artemisinin



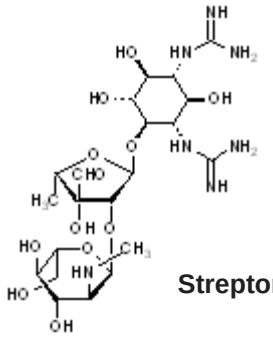
Artesunate

The majority of (small-molecule) APIs are manufactured by chemical synthesis.

Nevirapine



Biotechnological methods are used to produce “large molecules”, e.g., antibiotics.



Streptomycin

The three groups of manufacturing methods, including the use of (genetically engineered) micro-organisms in fermentation, are frequently combined in the pharmaceutical industries.

- Recommend approaches for demonstrating process and product understanding.
- Address the complexity of different manufacturing processes and products.
- Accommodate variable approaches to development and corresponding information to be provided as described in Q8 and Q8R.
- Address enhanced approaches to manufacturing that can also create a basis for alternative approaches to control the quality of a product and for the application of innovative technologies for the manufacture of APIs (e.g. continuous manufacture).
- Address systematic approaches to drug substance development, application of quality risk management, and concepts such as design space, control strategies (including real-time release) over the lifecycle of the product.

Topics already covered by other ICH guidelines such as analytical procedure validation (Q2), quality of biotechnological products (Q5 series), and GMP activities (Q7) will be cross-referenced in the new guideline, as appropriate.

Step 1: Consensus building stage began with the first meeting of the Q11-EWG in Portland, Oregon (USA) in June 2008, where the guideline topic/definitions were accepted. Draft No.0 was tabled for discussion in Brussels in November 2008. Initial discussions have revealed that ICH-Q11 may become the hardest ever document to elaborate because it will become a stand-alone document to cover a wide scope of not-yet-harmonized issues:

- Information on development and manufacture of drug substances in regulatory submissions;
- Chemical and biotechnological molecular entities;
- New chemical entities opposed to generic APIs;
- Current practice *versus* quality by design (QbD) approach

Many quality topics have not yet been the subject of ICH guidelines (e.g. drug substance synthesis) and the content of *Common Technical Document (CTD) for the Registration of Pharmaceuticals for Human Use: Quality – M4Q(R1)* is not totally harmonized.

Innovator pharmaceutical industries always develop a new chemical entity concurrently with the finished pharmaceutical product (FPP), while generic API industries are often isolated from the drug product manufacturers and the open part of the drug master file (DMF) is the technical link between them. The *CTD – Quality Questions and Answers/ Location Issues* (3) states that “Since the DMF systems differ in the three regions, ICH does not address this issue.”

A control strategy has always existed in the drug-substance industries but Q8 initiated a new way of thinking and many companies have adopted risk assessment (impact of process on safety and efficacy of API) and aim at more process understanding and the associated design space as well as process analytical technology (PAT) monitoring of critical manufacturing process parameters.

These illustrative examples intend to demonstrate that ICH Q11 is an important document both for industry and regulatory agencies and its impact goes beyond the ICH regions.

Notes and references

1. Biotech drug substances were defined as active pharmaceutical ingredients manufactured by biotechnological processes including, but not limited to, macromolecules (such as proteins, peptides and nucleic acids) and excluding vaccines.

2. The full text of the ICH-Q11 concept paper can be found at http://www.ich.org/LOB/media/MEDIA4523.pdf

3. http://www.ich.org/LOB/media/MEDIA620.pdf

Pharmacovigilance Update

Strategies for developing pharmacovigilance: an international focus

The 8th International Society of Pharmacovigilance (ISoP) conference, *Strategies for developing Pharmacovigilance*, held in Buenos Aires, Argentina, in October 2008 was hosted by the Argentine Society of Pharmacovigilance. This was the first ISoP meeting to be held in Latin America, which is a geopolitical region mainly composed of developing countries with a total population of more than 450 million people. Although political, economic and even ethnic conditions vary in the different Latin American countries, they are all affected in different degrees by similar problems concerning production, distribution and utilization of medicines.

The conference was attended by more than 350 participants from more than 50 countries. Among the audience were many medicines regulatory authorities, health professionals, and representatives of academia and pharmaceutical laboratories, student and patient organizations. Thirty participants were also sponsored to attend a pre-conference course *Pharmacovigilance: from fundamental basics to practice*. This course was organized by the Argentine Ministry of Health to allow health professionals from Argentina's provinces to attend the 8th ISoP conference.

The 8th ISoP conference was organized as a bilingual event in English and Spanish. Spanish is one of the most widely spoken languages in the world. Besides Spain, with 40 million inhabitants, there are nineteen Spanish-speaking countries in Central and South America and a growing Spanish-speaking population, around 45 million, in the USA.

The Scientific Programme included issues concerning pharmacovigilance and presented differences in organization, complexity and effectiveness in different regions. Harmonization in pharmacovigilance was approached in such a way as to discuss and compare the regulations of developed and developing regions. Two sessions were devoted to enhancing methodology and one to improving the efficacy of systems to prevent the circulation of counterfeit and substandard medicines (a summary of which is set out on page 276). The need to enhance pharmacovigilance in pregnant women, children and older people was also stressed.

Different approaches to pharmacovigilance in vaccines and a round-table discussion on strategies of risk management from a regulatory perspective dealt with two main topics in international pharmacovigilance. The need for monitoring of a relatively new group of medicines was the basis for the session about biological products and advanced therapies. The crucial role of communication in pharmacovigilance was also approached from different perspectives and focused on public and media communication. The evaluation of medicines for marketing authorization and the impact of this complex process on patient safety were tackled in three plenary lectures dealing

This article was prepared by Raquel Herrera Comoglio on behalf of the Argentine Society of Pharmacovigilance (www.safv.org.ar). Speaker authorization for publishing the summaries and reviews of lectures is kindly acknowledged.

with benefit/risk balance, off-label use, and the non-commercial sponsorship of clinical research.

Summaries of two sessions and a plenary lecture that have special importance for the Latin-American region are provided below and on the following pages.

The programme from the 8th ISoP conference is available at http://www.isop 2008.org/isop2008-final programme3.pdf.

Harmonization and pharmacovigilance*

The international harmonization of pharmacovigilance has an impact on drug licensing and utilization and on the health and disease burden worldwide, but its impact is greatest within trade alliances, like Mercosur or the European Union. The complex issue of pharmacovigilance harmonization has become a growing concern for regulators and presents considerable challenges.

Global markets and patient safety**
In the context of market globalization, the acceptance and perception of risk and benefit of drugs is influenced by social, structural and legal factors in different countries. The key question is whether harmonization of pharmacovigilance and regulatory action can be consolidated given the varying degrees of pharmacovigilance development observed in the different regions.

Pharmaceutical manufacturers act globally in an unequal world where not all countries have the opportunity to benefit from medical progress or access to health care and where medicines are often lacking. Many countries trading in common markets often have varying priorities in their fight against different diseases. Depending on the situation, these may focus on treating lifestyle diseases or on battling diseases of poverty and underdevelopment. There is also a broad diversity in the structure and quality of pharmaceutical markets, in the number of different products licensed, in the active ingredients and in sales figures. Advertising and promotion of medicinal products to health professionals and direct-to-consumer advertising are just a few of the challenges facing societies within a context of varying financial and human resources, social security systems and infrastructure.

Regulators have a responsibility to ensure patient health and safety and they are required to act within existing national structures and environments. However, their power to act decisively may also be influenced or hindered by overriding public health needs or politics.

The role of harmonization
Harmonization should use the best evidence of favourable or unfavourable drug effects to assess the benefit-to-harm relationship. Likewise, it should promote equal and fundamental rights for populations and the proper use of drugs in all settings in order to achieve high standards of safety.

The main preconditions for harmonization are availability of high quality information and transparency. It is necessary to define different levels of information in order to make appropriate decisions. For underdeveloped countries with difficult Internet access, WHO's role should be reinforced to achieve effective coverage of essential information.

In conclusion, harmonization should reflect and respect differences between countries and societies, but patient safety must have the highest priority. Full access

** Session chaired by Ulrich Hagemann, Pharmacovigilance Department, Federal Institute for Drugs and Medical Devices - BfArM, Germany and Pedro Lipszyc, Buenos Aires National University, Argentina.*
*** Presentation by Ulrich Hagemann.*

to data and exchange of information are key elements for collaboration and interchange between all stakeholders. Regulators should also be supported through international or regional networks and action tending to improve pharmacovigilance in poor or under resourced countries should continue to be strengthened by support from independent organizations.

Pharmacovigilance and the Pan American Network for Drug Regulatory Harmonization*

The objective of the Pan American Network for Drug Regulatory Harmonization (PANDRH) is to offer a forum to identify common activities among members. It aims to establish priorities in drug regulatory harmonization processes, facilitate continuity of technical agreements and encourage convergence of drug regulatory systems within the Americas.

PANDRH is made up of representatives from drug regulatory authorities of the 35 countries in the region, organisms for economic integration such as CARICOM and MERCOSUR, associations of the pharmaceutical industry, academia and nongovernmental organizations. Its main targets are:

- To strengthen drug regulatory agencies at country level.
- To promote constructive participation of all partners.
- To facilitate the establishment of a network of regulatory authorities.

Key concerns are to improve the access to safe and effective medicines of good quality in all countries of the region and to reduce unnecessary, duplicate requirements for drug registration. The group is working for the harmonization of international standards of quality, safety and efficacy and a pharmacovigilance working group was established in 2006 in order to:

- Develop and strengthen pharmacovigilance through activities and harmonized regulatory action that promotes the safe and rational use of medicines as a necessary component of public health policies in the WHO Region of the Americas.
- Promote the development and dissemination of knowledge, criteria and methodologies used in pharmacovigilance for training and education activities directed to all stakeholders.
- Develop, analyse and propose the use of tools to support harmonization of pharmacovigilance in the Region.

In order to improve adverse drug reaction reporting, there must be strong political commitment from each component of the health-care system. As an example, experience in Cuba has shown that appointing a focal point responsible for pharmacovigilance in each district hospital has led to a considerable increase in the number of adverse drug reaction reports.

Lessons learned from the development of pharmacovigilance in Spain*

Spontaneous reporting started in Catalonia in the 1980s, when pharmacovigilance was almost completely unknown to health authorities or health professionals in Spain. Establishment of the Catalonia pharmacovigilance system and research was mainly the result of development of a dynamic Clinical Pharmacology Unit at the University Hospital in Catalonia.

** Presented by Julian Pérez Peña, National Pharmacoepidemiology Development Center, Ministry of Public Health, Cuba.*

**Lecture presented by Joan-Ramon Laporte, Universidad Autonòma de Barcelona, Spain.*

In Catalonia, spontaneous reporting was established, and continues to be developed, as part of a broader communications strategy of drug monitoring between the Clinical Pharmacology Unit and prescribers. It also encompasses a continuous education activity, mainly for health professionals, health managers, policy makers, and politicians working in the health sector. A major contribution of the clinical pharmacology unit to public health was a change in prescription patterns in Catalonia. In 1984, many of the most highly prescribed pharmaceutical products in the health system lacked evidence of therapeutic efficacy, or were simply irrational fixed-dose combinations. In comparison, the most highly prescribed medicines in 2007 had better evidence of efficacy.

The initial pharmacovigilance system received very strong institutional support from the Ministry of Health, which understood the need for collaboration with health professionals independent from the Ministry of Health and public administration, and of communication and making alliances with people working in Universities and hospital structures because of their closer access to prescribers. Spain's integration into the European Union was also positive in establishing regulatory measures for the licensing of new drugs and safety monitoring

The programme was then extended to other Spanish regions and the Spanish Agency for Medicines and Health Products (AEMPS) now maintains a central database, FEDRA, containing 140 000 reports. All the 17 Pharmacovigilance Regional Centres regularly publish bulletins with information on their findings and on drug safety issues.

In all these twenty-seven to twenty-eight years since its establishment, the Spanish pharmacovigilance system has produced many important results in the field of public health.

***Examples of signals leading to market withdrawals**:*

agranulocytosis – cinepacide
hepatitis – bendazac
Guillain Barré syndrome – gangliosides
hepatitis – droxicam
hypersensitivity and hepatotoxicity – glafenine
agranulocytosis – pyrithyldione
hepatotoxicity – ebrotidine
rhabdomyolysis – cerivastatin
liver toxicity – nimesulide
hepatitis – green tea extract
extrapyramidal and psychiatric reactions – veralipride.

Examples of signals leading to changes in approved indications and conditions of use:

Parkinsonism and depression – cinnarizine and flunarizine
taste disorders – citiolone
acute dystonic disorders – clebopride
TB infection – infliximab
(This last signal was generated by a Sao Paulo University Hospital, where a Pharmacovigilance system was set up with the collaboration of the Catalan Institute of Pharmacology.)

Of note, many of the drugs involved had no evidence of efficacy, and this benefit-risk assessment was straightforward. In addition, many of the adverse reactions were type B (not related to the expected pharmacological effect, not dose-related, etc.).

Traditionally, monitoring of medicines safety has mainly relied on spontaneous reporting, especially for detecting type B effects. In Spain, spontaneous reporting also proved to be helpful in clearing the market of irrational and useless medicines – and even harmful and ineffective drugs. However, although spontaneous reporting has proved to be useful in detecting these type B reactions and some type A effects, the surveillance of medicines safety should include other

pharmacoepidemiological methods. Since the drug-induced disease burden consists mainly of type A effects, the challenge is a risk evaluation of these, not only in relative terms but in the amount of deaths or hospitalizations caused by drugs in our societies.

The following represent examples of pharmacoepidemiological methods used in recent years to asses some important drug safety problems:

1. Randomized clinical trials (RCTs) and meta-analysis of randomized clinical trials for assessing the relationship between:

- Hormone replacement therapy and breast cancer, myocardial infarction, thromboembolic disease, cerebrovascular accidents.
- SSRI antidepressants and suicide in children.
- Epoetins and hypertension and cardiovascular risk.

2. Longitudinal follow-up of unselected patients for assessing the relationship between risk of haemorrhage and use of oral anticoagulants.

3. Observational studies, meta-analysis of observational studies and meta-analysis of RCTs for assessing the risk of myocardial infarction with rofecoxib, other COX-2 and other NSAIDs.

4. Spontaneous reporting, observational studies, and meta-analysis of RCTs for gastrointestinal bleeding and NSAIDs and antiplatelet drugs.

5. Meta-analysis of RCTs for assessing the risk of myocardial infarction and death with inhaled anticholinergic drugs.

Special attention must also be paid to drug utilization patterns; not only how much medicine is consumed, but how it is consumed in real practice.

Reporting and publication of adverse drug reactions is a responsibility of regulatory agencies. However, adverse effects of medicines are experienced first hand in clinical practice, and therefore pharmacovigilance is mainly a matter of collaboration and communication within the health system and health care provider organizations and among all other partners of the health care system.

The Spanish pharmacovigilance system was conceived not only for regulatory purposes but also as part of a broader communication strategy between the university and prescribers.

Counterfeit and substandard medicines*

The ISoP session *Counterfeit Medicines and Illegitimate Drugs* tackled the growing problem of counterfeit and substandard medicines.

The World Health Organization defines a counterfeit medicine as “a medicine 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.”

Although an accurate estimate of counterfeit medicines available in markets is difficult to obtain, the number may be more than 10% of the global medicines market, with a probable worth estimate of 75 billion dollars in 2010. Medicines

** Session chaired and presented by Luis Alesso, Córdoba National University and Maria José Sánchez, Argentine Institute of Medicines (INaMe), National Administration of Food, Drug and Medical Technology (ANMAT), Argentina.*

counterfeiting affects individuals from both developing and developed countries. In Latin America, the extent of this problem is still unknown and weak borders between countries make appropriate controls even more difficult to establish.

Developing countries are more affected by this threat because they have, in general, weaker medicines regulatory systems, scarcity and/or erratic supply of basic medicines, unregulated markets and unaffordable prices. An estimated 25% of the medicines consumed in developing countries are believed to be counterfeit; and in some underdeveloped countries, the figure is thought to be as high as 50%.

Because it is a global, serious public health problem, medicines counterfeiting should be considered as a crime and not only as an intellectual property issue or commercial fraud. As a potential cause of serious risk to health which may be life-threatening, the battle against medicines counterfeiting demands the involvement of all social and economic actors from the public and private sectors.

Counterfeit medicines are part of a broader phenomenon of substandard products which can threaten the population's health. Altogether, counterfeit, adulterated medicines, stolen medicinal products, smuggled medicines, unregistered medicines, and expired medicines are generally considered "illegitimate medicines". The definition illegitimate medicines is a legal term, rather than one referring to the quality of a product. All illegitimate medicines are considered as substandard, even when they may have been legally and properly produced (i.e. stolen medicines), because it is impossible to know if they have been correctly stored and transported. It should be noted that some legitimate medicines can also be considered substandard if tests prove that they do not have the appropriate strength, pH, excipients or other chemical properties.

In countries where governments supply medicines for the treatment of specific diseases (such as haemophilia and AIDS), some high-priced medicines are provided free of charge to patients by the state health insurance systems. These products may sometimes be sold by patients to wholesalers and then reintroduced into the market (a process called "revolving").

During this ISoP session, an urgent need was identified for exhaustive and mandatory guidance for medicines purchase, as well as national laws punishing drug counterfeiting or adulteration and marketing of illegitimate, counterfeit and adulterated medicinal products.

Counterfeit and illegitimate medicines: a view from the Americas*

The WHO/Pan American Health Organization (PAHO) states that a counterfeit product cannot be considered a medical product because it has been manufactured and sold by withholding its real origin, evading regulatory controls with an arbitrary and, above all, unpredictable composition. Social and political conditions which help medicines counterfeiting to flourish include:

- Inadequate legislation.
- Weak regulatory oversight and enforcement.
- Inadequate cooperation between drug regulators, police, customs, prosecutors, health professionals, manufacturers, wholesalers, and retailers.

** Presentation made by José Luis Castro, Pan American Health Organization/World Health Organization, Argentina.*

- Trading through several intermediaries/ brokers, wholesalers and the distribution chain.
- Unregulated trade, Internet-based sales, transit through free zones.
- No or limited patient access to reliable health care and medicines supply.
- Lack of control over medicines destined for export.
- The high price of legal medicines.
- Illiteracy and poverty and lack of information or lack of access to information.

WHO/PAHO have undertaken many activities to help prevent and fight medicines counterfeiting: they support countries with technical advice to establish pharmaceutical policies and regulations and by developing guidelines for quality assurance, good manufacturing practices, purchasing, and distribution of medicines. WHO/PAHO coordinates the International Medical Products Anti-Counterfeiting Taskforce (IMPACT) launched to gather all actors in the fight against counterfeiting and target global action against this public health threat.

Adequate information exchange between governments and adviser groups is a priority and PAHO has set up an external quality control programme for national laboratories in the Americas and has developed a regional medicines prequalification system which is now being harmonized with the WHO Medicines Prequalification Programme.

Pan American Network for Drug Regulation Harmonization Anti-Counterfeiting Group

The Pan American Network for Drug Regulation Harmonization (PANDRH) Anti-Counterfeiting Group was created to promote the development of strategies to prevent and fight counterfeit medical products in the Americas. Representatives of national regulatory agencies from Argentina, Brazil, Canada, Colombia, Dominican Republic, Paraguay, St. Lucia, and USA participate in this Group. The pharmaceutical industry is represented by the Federación Latinoamericana de la Industria Farmacéutica (FIFARMA) and the Asociación Latinoamericana de industrias Farmacéuticas (ALIFAR).

The PANDRH Anti-Counterfeiting Group is working on defining indicators for counterfeit medicines and on a proposal, with a standardized procedure, for structural strengthening of national regulatory authorities (NRAs) through a specific executive unit. It is also working on a roadmap which would allow counterfeit medicines structured follow-up and on updating diagnostic studies and recommendations for industry, NRAs and governments in general.

In September 2007, with support from the Ministry of Health in Panama, the PANDRH Anti-Counterfeiting Group held a workshop to establish national and multisectorial task forces and launch coordinated action against counterfeiting. The Group is also working to define and establish a network of vital focal points of communication within and among countries and to draft an inspection guideline. This document was presented at the PANDRH Meeting in Buenos Aires in November 2007.

Argentine National Investigation Programme on Illegitimate Medicines*

In Argentina, the first case of a counterfeit medicine (quinine sulfate) was documented in 1858 but it was not until 1997 that the National Institute of Medicines Programme for the Investigation of Illegitimate Medicines was created. The primary aim of the Programme is to counteract the commerce of counterfeit

** Presentation made by Maria José Sánchez, Argentina*

drugs in order to guarantee quality, effectiveness and security of pharmaceutical products. It acts in joint action with the National Administration for Medicines, Food and Medical Technology (ANMAT), government prosecutors and the Federal Police. The pharmaceutical Industry and Academia also provide valuable collaboration.

The Programme is based on a strict control of the legal medicines marketing chain: it covers community and hospital pharmacies, wholesalers, distributors, and both private and public health-care institutions. The methodology is primarily based on:

- Visual inspection of pharmaceutical products.
- Request for documents proving product purchase.
- Medicines sampling throughout the national distribution chain.

The analysis of products discovered at sites manufacturing counterfeit medicines showed that there was no uniformity in the characteristics of batches, and the quantity of active ingredient varied between zero and 200% of the amount stated on the label. Both primary and secondary packaging were, in general, different from the original. Holograms also demonstrated differences with the originals.

All 12 inspectors of the Argentine Programme for the Investigation of Illegitimate Medicines are pharmacists and are supported by technical, administrative and legal staff. Since Argentina is a federal country, inspectors work in collaboration with the authorities from 23 provinces. In the 1990s, the main problem involved counterfeiting of inexpensive medicines with a high consumption rate. Nowadays, counterfeit or adulterated products are mainly high priced medicines for specific diseases (antiretrovirals, anticancer drugs, products for haemophilia).

In Argentina, there is no law specifically punishing medicines counterfeiting or marketing of illegitimate medicines and the current legislation considers trade in substandard medicines as a commercial offence. Currently, legislation has been proposed against medicines counterfeiting and adulteration and, also, a proposal has been made setting out the administrative requirements for purchase of medicines.

Administrative traceability requirements in medicines purchasing*

In Argentina, the only legislation covering purchasing by public health administration systems and public hospitals refers to the supplier's fiscal status. There is no specific legal rule for medicines purchasing.

In December 2004, at least 19 patients suffered iron poisoning and one of them died following the administration of a counterfeit iron product in a public hospital in Argentina. This product, containing iron citrate instead of iron sorbitex, had 3.5 times more iron than the branded product. The switch in active ingredient was apparently made to obtain the same colour as the original. The product was purchased from a third-party wholesale broker who had no links with the manufacturer. The wholesaler was prosecuted and the Argentine Medicines Agency, ANMAT, immediately published a list of recommendations to avoid the purchase of counterfeit products. But in May 2005, a pregnant woman suffered serious liver failure and premature labour because of the administration of the same counterfeit product in the same public hospital.

Presentation made by Rodolfo Rodriguez, Córdoba Provincial Administration Health Insurance (AProSS), Córdoba, Argentina.

Table: illegitimate medicines identified in Argentina in 2008*

- Rituximab: A physician reported adulteration in a vial; no active principle was found at all.
- Riluzol: Following an adverse drug reaction report. Packaging was adulterated.
- Two rHu-eritropoyetin products: Adulterated products were found in a dialysis centre during an INaMe inspection.
- Epoetin alfa recombinant: Following a physician's report; adulterated packaging.
- Erlotinib: Following a patient report. Adulterated packaging and blister pack with capsules instead of coated tablets. Capsules did contain erlotinib 100 mg.
- Rituximab: A wholesaler reported adulteration in packaging. Reported products had not been legally imported and belonged to batches marketed in other Latin-American countries.
- Trastuzumab: A nurse reported a different color in the vial content. Both packaging and vial had been adulterated; no active principle was found at all.
- Interferon Beta 1-A, Rituximab, parenteral Vitamins: Reported products had not been imported and belonged to batches marketed in other Latin-American countries (Interferon and rituximab) and Spain (Cervenit®).
- Six batches of Concentrated VIII Factor, manufactured in Germany. Following patients' reports (with samples). Samples showed adulteration (pierced stopper, manipulated top, content different from the original in quantity) and fungal development when reconstituted. Original ampoules had been re-utilized.
- Efavirenz: Blisters did not show the expiration date, with ink traces saying "not for sale". Blisters are believed to come from AIDS programmes providing free medicines (community pharmacy).
- One batch of ritonavir, identified in a community pharmacy because of adulterated packaging.

** www.anmat.gov.ar: National Administration of Food, Drugs and Medical Technology (ANMAT), Argentine Health Minister, legal rules N° 193/08, 1185/08, 1416/08, 1943/08, 2599/08, 2831/08, 3307/08, 3351/08, 4125/08, 4143/08, 4244/08, 4543/08, 5647/08, 5650/08, 6110/08*

Before and since then, many other illegitimate products have been found both in public and private health-care institutions, some of them with a sound reputation. In 2008, ANMAT published, among others, 15 legal resolutions withdrawing highly priced products based on laboratory, health care professional or patient reports (see table above).

Marketing authorization holders (MAH) of branded marks add identification devices and traceability systems. However, the fight against the sale of illegitimate medicines also needs concurrent approaches from all partners involved. Health insurance systems have a key role in avoiding counterfeit or illegitimate medicines purchasing.

According to international and National recommendations, Córdoba Province Health Insurance Administration (AProSS) has established a mandatory

list of requirements for wholesalers. It demands wholesalers to supply proof of marketing authorization, wholesaler licensure, inspection results, and a list of any disciplinary action against the wholesaler**.** Packing lists and invoices are also requested in order to ensure legitimacy of medicines. This is an inexpensive and effective traceability system to avoid the purchase of adulterated or illegitimate medicines.

Industry commitment in the battle against fraud and counterfeiting*

For many years, medicines manufacturers' associations have participated in WHO and PAHO Working Groups against medicines counterfeiting, and the pharmaceutical industry is actively engaged in this battle worldwide. The Argentine National Investigation Programme on Illegitimate medicines has been supported by manufacturers' associations and significant outcomes in terms of deactivation of clandestine laboratories, impounding medicines and prosecuting individuals have been achieved.

Argentine medicines manufacturers have identified a need to improve procedures for the public acquisition of medicines, and to identify more funds for the control and monitoring of pharmaceutical wholesalers and pharmacies in provinces. The outstanding role of the PANDRH Network and PAHO in promoting preventive effective action, which are being undertaken and executed by national regulatory authorities in the region, especially ANMAT (Argentina), ANVISA (Brazil), INVIMA (Colombia) and COFEPRIS (Mexico) are recognized.

With regard to measures to prevent counterfeiting and illegal trade of medicines, a stricter authorization process for marketing and approval of facilities and regular audits along the commercialization chain (manufacturing laboratories, pharmaceutical wholesalers and distribution companies, pharmacies and hospitals and health institutions) are essential. An accurate system of medicines traceability and legal rules and procedures to remove manufacturing machines and equipment is also needed. In the search and detection of illegal medicines in unauthorized facilities, it is necessary to collaborate jointly and synchronize actions among the health authorities, police and judicial system.

Manufacturers are involved in intensifying the communication network and providing training to the highest possible number of regulatory agencies in the region. Manufacturers support and are committed to actions of vigilance and control of medicines marketing, the distribution chain, and of unauthorized marketing premises/facilities. It is also essential to improve the education of patients and consumers and to pass clear and strict laws and regulations in order to track down and sanction this crime against public health.

** Presented by Miguel Maito, Cilfa, Industrial Chamber of Argentine Pharmaceutical Laboratories.*

Access to Medicines

Better medicines for children: the way forward

Every second year, the World Health Organization (WHO) convenes the International Conference of Drug Regulatory Authorities (ICDRA). The ICDRAs provide drug regulatory authorities with a regulators-only forum to meet and discuss ways to strengthen collaboration. ICDRA pre-meetings are organized to discuss selected topics of interest linked to regulatory affairs for which participation of regulators and other interested stakeholders gives added value.

The theme of the two day pre-meeting linked to this year's 13th ICDRA in Berne, 14-15 September 2008, was "Better Medicines for Children: the way forward". The meeting was unique in being the first time that regulators, industry, clinicians, civil society and academics worldwide were invited to meet and discuss challenges and seek solutions to ensuring better access to medicines for children. The meeting involved more than 240 participants from 75 countries.

Presentations were given by members of academia, industry and regulatory agencies. They offered perspectives on issues involving the safety, quality and dosing of medicines for children, and the ethical challenges of conducting trials, particularly in children of the developing world. The conference was divided overall into two tracks with presentations focusing on medicines, and biologicals and vaccines.

Discussion included strategies for developing fixed dose combinations for children, alternate dosage forms for children (both liquid and non-liquid formulations). Additionally, it identified gaps and challenges in paediatric research, gave an update on clinical trials in neonates, and presented issues from the WHO Medicines Prequalification Programme. Other presentations focused on challenges in the development, regulation and supply of vaccines and biologicals, as well as issues surrounding safety and pharmacovigilance of vaccines in children.

A summary of the main themes to emerge from the presentations is outlined below. A series of recommendations that have arisen as a result of these discussions is presented on page 257. Detailed information on each of the presentations can be accessed through the following link: http://www.who.int/medicines/

The current situation

- The global mortality rate in children under five years remains inequitable and a significant problem.

- Children's medicines are an identified priority, as stated in the World Health Assembly Resolution on Better Medicines for Children (WHA60.20), and as expressed in the Millennium Development Goals.

- Advances in knowledge and technology have led to:

  - better understanding of paediatric growth and development and the associated changes in paediatric physiology;

  - methodological advances in clinical trials and population health, including adaptive and bridging trials;

- pharmacokinetic modelling techniques; and

- databases of information on medicines safety.

• Positive achievements and developments have been made in regulatory structures with incentives to promote the development of medicines for children, with some additional advances in innovative technology for age appropriate dosage forms.

• Although clinical evidence on how best to use medicines effectively and safely in children has started to be collated, many gaps in knowledge, particularly about the safety of medicines in children and optimal doses remain.

For vaccines and biological products

• Many potential future vaccines for priority diseases are currently in development. However, despite advances in the field, barriers to research and development — including increased technological complexity and safety requirements, high clinical research costs, and ongoing public concerns over vaccine safety — mean that vaccines still occupy only a small portion of the pharmaceutical market.

• Post marketing efficacy data and vaccine pharmacovigilance is an important aspect of vaccine development. Approaches to post marketing surveillance include passive (vaccine adverse event reporting system) and active approaches (phase IV studies, FDA sentinel initiative and CDC's Vaccine Safety Datalink), as well as the use of electronic databases. Advantages and limitations are present with all methods.

• Forty per cent of venomous snake bite victims are children and there is a shortage of appropriate antivenoms throughout world. Improving the quality, quantity and distribution of antivenoms, through support of manufacturers, preclinical and clinical testing, community education, and training of medical personnel is essential.

• Integrating immunization and other child health interventions in a campaign style delivery such as child health days for high-priority health services has proven successful if adequately supported by logistics, distribution, storage systems, supply chain management, tracking and monitoring of supplies.

First steps

The following actions were identified as essential in order to ensure availability and affordable access to appropriate medicines for children:

• Strengthening political commitment to ensure that childhood survival remains a high topic of priority on the agenda.

• Movement towards primary health care, up-scaling high impact interventions at community level, strengthening of health systems, and continued advocacy.

• A global collaborative stakeholder approach – to include patients and carers, health professionals, academics and manufacturers, as well as regulators and policy makers is needed.

• Optimal age-appropriate dosage forms should be developed as a priority.

• Better quality research involving children is required. Capacity building to strengthen ethical and high quality clinical trials globally and increasing the capacity and capability of ethics committees to review and monitor clinical trials is essential. Global standards for clinical trials in children need to be agreed and implemented.

• Unnecessary duplication of research should be avoided. Existing literature, including clinical trials and pharmacokinetic studies in relevant populations

needs to be collated and synthesized. Methods for ensuring transparency of information about existing clinical trials and licensed products need to be developed and implemented globally.

- Strengthening of manufacturing capacity and health systems infrastructure, particularly for vaccines is needed.
- Global strategies need to be developed to promote efficient and effective registration/licensing of medicine for children, with due consideration of risks and benefits.
- Methods to ensure increased safety of medicines for children need to be developed, in particular through monitoring of adverse drug reactions.

In conclusion, the pre-ICDRA meeting dedicated to children's medicines has successfully achieved its objectives and the recommendations will lead to follow-up activities. It is expected that a progress report will be presented to the 14th ICDRA to be held in Singapore in 2010.

Safety and Efficacy Issues

Erlotinib: hepatic failure and hepatorenal syndrome

United States of America — Healthcare professionals have been informed of cases of hepatic failure and hepatorenal syndrome, including fatalities, reported during use of erlotinib (Tarceva®), particularly in patients with baseline hepatic impairment. Patients with hepatic impairment receiving erlotinib should be closely monitored during therapy and the product should be used with extra caution in patients with total bilirubin >3x ULN.

Dosing should be interrupted or discontinued if changes in liver function are severe, such as doubling of total bilirubin and/or tripling of transaminases in the setting of pretreatment values outside the normal range. New information from a pharmacokinetic study in patients with moderate hepatic impairment associated with significant liver tumour burden has been provided in the revised prescribing information.

Reference: Communication from OSI Pharmaceuticals and Genentech. September 2008 and information from FDA, 14 November 2008, at http://www.fda. gov/medwatch

Botulinum toxin type A and distant toxin spread

Canada — Botulinum toxin health products have recently been the subject of safety notices because of their suspected association with the potential spread of the toxin to sites in the body distant from the sites of administration (distant or systemic toxin spread) (1, 2). In Canada, botulinum toxin type A is marketed as Botox® and Botox Cosmetic®. Botox® is indicated for the treatment of cervical dystonia, blepharospasm associated with dystonia, strabismus, dynamic equinus due to spasticity in paediatric cerebral palsy patients, hyperhidrosis of the axilla and focal spasticity (3). Botox Cosmetic® is indicated for the treatment of facial wrinkling (4).

Toxin spread may occur locally, when botulinum toxin disperses to surrounding tissues, as in the case of dysphagia reported with the use of botulinum toxin type A in patients with cervical dystonia (3). In addition, adverse reactions (ARs) suggestive of botulism have also been reported and may occur as the result of systemic toxin spread beyond the site of injection (2). Symptoms of botulism can include muscle weakness or paralysis, dysarthria, dysphagia and dysphonia (5). Serious complications of botulism include respiratory depression and dysphagia which may lead to aspiration pneumonia. These manifestations may be fatal if untreated (5,6).

Extracted from the Canadian Adverse Reactions Newsletter, Volume 18, Issue 4, October 2008.

References

1. Health Canada reviewing issue of distant toxin spread potentially associated with Botox® and Botox Cosmetic®. Ottawa: Health Canada; 20 February 2008.

2. Early communication about an ongoing safety review - Botox and Botox Cosmetic (botulinum toxin type A) and Myobloc (botulinum toxin type B). Rockville (MD): US Food and Drug Administration, 2008.

3. Botox (botulinum toxin type A for injection) [product monograph]. Markham (ON): Allergan Inc.; 2007.

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6. Palmer JL, Metheny NA. Preventing aspiration pneumonia in older adults with dysphagia. *Am J Nurs* 2008;**108**(2):40–8.

Safety review of bisphosphonates

United States of America — On 1 October 2007, the Food and Drug Administration (FDA) announced that it was reviewing safety data on a potential increased risk for atrial fibrillation in patients treated with a bisphosphonate drug (1).

Bisphosphonates are a class of drugs used primarily to increase bone mass and reduce the risk for fracture in patients with osteoporosis. Bisphosphonates are also used to slow bone turnover in patients with Paget disease of the bone and to treat bone metastases and lower elevated levels of blood calcium in patients with cancer. Bisphosphonate products include: alendronate (Fosamax®, Fosamax Plus D®), etidronate (Didronel®), ibandronate (Boniva®), pamidronate (Aredia®), risedronate (Actonel®, Actonel W/Calcium®), tiludronate (Skelid®), and zoledronic acid (Reclast®, Zometa®).

An article and an accompanying letter to the editor in the 3 May 2007 issue of *The New England Journal of Medicine* described increased rates of serious atrial fibrillation in two different studies of women ages 65 to 89 years old with osteoporosis treated with the bisphosphonates, Reclast® and Fosamax®. Data showed an increased risk of serious atrial fibrillation and this risk was reflected in the Reclast® labelling.

On 1 October 2007, FDA began requesting placebo-controlled clinical trial information from the sponsors of alendronate, ibandronate, risedronate, and zoledronic acid in order to explore the potential risk for atrial fibrillation in male and female patients treated with these bisphosphonate drugs.

The data submitted by the four sponsors included data on 19 687 bisphosphonate-treated patients and 18 358 placebo-treated patients who were followed for 6 months to 3 years. The occurrence of atrial fibrillation was rare within each study, with most studies containing 2 or fewer events. The absolute difference in event rates between each of the bisphosphonate and placebo arms varied from 0–3 per 1000.

One large study of zoledronic acid showed a statistically significant increase in the rate of serious atrial fibrillation events. However, across all studies, no clear association between overall bisphosphonate exposure and the rate of serious or non-serious atrial fibrillation was observed. Increasing dose or duration of bisphosphonate therapy was also not associated with an increased rate of atrial fibrillation.

References:

1. http://www.fda.gov/cder/drug/early_comm/bisphosphonates.htm

2. FDA Information at www.fda.gov/medwatch/ 12 November 2008

Ergot-derived dopamine agonists: fibrotic reactions

United Kingdom/European Union — The European Medicines Agency (EMEA) has recommended new warnings and contraindications for ergot-derived dopamine agonists as a result of the risk of fibrosis, particularly cardiac fibrosis, associated with chronic use. The risk of

cardiac fibrosis is higher with cabergoline and pergolide than with the other ergot-derived dopamine agonists. Cabergoline, pergolide, and bromocriptine are indicated for the treatment of Parkinson disease.

Cabergoline (brand leader Dostinex®) is used in hyperprolactinaemia. Bromocriptine (brand leader Parlodel®) is indicated for chronic endocrine disorders such as hyperprolactinaemia and acromegaly. This new advice applies only to treatment of chronic endocrine disorders with these agents — it does not apply to the inhibition of lactation.

Cabergoline and bromocriptine

- Exclude cardiac valvulopathy as determined by echocardiography before treatment.
- Monitor patients for signs or symptoms of pleuropulmonary disease (e.g., dyspnoea, shortness of breath, persistent cough, or chest pain) and retroperitoneal disorders during treatment. Renal insufficiency or ureteral or abdominal vascular obstruction might occur, with pain in the loin or flank and leg oedema. Abdominal masses or tenderness could suggest retroperitoneal fibrosis.

Cabergoline

- Monitor patients for signs of cardiac fibrosis during treatment.
- Echocardiography should be done within 3–6 months of starting treatment and subsequently at 6–12-month intervals.
- Stop treatment if echocardiography shows new or worsened valvular regurgitation, valvular restriction, or valve leaflet thickening.
- Pregnancy should be excluded before administration of cabergoline.
- Women who are planning pregnancy should stop taking cabergoline one month before they try to conceive.

References

1. *MHRA Drug Safety Update*. Volume 2, Issue 3, October 2008 at http://www.mhra.gov.uk/mhra/drugsafetyupdate.

2. http://www.emea.europa.eu/pdfs/human/press/pr/32239508en.pdf.

3. Zanettini R et al. Valvular Heart Disease and the Use of Dopamine Agonists for Parkinson's Disease. *N Engl J Med* 2007; 356–39.

4. Schade R et al. Dopamine Agonists and the Risk of Cardiac-Valve Regurgitation. *N Engl J Med,* 2007; 356–29.

Use of antibiotics in premature labour

United Kingdom —In the ORACLE Children Study (a 7-year follow-up of a large randomized, placebo controlled trial to investigate the effects of erythromycin and co-amoxiclav in premature labour) parents reported small increases in the number of children with mild functional impairment or cerebral palsy born to mothers whose membranes were intact and who had received antibiotics.

In women who presented with spontaneous premature labour without rupture of the membranes, prophylactic antibiotics had neither beneficial nor harmful short-term effects for babies.

Advice for healthcare professionals

- This research was conducted in a very specific group of women and so the results do not mean that antibiotics are generally unsafe for use in pregnancy. Untreated infections can be dangerous and potentially life threatening for pregnant women and their unborn babies, and antibiotics should continue to be prescribed in line with current guidance and the product licence.

- The study confirms existing practice that antibiotics should not be given routinely to women who are in premature labour with intact membranes and who have no obvious infection.

- These results were unexpected and the mechanism by which this reported association occurred in women with intact membranes is unclear, particularly as no increase in functional impairment or cerebral palsy was reported in the children of mothers who received the same antibiotics but whose membranes had ruptured. Additional research is required to shed light on these findings.

References

1. *MHRA Drug Safety Update*. Volume 2, Issue 3, October 2008 at http://www.mhra.gov.uk/mhra/drugsafetyupdate.

2. Oracle Children Study website at http://www.le.ac.uk/cm/rs/oracle/

Intravenous immune globulin: transfusion–related lung injury

Canada — Transfusion-related acute lung injury (TRALI) is a clinical syndrome that presents as acute hypoxaemia and noncardiogenic pulmonary oedema during or within 6 hours after blood transfusion (1, 2). TRALI is an important cause of transfusion-associated death, even though it is probably still underdiagnosed and underreported (2). There have been few literature reports of TRALI in patients administered intravenous immune globulin (IVIG) (3). The Canadian product monograph for Gamunex® (human IVIG 10%) recommends that IVIG recipients be monitored for pulmonary adverse reactions (4).

Health Canada has received a report of a 38-year-old man who had received Gamunex® for the treatment of streptococcal thoracic cellulitis, which had also required débridement. Subsequently, the patient experienced hypotension and dyspnoea and the infusion was stopped. The results of a chest radiograph were compatible with a diagnosis of TRALI. The patient was transferred to the intensive care unit, where he required intubation. The result of an anti-human leukocyte antigen test was pending at the time of reporting.

Extracted from the Canadian Adverse Reactions Newsletter, Volume 18, Issue 4, October 2008.

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3. Rizk A, Gorson KC, Kenney L, et al. Transfusion-related acute lung injury after the infusion of IVIG. *Transfusion* 2001; **41**(2): 264–8.

4. Gamunex® (immune globulin intravenous human 10%) [product monograph]. Toronto: Bayer Inc; 2005.

Alemtuzumab: infection–related deaths

Canada — Health Canada has informed health-care professionals of important safety information regarding the use of alemtuzumab (Mabcampath®) as consolidation therapy following combination treatment with other chemotherapeutic or biologic agents.

Alemtuzumab is a recombinant humanized monoclonal antibody and is currently authorized for the treatment of B-cell chronic lymphocytic leukaemia (B-CLL) in

patients treated with alkylating agents and who have failed fludarabine therapy. Alemtuzumab is not authorized for use as consolidation therapy.

Preliminary safety information from the CALGB10101 clinical trial conducted in the United States, reported 6infection-related deaths out of 51 patients who received 3 chemotherapeutic agents followed by consolidation therapy with Mabcampath®). The potential for an increased risk of infection-related complications may exist following treatment with multiple chemotherapeutic or biological agents.

The phase II CALGB10101 clinical trial reported six infection-related deaths out of 51 patients who received the three chemotherapeutic agents. The six fatal infections were reported as: Viral meningitis, *Listeria* meningitis, *Legionella* pneumonia, cytomegalovirus infection, *Pneumocystis jiroveci* pneumonia, and Epstein Barr virus associated lympho-proliferative disorder.

Reference: Health Canada. MedEffect Alert, 18 November 2008 at http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/_2008/mabcampath_nth-aah-eng.php

Theophylline: narrow therapeutic index and potential for misuse

United Kingdom — Several products that contain theophylline or aminophylline are available as pharmacy medicines that can be dispensed without a prescription. Theophylline—a bronchodilator—interacts with several medicines and has a narrow margin of safety between therapeutic and toxic doses. Therefore, community pharmacists are reminded to check whether patients who buy theophylline without a prescription are also taking any other medicines (including theophylline on prescription).

Reference: *MHRA Drug Safety Update*. Volume 2, Issue 3, October 2008 at http://www.mhra.gov.uk/mhra/drugsafetyupdate.

Cesium chloride and ventricular arrhythmias

Canada — Nonradioactive cesium chloride (CsCl) is used orally as a natural health product. Although not authorized for therapeutic use in Canada, unauthorized cesium products are accessible for purchase (e.g., on the Internet) and are used for the self-treatment of cancer. As of 28 May 2008, Health Canada received 3 reports of prolonged QT interval and ventricular tachyarrhythmia suspected of being associated with the oral use of CsCl.

CsCl's effects on cardiac rhythm have been demonstrated in animal studies, where it has been used to experimentally induce ventricular arrhythmias (3). Although the mechanism is not fully understood, CsCl is known to block a variety of potassium channels, including many of those involved in the cardiac action potential (4,5).

Extracted from the Canadian Adverse Reactions Newsletter, Volume 18, Issue 4, October 2008.

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1. Lyon AW, Mayhew WJ. Cesium toxicity: a case of self-treatment by alternative therapy gone awry. *Ther Drug Monit* 2003;**25**(1):114-6.

2. Pinter A, Dorian P, Newman D. Cesium-induced torsades de pointes. *N Engl J Med* 2002;**346**(5):383-4.

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5. Zhang S. Isolation and characterization of IKr in cardiac myocytes by Cs+ permeation. *Am J Physiol Heart Circ Physiol* 2006;**290**(3): H1038-49.

Drug–induced hyponatraemia

Australia — The Australian Adverse Drug Reactions Committee (ADRAC) continues to receive reports of hyponatraemia (1) in association with various medicines. Severe hyponatraemia is a potentially devastating condition that can develop rapidly and without obvious prior symptoms, particularly in the elderly. Once severe hyponatraemia develops, specialist management is required to achieve a favourable outcome (2).

Since May 2005, ADRAC has received 307 reports of hyponatraemia, several of which also described syndrome of inappropriate antidiuretic hormone secretion. 227 (74%) of the reports implicate a single drug as the suspected cause: mainly diuretics (126 reports) and antidepressants (78 reports, 33 of which were with an SSRI or SNRI).

Severe hyponatraemia, which can cause significant and permanent neurological injury or death (1), was documented in 101 of the reports. Individual drugs most commonly associated with the severe form were hydrochlorothiazide, indapamide, carbamazepine, paroxetine, venlafaxine and sertraline.

Eighty of the 307 reports describe hyponatraemia in association with more than one agent; virtually all of these involved the combined use of a diuretic (hydrochlorothiazide or indapamide) with an ACE inhibitor or an angiotensin II receptor blocker or with an SSRI or SNRI. The combination of carbamazepine with an antihypertensive agent and a diuretic or with an antidepressant was also described.

Older age is generally acknowledged to be a risk factor for hyponatraemia. Two-thirds of the reports received since 2005 describe patients aged over 70 years and over 70% involved women. Onset of hyponatraemia occurred within the first month in 74% of cases that provided this information (median, 11 days).

The clinical presentation varied greatly but the most commonly described disorders were: neurological (including convulsions, postural hypotension, syncope, altered consciousness or coma, somnolence, headache, ataxia, tremor, abnormal gait, visual disturbances and cerebral oedema), psychiatric (including confusion, delirium, agitation and hallucinations) and gastrointestinal (including anorexia, nausea and vomiting).

This series of reports included two deaths which were considered attributable to hyponatraemia.

Although a few reports described hyponatraemia as an incidental finding on routine laboratory testing in asymptomatic patients, there is evidence that even mild levels of chronic hyponatraemia may contribute to an increased rate of falls (3). In fact, nine falls were documented in this series of reports.

Extracted from the Australian Adverse Drug Reactions Bulletin, Volume 27, Number 5, October 2008 at http//www.tga.gov.au/adr

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Slimming health products adulterated with sibutramine

Singapore — In recent months, the Pharmacovigilance Branch of the Health Sciences Agency (HSA) has received three reports of adverse drug reactions (ADR) associated with two slimming health products. On further investigation, the products namely, Relacore® and Lami®, were found to contain sibutramine, an undeclared western drug ingredient used as an appetite suppressant in the management of obesity.

In June 2008, HSA issued a press statement to alert the public of the adulterated product labelled as Relacore®. This was prompted by two ADR reports involving two adult patients (a male and female) in their early twenties. Both patients admitted to purchasing the slimming product over the Internet from a Chinese website. The product was subsequently tested by HSA's analytical laboratory and found to contain 12.22 mg of sibutramine in each capsule.

The adulterated product labelled as Relacore® (which could be a counterfeit of the product sold in the USA) was promoted as a dietary supplement.

Sibutramine-induced psychosis
Sibutramine is a noradrenaline and serotonin reuptake inhibitor indicated for weight loss. Commonly reported ADRs include insomnia, headache and anxiety. Tachycardia and hypertension have also been reported in some patients.

Sibutramine is also known to exhibit significant dopamine reuptake inhibition and some authors have postulated that this could possibly lead to the development of psychotic symptoms, especially in the event of an overdose (1). This is based on the postulation that the dopamine reuptake inhibition could result in excess dopamine in the synaptic clefts and a consequent increased dopaminergic neurotransmission, in line with the dopamine hypothesis of psychosis (2, 3).

Be mindful of Internet purchase of drug & health products
Given the increasing trend of consumers turning to the Internet for purchase of health products, health-care professionals are encouraged to ask patients about the consumption of such complementary medicines or health supplements. Very often, patients may not regard these products as medicines and not mention them to doctors. The information may be important to physicians in making a differential diagnosis of the adverse events experienced by patients.

References

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Phenytoin and fosphenytoin: serious skin reactions

United States of America — The Food and Drug Administration (FDA) is investigating new preliminary data regarding a potential increased risk of serious skin reactions including Stevens Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) from phenytoin (Dilantin®, Phenytek®) therapy in Asian patients positive for a particular human leukocyte antigen (HLA) allele, HLA-B*1502. This allele occurs almost exclusively in patients with ancestry across broad areas of Asia, including Han Chinese, Filipinos, Malaysians, South Asian Indians, and Thais. Because

fosphenytoin is a prodrug and is converted to phenytoin after administration, any concern regarding this association is also applicable to fosphenytoin (Cerebyx®). Phenytoin and fosphenytoin are used to control tonic-clonic (grand mal) and complex-partial seizures in epilepsy. A recent FDA information sheet (12/12/2007), described an increased risk of SJS/TEN with another anti-epileptic drug, carbamazepine, in Asian ancestry patients with the HLA-B*1502 allele.

The FDA is working to identify additional information to evaluate the possible risk of SJS/TEN from phenytoin and fosphenytoin in patients with HLA-B*1502. Until the evaluation is completed, health-care providers who are considering the use of phenytoin or fosphenytoin should be aware of the risks and benefits described in the current prescribing information for this drug.

Because this new data suggests a possible association between HLA-B*1502 and phenytoin or fosphenytoin-induced SJS/TEN, and because of the known association between phenytoin and SJS/TEN, health-care providers should consider avoiding phenytoin and fosphenytoin as alternatives for carbamazepine in patients who test positive for HLA-B*1502.

Reference: *FDA Alert,* 24 November 2008 at www.fda.gov/medwatch/

Etoricoxib: hypertension risks

United Kingdom/European Union — Health-care professionals have previously been informed of the risk of hypertension-related adverse events associated with use of etoricoxib, and of the contraindication for use of etoricoxib in patients with hypertension whose blood pressure (BP) is not adequately controlled.

The European Medicines Agency (EMEA) has recently completed a review of the benefits and risks of 90 mg etoricoxib (Arcoxia®) in the treatment of rheumatoid arthritis and in ankylosing spondylitis. The review included analyses from an observational database (General Practice Research Database) study, which suggest that a substantial number of patients with systolic BP >150mmHg and/or diastolic BP >90mmHg have been initiated on etoricoxib despite earlier recommendations.

Prescribers are therefore asked to note the following updated and strengthened safety recommendations:

- Etoricoxib should not be used in patients with hypertension whose BP is persistently elevated above 140/90 mmHg and has not been adequately controlled.
- In all patients starting treatment with etoricoxib, BP should be monitored within two weeks after initiation, and periodically thereafter.

Reference: Medicines and Healthcare Products Regulatory Agency, September 2008, at http://www.mhra.gov.uk/mhra.

Efalizumab: updated labelling

United States of America — The Food and Drug Administration (FDA) has announced labelling changes to highlight the risks of life-threatening infections, including progressive multifocal leukoencephalopathy (PML), with the use of efalizumab (Raptiva ®). The FDA is also requiring the submission of a Risk Evaluation and Mitigation Strategy (REMS), which will include a Medication Guide for patients and a timetable for assessment of the REMS.

Efalizumab is a once-weekly injection approved for adults with moderate to severe plaque psoriasis who are candidates for systemic (whole body) therapy or phototherapy to control their psoriasis.

The FDA has received reports of serious infections leading to hospitalization and death. The Boxed Warning will highlight the risk of bacterial sepsis, viral meningitis, invasive fungal disease, progressive multifocal leukoencephalopathy and other opportunistic infections.

Additionally, labelling will be updated to include data from juvenile animal studies in mice (age equivalent to a 1–14 year old human). These data indicate a potential risk for the permanent suppression of the immune system with repeat administration of efalizumab in this age group. Raptiva® is not approved for children under 18 years of age.

Efalizumab works by suppressing the immune system to reduce psoriasis flare-ups. However by suppressing the body's natural defence system, it can also increase the risk of serious infections and malignancies in patients.

Patients identified to begin therapy with Raptiva® should have received all their age-appropriate vaccinations before starting the drug. Vaccinations should not be administered to patients taking Raptiva® because immunity to the vaccination virus may not be conferred.

Reference: *FDA News*, 16 October 2008 at http://www.fda. gov/medwatch/

Oseltamivir: hepatic and skin disorders

World Health Organization —The antiviral agent oseltamivir is a selective inhibitor of influenza virus A and B neuraminidase. It is indicated for the treatment and prophylaxis of influenza virus infection types A and B although vaccination is preferred for prophylaxis. It should be commenced early in the course of illness to achieve maximum benefit.

WHO has recommended its use for treating avian influenza A (H5N1) (1).

In 2007 the Uppsala Monitoring Centre (UMC) undertook a review of the international adverse reaction reports attributed to oseltamivir in the WHO Global Individual Case Safety Report Database, Vigibase, as well as the relevant literature and product information. This review did not identify any clearly defined signals of unsuspected serious adverse reactions not already in the product information or regulatory authority alerts, the latter concerning neuropsychiatric reactions.

Reports of serious skin disorders
Reports of Stevens Johnson syndrome and toxic epidermal necrolysis have been reported in Vigibase. These disorders are listed under adverse reactions in product information for Tamiflu® (oseltamivir) but causality has not been established (2). The Vigibase reports did not provide additional information on causality.

Oseltamivir and hepatic disorders
Despite the lack of a clear signal, reports in Vigibase of serious hepatic disorders occurring in association with oseltamivir use were of concern. Reports of hepatic failure, hepatic necrosis, hepato-renal syndrome, jaundice and bilirubinaemia were statistically disproportionate to the background data. Product information for oseltamivir (Tamiflu®) indicated that hepatitis and abnormal liver function tests had been identified during post-marketing experience but that it was not possible to establish a causal relationship with oseltamivir exposure.

Patient characteristics
At the time of the review, Vigibase held 770 reports for oseltamivir. There were 46 non-duplicated reports of hepatic reactions including reports of hepatic failure and necrosis. Numbers of males and females affected were similar and the age range was 18 to 88 years apart from two infants aged 12 months.

Duration of oseltamivir use
Data provided in 25 reports showed patterns of use, duration and reaction onset. Overall, oseltamivir was used for one to five days in 17 patients. The longest periods of use were 8 days and 19 days. In 16 patients, onset of hepatic manifestations occurred up to one week after oseltamivir was discontinued. Hepatic reactions to medicines usually become evident between five and ninety days after first exposure (3). For this reason eight patients with onset one to two days after first exposure and one patient for whom onset was 120 days after exposure were excluded from further analysis.

Dechallenge and rechallenge
No reports had valid dechallenge or rechallenge data.

Hepatic failure, hepatic necrosis and serious hepatocellular reactions
Five reports of hepatic failure and/or hepatic necrosis were identified that contained information on time to onset from first exposure that was appropriate for drug-induced hepatotoxicity. Oseltamivir was the only medicine considered suspect in two of these reports. There were no reports of cholestatic hepatitis occurring within five and ninety days of oseltamivir use. There were five reports of hepatocellular damage but these were poorly documented in terms of exposure duration and other medicines were often co-suspect.

The original copies of eight reports of jaundice and/or bilirubinaemia together with elevated hepatic enzymes or hepatitis were requested from the countries of origin in order to identify serious hepatocellular reactions that are likely to progress to hepatic failure (4). Three such reports were obtained. Two of these patients progressed to the hepatic failure group described above. The third patient had not taken other suspect medicines apart from low dose paracetamol.

Thus oseltamivir appeared to be the most likely causal medicine in two reports of hepatic failure and one serious hepatocellular reaction. It is of note that one patient with hepatic failure had pre-existing renal failure and was taking the maximum recommended daily dose of oseltamivir.

Causality
While oseltamivir appeared to be the most likely causal medicine in three reports of the most serious suspected hepatic reactions, no details of investigations for other potential causes, e.g., viral studies, were provided. The other reports of serious hepatic disorders could not readily be assigned a causality classification. There are difficulties in assigning causality to hepatic reports with oseltamivir for the following reasons:

1. Prodromal symptoms of hepatic disorders may mimic influenza symptoms.

2. Dechallenge data is largely unhelpful as oseltamivir has usually been discontinued before the reaction is evident.

3. If patients have influenza symptoms they are likely to take other medicines that can be hepatotoxic e.g., nonsteroidal anti-inflammatory medicines and paracetamol.

4. A number of patients were also taking antibiotics as well as oseltamivir and many of these are also potentially hepatotoxic.

Items (1) and (2) describe problems that make it almost impossible to assign a “probable” rather than “possible” causality to hepatic reactions attributed to oseltamivir. However, one advantage is that the usual short duration of oseltamivir treatment means that more serious injury may be avoided in many cases, if the association is causal. Most of these difficulties also apply when assessing causality of serious skin disorders following exposure to oseltamivir.

Summary and recommendations

There are reports of hepatic reactions attributed to oseltamivir in Vigibase that are more serious than those described in the product information. Where identifiable, the reports appeared to be predominantly of hepatocellular disorders. There is no clear evidence of causality because it is difficult to discriminate influenza and early symptoms of hepatic disease, because of common concurrent use of other hepatotoxic medicines and because of the usual short duration of oseltamivir use.

There is a strong argument for alternative explanations (described above) for these reports, particularly the likelihood that oseltamivir was used to treat prodromal symptoms of hepatic disease rather than influenza. However, given the potential widespread and unsupervised use of oseltamivir a cautious approach should be considered. This could involve:

1. Alerting patients to the possibility of hepatic and serious skin reactions as well as other documented adverse effects, at the time of prescription.

2. Discontinuation of oseltamivir with hepatic function testing where patients are slow to recover from presumed influenza, or relapse. Such testing would identify both those patients whose hepatic disorder had not been diagnosed earlier because they were presumed to have influenza and those who are developing an adverse reaction to oseltamivir. Oseltamivir will not provide any benefit at this stage and discontinuation may avoid more serious outcomes.

3. Prompt discontinuation of oseltamivir if a serious skin disorder occurs. Patients should also be advised to consult their medical attendant prior to taking this medicine if they have renal impairment, as they may need to take a reduced dose.

References

1. World Health Organization: Clinical management of human infection with avian influenza A (H5N1) virus, at http://www.who.int/csr/disease/avian_influenza/guidelines/Clinical Management07.pdf

2. Tamiflu capsules® (Roche). Physician's Desk Reference. Revised January 2008.

3. Lee WM. Drug-induced hepatotoxicity. *N Engl J Med* 2003;**349**(5): 474-485.

4. Reuben A. Landmarks in Hepatology. Hy's Law. *Hepatology* 2004;**39**(2): 574–578.

5. Report from Vigibase at the WHO Collaborating Centre for International Drug Monitoring, Uppsala, Sweden.

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

Regulatory Action and News

Rimonabant: suspension of marketing authorization

United Kingdom/European Union — The European Medicines Agency (EMEA) has completed a review of rimonabant (Acomplia®), a treatment for obesity, after concerns about its psychiatric safety. The review has found that the benefits of rimonabant do not outweigh the risks of psychiatric reactions in clinical use. The marketing authorization for this medicine will be suspended across the European Union.

Prescribers should not issue any prescriptions for rimonabant and should review the treatment of those who are currently taking this medicine.

Patients who are currently enrolled in clinical trials of rimonabant may wish to contact the trial investigator for more information.

References

1. MHRA Drug Alert, DDL/001/23Oct08 at https://www.cas.dh.gov.uk/ and http://www.mhra.gov.uk/Safetyinformation/ and safetyalerts@dh.gsi.gov.uk

2. *EMEA Press Release*, Doc. Ref. EMEA/CHMP/537777/2008. 23 October 2008. http://www.emea.europa.eu

Vaccines for use in the 2009 influenza season

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

- an A/Brisbane/59/2007 (H1N1)-like virus [A/South Dakota/6/2007 (an A/Brisbane/59/2007-like virus) is a current vaccine virus used in live attenuated vaccines].
- an A/Brisbane/10/2007 (H3N2)-like virus [A/Brisbane/10/2007 and A/Uruguay/716/2007 (an A/Brisbane/10/2007-like virus) are current vaccine viruses].
- a B/Florida/4/2006-like virus [B/Florida/4/2006 and B/Brisbane/3/2007 (a B/Florida/4/2006-like virus) are current vaccine viruses].

Vaccine viruses (including reassortants) and reagents for use in the laboratory standardization of inactivated vaccine may be obtained from: Immunobiology Section, Office of Laboratory and Scientific Services, Therapeutic Goods Administration, P.O. Box 100, Woden ACT, 2606 Australia (fax: +61 2 6232 8564, web site: http://www.tga.gov.au); Division of Virology, National Institute for Biological Standards and Control, Blanche Lane, South Mimms, Potters Bar, Hertfordshire, EN6 3QG England (fax: +44 1707 641050, e-mail: enquiries@nibsc.ac.uk, web site: http://www.nibsc.ac.uk/flu_site/index.html); or Division of Product Quality, Center for Biologics Evaluation and Research, Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20892, United States (fax: +1 301 480 9748).

Requests for reference strains for antigenic analysis should be addressed to the WHO Collaborating Centre for Reference and Research on Influenza, 45 Poplar Road, Parkville, Victoria 3052, Australia (fax: +61 3 9389 1881, web site: http://www.influenzacentre.org); the WHO Collaborating Centre for Reference and Research on Influenza, National Institute of Infectious Diseases, Gakuen 4-7-1,

Musashi-Murayama, Tokyo 208-0011, Japan (fax: +81 42 561 0812 or +81 42 565 2498, web site: http://www.nih.go.jp/niid/index.html); the WHO Collaborating Center for Surveillance, Epidemiology and Control of Influenza, Centers for Disease Control and Prevention, 1600 Clifton Road, Mail Stop G16, Atlanta, GA 30333, United States (fax: +1 404 639 0080, web site: http://www.cdc. gov/flu/); or the WHO Collaborating Centre for Reference and Research on Influenza, National Institute for Medical Research, The Ridgeway, Mill Hill, London NW7 1AA, England (fax: +44 208 906 4477, web site: http:/ www.nimr. mrc.ac.uk/wic). Updated epidemiological information is available on the WHO website at http://www.who.int/influenza.

Reference: *Weekly Epidemiological Record* (WER), **83**(41) 365–372, 10 October 2008.

Australian Adverse Drug Reaction Committee (ADRAC) to be replaced

Australia — The Australian Adverse Drug Reaction Committee (ADRAC) is to be abolished and a new committee set up to take a more pro-active approach to drug safety and post-marketing surveillance of medicines.

ADRAC will be replaced by a Medicines Safety Committee as part of a 'whole-of-lifecycle' approach to pharmacovigilance for prescription medicines. The new approach will also bring in drug audits, the appointment of an individual 'drug monitor' to oversee safety of specific drugs and a more flexible protocol that will allow drugs to be suspended rather than withdrawn or recalled when safety issues arise.

In the reforms planned for next year, the Therapeutic Goods Administration (TGA) says it will also improve access to drug data and increase transparency, with the regulatory body pledging to release more information about listed drugs and inviting consumers to sit on all its committees. As part of this effort, the TGA says it will be publishing consumer medicines information for all drugs and make this available on the TGA web site.

The legislative amendments needed are expected to be introduced in the autumn 2009 sitting of the Australian Parliament.

References:

1. http://www.tga.gov.au/docs/html/tganews/news57/tganews57.htm

2. http://www.tga.gov.au/regreform/common.htm

3. http://www.6minutes.com.au/dirplus/images/6minutes/newspluspharma/13_11_2008.pdf

50th orphan medicine receives positive opinion

European Union — Efforts in combating rare diseases reached a new milestone this October, with the 50th positive opinion on an orphan medicine being adopted by the EMEA's Committee for Medicinal Products for Human Use (CHMP).

To date, a total of 569 medicines have been awarded orphan-designation status by the European Commission, based on recommendations of the EMEA's Committee for Orphan Medicinal Products (COMP).

Developed specifically for the diagnosis, treatment or prevention of rare diseases, these medicines have the potential to offer relief to many thousands of European citizens suffering from chronic and often debilitating diseases who would otherwise have few treatment options available.

A listing of the 50 orphan medicines to have received a positive CHMP opinion is available at http://www.emea.europa.eu/

pdfs/human/comp/56357508en.pdf and Orphan drugs and rare diseases at a glance http://www.emea.europa.eu/pdfs/human/comp/29007207en.pdf

Reference: EMEA website http://www.emea.europa.eu/htms/human/orphans/intro.htm

Telavancin: withdrawal of marketing authorization application

European Union — The European Medicines Agency (EMEA) has been formally notified of the decision to withdraw the application for a centralized marketing authorization for the medicinal product telavancin (Vibativ®) 15 mg/ml powder for concentrate for solution for infusion.

Vibativ® was expected to be used for the treatment of complicated skin and soft tissue infections in adults. In its official letter, the company stated that the withdrawal was based on the CHMP's communication that the data provided were not sufficient to allow it to conclude a positive benefit-risk balance for Vibativ® for the applied indication at that time.

Reference*: Press Release*, Doc. Ref. EMEA/562428/2008 24 October 2008. http://www.emea.europa.eu

Docetaxel: no extension of indication

European Union —The European Medicines Agency (EMEA) has been notified by the manufacturer of its decision to withdraw the application for an extension of indication for the centrally authorized medicines containing docetaxel (Taxotere® 20 mg/0.5 ml and 80 mg/2 ml, concentrate and solvent for solution for infusion and Docetaxel Winthrop® 20 mg/0.5 ml and 80 mg/2 ml, concentrate and solvent for solution for infusion).

Taxotere® and Docetaxel Winthrop® were expected to be used for the adjuvant treatment of patients with operable breast cancer whose tumours overexpress HER2 in the following combinations:

- in combination (given simultaneously) with trastuzumab following a chemotherapy regimen based on doxorubicin and cyclophosphamide.
- in combination with trastuzumab and carboplatin.

Taxotere® and Docetaxel Winthrop® are currently indicated for the treatment of breast cancer, non-small cell lung cancer and prostate cancer, gastric adenocarcinoma and head and neck cancer.

Withdrawal is based on the CHMP's opinion that the study design did not adequately define the contribution of Taxotere® and Docetaxel Winthrop®.

Reference: *Press Release,* Doc. Ref. EMEA/610719/2008 17 November 2008. http://www.emea.europa.eu

Ciclosporin eye drops: withdrawal of marketing authorization application

European Union — The European Medicines Agency (EMEA) has been formally notified by the manufacturer of withdrawal of the application for a centralized marketing authorization for the medicine ciclosporin 0.05% eye drops (Vekacia®). Vekacia® was expected to be used for the treatment of vernal keratoconjunctivitis and was designated as an orphan medicine on 6 April 2006.

Withdrawal of the application was based on the CHMP's view that the data provided did not allow the Committee to conclude on a positive benefit-risk balance for Vekacia® at that time.

Reference: Press Release. Doc. Ref. EMEA/610677/2008. 17 November 2008. http://www.emea.europa.eu

Positive opinions on paediatric investigation plans

European Union — A paediatric investigation plan (PIP) sets out a programme for the development of a medicine in the paediatric population. The PIP aims to generate the necessary quality, safety and efficacy data through studies to support the authorization of the medicine for use in children of all ages. These data have to be submitted to the EMEA as part of an application for a marketing authorization for new medicinal products or products covered by a patent. In some cases, a PIP may include a waiver to study one or more age groups of children, or a deferral when it is appropriate to conduct studies in adults prior to initiating studies in the paediatric population, or when studies in the paediatric population would take longer to conduct than studies in adults.

The Paediatric Committee (PDCO) adopted positive opinions on PIPs for the following medicines:

- Everolimus (oncology); TGplPTH1-34 (Osteogenic Gel I-040302) (endocrinology, gynaecology, fertility and metabolism); AEB0713-(1H-indol-3-yl)-4-(2-(4-methyl-1-piperazinyl)-4-quinazolinyl)-1H-pyrrole-2,5-dione acetate(1:1), (dermatology); Alipogene tiparvovec (cardiovascular diseases); Human Normal Immunoglobulin (immunology and rheumatology); Telbivudine (gastroenterology); Maraviroc (infectious diseases); Tigecycline (infectious diseases).

The PDCO adopted a negative opinion on a PIP for sitagliptin phosphate monohydrate-metformin hydrochloride (endocrinology, gynaecology, fertility and metabolism). The PDCO subsequently adopted on its own motion a positive opinion on full waiver for this medicine in all subsets of the paediatric population, on the grounds that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments for paediatric patients.

The PDCO adopted an opinion on the modification of an agreed PIP for Clopidogrel in the therapeutic area of cardiovascular diseases. Modifications to an agreed PIP can be requested by the applicant when the plan is no longer appropriate or there are difficulties that render the plan unworkable.

The PDCO adopted positive opinions for product-specific waivers recommending that the obligation to submit data obtained through clinical studies with children be waived in all subsets of the paediatric population for the following medicines:

- Lenalidomide (oncology); Ibuprofen - diphenhydramine hydrochloride, from (pain); HIN1, H3N2, and B vaccine; Omega-3-acid (ethyl esters of eicosapentaenoic acid (EPA) - docosahexaenoic acid (DHA)) - simvastatin (cardiology, endocrinology and metabolism).

Waivers can be issued if there is evidence showing that the medicinal product concerned is likely to be ineffective or unsafe in the paediatric population, or that the disease or condition targeted occurs only in adult populations, or that the medicinal product does not represent a significant therapeutic benefit over existing treatments for paediatric patients.

Guideline on neonates
The PDCO reviewed comments made during the public consultation on the guideline on the investigation of medicinal products in preterm and term neonates.

The guideline aims to provide guidance for the development of medicines for use in neonates. It is based on several concept papers released by the Paediatric Working Party (PEG) — the Agency's former expert working party on paediatric medicines, which addressed the impact of immaturity of different organ systems when investigating medicines in neonates.

Neonates represent a particularly vulnerable subgroup of the paediatric population. Whilst they account for a low percentage of the total use of medicines in childhood, up to 90% of medicines are used without a marketing authorization or off-label in this population.

Reference: *Press Release,* Meeting highlights from the Paediatric Committee, 15-17 October 2008. Doc. Ref. EMEA/PDCO/552811/2008. 24 October 2008. http://www.emea.europa.eu

Biosimilar products: a regulatory update

Singapore — A biosimilar medicine is a medicinal product which is similar to a biological medicine that has already been registered with a drug regulatory authority and is submitted for medicinal product registration by an independent applicant after the patent period for the original product has expired.

As the cost of innovative biological products is generally high, thereby limiting use, the expiration of patents on many biological products such as human growth hormone and erythropoietin has prompted the development and licensing of biosimilar products. A biosimilar product would have an abbreviated nonclinical and clinical development programme leveraging on the existing information of the original product and focusing on demonstration of similarity with the original product, also known as the reference product.

Biosimilar products such as Valtropin® and Omnitrope® (both are somatropins) and Binocrit® (which contains epoetin alpha) are registered in the European Union. There are no biosimilar products registered in Singapore as yet but such products will eventually enter the market, subject to approval by HSA.

How are biosimilar products different from generic chemical products?
Biosimilar products may commonly be mistaken for generic versions of the reference biological product. Unlike generic chemical drugs, whereby the chemical structure is identical to that of the reference chemical product, a biosimilar product does not usually have an identical structure to the reference biological product. Hence, even though these biological/biotechnology-derived proteins may be approved by regulatory authorities to be similar in terms of quality, safety and efficacy to a reference biological medicine to which it has been compared, there is a chance that these products may cause adverse reactions which may be different from that of their reference products. One such adverse reaction may be differing immunological response of the patient.

How are biosimilar products assessed?
Biosimilar products are assessed based on comparability data between the biosimilar product and the reference product in terms of quality of product, nonclinical studies (e.g. animal pharmacodynamic studies and toxicity studies) and clinical studies (e.g. pharmacokinetic and pharmacodynamic studies in human subjects). The eventual approval for the biosimilar product may be for the same indication and patient group as that of the corresponding reference product registered in Singapore, or it may be for more restricted indications and patient groups.

Important information concerning biosimilar products

Biosimilar products are similar but NOT identical to an existing biological product.

A biosimilar product may have the same or a more restricted indication for use compared to the existing biological product.

When prescribing a biosimilar product, the brand name of the product should be clearly stated on the prescription.

When dispensing/administering a biosimilar product, only the product with the correct brand name should be dispensed/administered. There should NOT be any substitution with another product with the same international nonproprietary name (INN) without seeking clarification from the prescribing doctor.

When reporting an adverse reaction, the brand name and batch number of the product should be clearly stated.

How should a biosimilar product be prescribed and dispensed?

The decision by a doctor whether to prescribe a biosimlar product or the innovator biological product is dependent on factors relevant to the patient and the institution in which he practises. However when prescribing such products, it is important to use the brand name of the selected product. A biosimilar product may have the same international nonproprietary name (INN) as the reference biological product but they should not be presumed to be identical. Using the brand name will help avoid the issue of automatic substitution of the product when dispensed in the pharmacy, or during administration of the product.

How are adverse drug reactions (ADRs) to biosimilars reported?

In view of the complexity of biological molecules and for the reasons mentioned above, it is pertinent to report the brand name of the biosimilar which is suspected to cause an ADR rather than the name of the substance (e.g. Genotropin® instead of somatropin), together with the batch number of the product used.

References

1. http://www3.niaid.nih.gov/research/resources/DAIDSClinRsrch/Glossary.htm

2. Drug Safety Update Vol. 1, Issue 7 February 2008 from MHRA and CHM

3. *Adverse Drug Reaction News,* Vol. 10 No. 3, December 2008. http://www.hsa.gov.sg

ATC/DDD Classification

ATC/DDD Classification (Temporary)

The following anatomical therapeutic chemical (ATC) classifications and defined daily doses (DDDs) were agreed by the WHO International Working Group for Drug Statistics Methodology in 27–28 October 2008. Comments or objections to the decisions from the meeting should be forwarded to the WHO Collaborating Centre for Drug Statistics Methodology at whocc@fhi.no. If no objections are received, the new ATC codes and DDDs will be considered final and included in the January 2010 issue of the ATC index.The inclusion of a substance in the lists does not imply any recommendation of use in medicine or pharmacy.

ATC level	INN/Common name	ATC code
New ATC level codes (other than 5th levels):		
Agents for atopic dermatitis, excluding corticosteroids		D11AG
Peripheral opioid receptor antagonists		A06AH
New ATC 5th level codes:		
	Aciclovir, combinations	D06BB53
	Alvimopan	A06AH02
	Asenepine	N05AH05
	Bacitracin	J01XX10
	Bazedoxifene	G03XC02
	Becaplermin	A01AD08
	Benzethonium chloride	D08AJ08
	Bromfenac	S01BC11
	Casopitant	A04AD13
	Cefcapene	J01DD17
	Cevimeline	N07AX03
	Cilostazol	C04AX33
	Corifollitropin alfa	G03GA09
	Dalbavancin	J01XA04
	Dapsone	D10AX05
	Dexmethylphenidate	N06BA11
	Doxercalciferol	H05BX03
	Eltrombopag	B02BX05
	Eperisone	M03BX09
	Everolimus	L01XE10
	Fluocinolone acetonide	S02BA08
	Golimumab	L04AB06
	Iclaprim	J01EA03
	Lansoprazole, amoxicillin and clarithromycin	A02BD07

ATC level	INN/Common name	ATC code
	Lisinopril and amlodipine	C09BB03
	Meningococcus, tetravalent purified polysaccharide antigen conjugated	J07AH08
	Meptazinol	N02AX05
	Methylnaltrexone bromide	A06AH01
	Mitiglinide	A10BX08
	Nabiximols	N02BG10
	Nalfurafine	V03AX01
	Oritavancin	J01XA05
	Pazopanib	L01XE11
	Pegloticase	M04AX02
	Phenazone	S02DA03
	Potassium acetate	B05XA17
	Pralatrexate	L01BA05
	Regadenoson	C01EB21
	Saxagliptin	A10BH03
	Silodosin	G04CA04
	Sodium fluoride (18F)	V09IX06
	Sodium levofolinate	V03AF10
	Stavudine, lamivudine and nevirapine	J05AR07
	Tamsulosin and dutasteride	G04CA52
	Valsartan, amlodipine and hydrochlorothiazide	C09DB03
	Vinflunine	L01CA05

INN/Common name	Previous ATC code	New ATC code
ATC code changes:		
Alitretinoin	D11AX19	D11AG04
Clotiapine	N05AX09	N05AH06
Cromoglicic acid	D11AX17	D11AG03
Paricalcitol	A11CC07	H05BX02
Pimecrolimus	D11AX15	D11AG02
Tacrolimus	D11AX14	D11AG01

Previous name	New name	New ATC code
ATC name changes:		
Angiotensin II antagonists and calcium channel blockers	Angiotensin II antagonists and calcium channel blockers, including combinations with diuretics	C09DB
Diazepines, oxazepines and thiazepines	Diazepines, oxazepines, thiazepines and oxepines	N05AH

New DDDs:

INN/common name	DDD	Unit	Adm.R	ATC code
Cefcapene	0.45	g	O	J01DD17
Cefotiam	1.2	g	O	J01DC07
Cevimeline	90	mg	O	N07AX03
Cilostazol	0.2	g	O	C04AX33
Dabigatran etexilate	0.22	g	O	B01AE07
Doripenem	1.5	g	P	J01DH04
Eperisone	0.15	g	O	M03BX09
Febuxostat	80	mg	O	M04AA03
Icatibant	30	mg	P	C01EB19
Meptazinol	1.2	g	O,P	N02AX05
Methylnaltrexone bromide	6	mg	P	A06AH01
Micafungin	0.1	g	P	J02AX05
Mitiglinide	30	mg	O	A10BX08
Polymyxin B	0.3	MU	O	A07AA05
Rilonacept	23	mg	P	L04AC04
Romiplostim	30	mcg	P	B02BX04
Sodium levofolinate	30	mg (1)	P	V03AF10
Tafluprost	0.3	ml (2)		S01EE05

(1) Expressed as levofolinic acid
(2) Single dose package

Change of DDDs

INN/common name	Previous DDD	New temporary DDD	ATC Code
Risperidone*	1.8 mg P depot	2.7 mg P depot	N05AX08

**Please note that the changes will not be implemented before January 2010*

ATC/DDD Classification

ATC/DDD Classification (Final)

The following anatomical therapeutic chemical (ATC) classifications and defined daily doses (DDDs) were agreed by the WHO International Working Group for Drug Statistics Methodology in March 2008. They will be included in the January 2009 issue of the ATC index. The inclusion of a substance in the lists does not imply any recommendation of use in medicine or pharmacy. The WHO Collaborating Centre for Drug Statistics Methodology can be contacted at whocc@fhi.no

ATC level	INN/Common name	ATC code
New ATC 5th level codes:		
	Alipogene tiparvovec	C10AX10
	Arbekacin	J01GB12
	Capsaicin	M02AB01
	Catumaxomab	L01XC09
	Ciclosporin	S01XA18
	Decitabine	L01BC08
	Degarelix	L02BX02
	Doripenem	J01DH04
	Eslicarbazepine	N03AF04
	Icatibant	C01EB19
	Liraglutide	A10BX07
	Mepolizumab	L04AC06
	Oxycodone, combinations	N02AA55
	Panipenem and betamipron	J01DH55
	Peginterferon alfa-2a, combinations	L03AB61
	Perindopril and amlodipine	C09BB04
	Plerixafor	L03AX16
	Pneumococcus purified polysaccharide antigen and *Haemophilus influenzae*, conjugated	J07AL52
	Prucalopride	A03AE04
	Rilonacept	L04AC04
	Romiplostim	B02BX04
	Tocilizumab	L04AC07
	Tocofersolan	A11HA08
	Ustekinumab	L04AC05
	Zucapsaicin	M02AB02

Previous name	New name	New ATC code
ATC name changes:		
Capsicum preparations and similar agents	Capsaicin and similar agents	M02AB
Clostridiopeptidase	Collagenase	D03BA02*
Clostridiopeptidase, combinations	Collagenase, combinations	D03BA52*
House dust	House dust mites	V01AA03*

** Correction of names to be decided at the Working Group meeting in October 2009*

New DDDs:

INN/common name	DDD	Unit	Adm.R	ATC code
Anidulafungin	0.1	g	P	J02AX06
Arbekacin	0.2	g	P	J01GB12
Cefmetazole	4	g	P	J01DC09
Cerolizumab pegol	14	mg	P	L04AB05
Clevudine	30	mg	O	J05AF12
Eculizumab	64	mg	P	L04AA25
Fluticasone furoate	0.11	mg	N	R01AD12
Fosaprepitant	95	mg (1)	P	A04AD12
Raltegravir	0.8	g	O	J05AX08
Rivastigmine	9.5	mg	TD	N06DA03
Tiotropium bromide	5	mcg	Inhal solution	R03BB04
Vildagliptin	0.1	g	O	A10BH02

(1) Expressed as fosaprepitant.

Recent Publications, Information and Events

FIP and the future of hospital pharmacy

The Global Conference on the Future of Hospital Pharmacy was convened as part of the 68th Annual Congress of the International Pharmaceutical Federation (FIP). Hospital pharmacists from around the world met 30–31 August 2008 in Basel, Switzerland and successfully developed 74 consensus statements reflecting the profession's preferred vision of practice in the hospital setting.

The FIP Global Conference on the Future of Hospital Pharmacy has been in planning for nearly three years, during which time a survey of hospital pharmacy practice was conducted. The survey, describing the nature and scope of pharmacy practice worldwide, included responses from 85 nations representing 86% of the world's population.

All of the approved consensus statements, along with evidence-based literature reviews that support the statements, will be published in early 2009 in a special supplement of the *American Journal of Health-System Pharmacy*. Free access to the full proceedings will be made possible through the Journal web site.

Reference: http://www.fip.org/globalhosp

Assessing, monitoring and evaluating pharmaceutical situations

Pharmaceutical sector assessment allows the monitoring and evaluation of access to essential medicines, safety, effectiveness and good quality, and proper use.

The WHO Operational package for assessing, monitoring and evaluating country pharmaceutical situations is intended as a useful tool for researchers, policy-makers, planners and others who need to use standardized measurement tools to gather data and other information. The tools presented have already been used for several years at global and country levels. In addition, the operational package can be used by international agencies and donors, by professional groups and nongovernmental organizations.

Reference: *WHO Operational package for assessing, monitoring and evaluating country pharmaceutical situations.* Guide for coordinators and data collectors. WHO/TCM/2007.2 at http://www.who.int/entity/medicines/publications/WHO_TCM_ 2007.2.pdf

European Pharmaceutical Forum success

The final report of the Pharmaceutical Forum was presented on 18 October 2008 in Brussels setting out principles and recommendations on three key challenges in the pharmaceutical sector. Firstly, how to improve information on diseases and treatments, secondly, how to compare medicines and identify the most effective ones, and thirdly, how to balance access and reward for innovation within limited health-care budgets.

The Pharmaceutical Forum brought together European Union countries and stakeholders, including patient organizations, health professionals, industry and insurers. The final report comprises a set of principles and recommendations to increase cooperation in three key areas.

The Forum adopted the following recommendations:

Enhance quality of information
Core quality principles for the development of information to patients will improve the quality of information by providing a clear and defined framework and also identify information of poor quality. The Forum invites all health actors to refer to the agreed principles. The ban on advertising of prescription medicines should continue.

Increase accessibility
More information to citizens in effective communication formats should be provided (by electronic and non-electronic means), taking account of local traditions, health-care systems and languages.

Generation of information by making the best use of all actors
The Forum recommends that Member States, the Commission and health actors consider strengthened collaboration in the field of information to patients. Such collaboration should respect the minimum ethical requirements of transparency, disclosure of financial and other support and a definition of responsibilities.

Relative effectiveness
Member States, payers and patients face the common challenge of containing health care budgets, including pharmaceutical costs, while promoting and sustaining innovation. They therefore need to recognize the value of identifying the most effective medicines.

Pricing and reimbursement
Final pricing and reimbursement decisions are usually required before patients can access new health solutions and innovative companies can obtain reward for their research. Although pricing and reimbursement decisions are made by individual Member States, they share the concern on balancing access and reward with limited resources.

Optimal use of resources
A toolbox of knowledge should help to use limited resources optimally and address specific mechanisms like risk-sharing/conditional pricing and tendering and adopted Guiding Principles to help national authorities find a balance between expenditure, access and innovation.

Reward for innovation
The expected value of innovation and potential reward mechanisms for innovative medicines have been analysed in order to better match public health needs and long-term investments in research and development.

Follow-up
Member States and stakeholders are invited to implement the recommendations of the Forum. The Commission will provide support to the strengthening of the cooperation tools.

Reference: Report of the European Pharmaceutical Forum, Brussels, 2 October 2008 at http://ec.europa.eu/pharmaforum

Procurement and supply management toolbox

Since the Procurement & Supply Management Toolbox web site went live in December 2007, 27 new tools have been added making a total of 116 English tools.

A separate toolbox has now been developed in French and contains 27 tools. The tool categories are:

1. Policy
2. Selection
3. Quantification
4. Procurement
5. Inventory Management
6. Use
7. Monitoring & Evaluation
8. Pricing
9. Capacity Building

The web site now also contains demo videos, which illustrate how to use the different features of the web site (http://www.psmtoolbox.org/demos.php).

Reference: Vincent Habiyambere at WHO/AMDS habiyamberev@who.int and IDA Solutions cmorris@idasolutions.org. Website at http://www.psmtoolbox.org

Report on essential medicines for children

A draft report of the meeting of the Second Subcommittee on Selection and Use of Essential Medicines for Children, including the draft second Model List of Essential Medicines for Children has now been published as an agenda paper for the March 2009 Expert Committee Meeting.

Reference: Information from World Health Organization at http://www.who.int/selection_medicines/committees/expert/17/en/index.html

Uganda's antimalarials market

The Medicines for Malaria Venture (MMV) has just released a new report mapping the antimalarials market in Uganda. The report highlights a new focus in gathering an evidence base about the structure and size of the antimalarials market in order to guide new initiatives to increase access to high quality malaria medicines.

Understanding the Antimalarials Market: Uganda 2007 — An Overview of the Supply Side provides a wealth of interesting facts about the structure of the antimalarials market in rural Uganda. The study identifies the types of antimalarials available on the market, availability of product by outlet type, range of prices, affordability, supply chain structure, and price mark-ups.

By mapping a detailed record of the range of antimalarials available, where people can access them, and how much they pay, this study provides an evidence base for policy makers in Uganda and internationally to guide initiatives to replace older, ineffective medicines with affordable high quality ACTs.

Reference: *Understanding the Antimalarials Market: Uganda 2007 — An Overview of the Supply Side* http://www.mmv.org and coghlanr@mmv.org

Right to access to medicines

A resolution calling on the African Commission on Human and Peoples' Rights to recognize the human right to access for needed medicines was passed at a meeting of African Human Rights organizations in Abuja, Nigeria, on 10 November 2008.

The NGO forum is composed of approximately 100 human rights organizations in Africa with observer status before the African Human Rights Commission. The resolution will now be transmitted to the African Commission for consideration in its biannual meeting.

The resolution adopted by the Forum calls on the African Commission to recognize "access to needed medicines as a fundamental component of the right to health ...". It specifically calls on the Commission to recognize duties to respect, protect and fulfil rights to access to medicines, including by taking "full advantage of all flexibilities in the WTO Agreement on Trade Related Aspects of Intellectual Property that promote access to affordable medicines." A full copy of the resolution is available at http://wcl.american.edu/pijip/go/humanrights and http://www.wcl. american.edu/pijip/go/resolution-abuja

Reference: African NGO Forum Resolution on Right to Access to Needed Medicines at http://www.wcl.american.edu/pijip/go/resolution-abuja.

New issue of WHO/HAI pricing bulletin

In September, the United Nations Millennium Development Goals (MDG) Gap Task Force reported that medicines are too costly and availability is often poor. The lead article in the *WHO/HAI Pricing Bulletin* outlines key findings in the UN report, and lists national and global targets to reduce prices and improve availability.

Other articles in the bulletin:

- New legislation aimed at making medicines more affordable in the Philippines.
- Actions taken by the Lebanese Government to lower prices and improve transparency.
- The improved availability of artemether/lumefantrine in Kenya.
- What's new in the 2nd edition of the survey manual.
- Key findings from a medicine price and availability survey in Thailand.

Reference: Health Action International website http://www.haiweb.org and http://www.haiweb.org/GlobalDatabase/Main.htm