

# WHO Drug Information

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# International Regulatory Harmonization

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## International Conference of Drug Regulatory Authorities

The 15th International Conference of Drug Regulatory Authorities (ICDRA) took place in Tallinn, Estonia, 23–26 October 2012. The event was hosted by the Ministry of Social Affairs and the State Agency of Medicines of Estonia in collaboration with the World Health Organization. It was attended by over 300 participants from 100 countries. The warm hospitality and excellent logistical support provided by the Agency was greatly appreciated.

The success of the ICDRA was again demonstrated by the increasing number of participants and its ability to respond to the needs and challenges of countries from all parts of the world through development of a relevant, balanced and up-to-date programme. The scope and diversity of topics responded to major trends encountered in the operation of medicines agencies including those issues having an impact on regulatory affairs in a globalized environment. The State Agency of Medicines also organized a one-day visit to their premises in Tartu to offer an overview of activities carried out by a small-country agency. The visit was attended by over 50 people including three from the US Food and Drug Administration.

Regulatory officials contributed to the programme sessions with technical presentations followed by focused discussion. Targeted recommendations were drafted which were considered important in raising awareness of the difficulties faced by agencies or which focused on the continuity and improvement of functionality, networking, collaboration and cooperation. These recommendations are set out below and on the following pages. Presentations made during the ICDRA are available on the WHO web site at <http://www.who.int/medicines/icdra> and on the ICDRA web site at <http://www.icdra.ee> (for a limited time period of six months).

In addition, a pre-ICDRA meeting was convened, 21–22 October 2012, entitled «Quality of medicines in a globalized world: focus on active pharmaceutical ingredients». The objective of the meeting was to offer an opportunity for greater interaction between regulatory officials and other interested parties, such as industry, civil society, scientific institutions and nongovernmental organizations. A brief summary and recommendations from the sessions is set out on pages 352–361.

## 15th ICDRA recommendations

### Plenary 3. Ensuring the quality of active pharmaceutical ingredients

Ensuring the quality of active pharmaceutical ingredients is currently a hot topic for both regulators and industries. Several countries and regions have recently changed their API regulatory requirements. For example, new legislation in the European Union (EU) has reformed the rules for importing APIs for medicinal products for human use. As of 2013, for imported active substances it has to be demonstrated that they have been manufactured in compliance with standards of good manufacturing

practice (GMP) at least equivalent to EU GMP. The first option is that the GMP requirements in the exporting country have been assessed by the EU and the country has been put on the list of equivalent countries. Another option is a written confirmation of GMP compliance from the competent regulatory authority of the exporting country. Additionally, the manufacturing units where the active substance was produced should be subject to control and enforcement of GMP at least equivalent to that in the EU. As a third option, and in exceptional cases to avoid drug shortages, the importing country may decide to accept a GMP certificate issued by an EU inspectorate.

The plenary also looked at existing collaborative arrangements between regulators to ensure API quality and discussed the report from the two-day pre-ICDRA meeting which had been focused exclusively on the broader issues linked to ensuring API quality.

#### **Moderators**

*Andrzej Rys, European Commission, EU and Xinyu Weng, SFDA, China*

#### **Presentations**

*International partnerships in response to globalization of manufacturing of APIs: tools, agreements and networks. Janice Soreth, FDA, USA.*

*Report from the pre-ICDRA meeting. Susanne Keitel, EDQM/Council of Europe, EU.*

### **Recommendations**

#### **Medicines regulatory authorities should:**

- Ensure the quality of active pharmaceutical ingredients (APIs).
- Exporting countries should work closely with the medicines regulatory authorities of importing countries through cooperation, networking and building trust.

#### **Manufacturers should:**

- Purchase APIs from qualified API manufacturers: price alone should not be the determinant for selection.

#### **Medicines regulatory authorities and manufacturers should:**

- Follow international standards, such as those set out in the WHO Pharmaceutical Starting Material Certification Scheme (SMACS), to facilitate international supply of APIs.

#### **Recommendations reported from the pre-ICDRA meeting «Quality of medicines in a globalized world: focus on active pharmaceutical ingredients (APIs)»**

*An overview and recommendations from the pre-ICDRA meeting «Quality of medicines in a globalized world: focus on active pharmaceutical ingredients (APIs)» is set out on page 352. A full report will be published and posted on the WHO web site at <http://www.who.int/medicines>*

#### **National authorities should:**

- Tighten national and regional regulatory oversight of APIs and excipients by implementing control measures throughout the entire legitimate supply chain.

**National authorities and manufacturers should:**

- Carry out and share global intelligence and data on quality APIs.
- Increase enforcement activities to ensure the quality of APIs.

**National authorities and WHO should:**

- Increase measures to ensure consumers are aware of the dangers when purchasing medicines outside of the legitimate supply chain.
- Develop new tools and technologies to enable quality control laboratories to detect falsified/counterfeit APIs.

**Plenary 4. Regulatory collaboration and networking**

Regulators in all countries and throughout all regions are facing many common challenges such as growing interdependence, increasing workload and limited resources. Recently, a series of discussions have emerged in different fora aiming to find new innovative ways to improve collaboration. This plenary forms part of the continuum of discussions between high-level regulatory officials from all six WHO Regions.

**Moderators**

*Guido Rasi, EMA, EU and John Lim, Singapore.*

**Presentation**

*Challenges of the global health system. Dirceu Bras Barbano, Brazil.*

**Panel discussion**

*Youjun Xu, China; B.R. Jagashetty, India; Haged M. Hashan, Saudi Arabia; Hiiti Sillo, Tanzania; Oleksii Sloviov, Ukraine; Mary Lou Valdez, USA.*

**Recommendations**

- Encourage innovative global movements to enhance international regulatory collaboration to yield tangible results beyond what has been achieved to date and taking into account the capacity of medicines regulatory authorities.
- Medicines regulatory authorities should step up commitments to disseminate information that assists regulatory decision-making by other regulatory authorities.
- International collaborative efforts should look at abbreviating processes and establish reasonable and practical targets so that clear progress can be tracked.

**Plenary 5. Pharmacovigilance: vision for the future**

The safety of medicines is an increasing concern for all stakeholders, and regulators have an important role in advancing pharmacovigilance systems. This plenary session was organized in response to a recommendation from the 14th ICDRA to include pharmacovigilance as a main topic at the 15th ICDRA.

The call was consistent with growing awareness of the importance of pharmacovigilance as a component of medicines safety and its worldwide implications, and the perceived urgency to build and strengthen global standards and capacity in pharmacovigilance. In several countries and regions new legislative and organizational initiatives are developing to build more robust pharmacovigilance systems able to monitor safety throughout the product life-cycle.

During the session, the panel on pharmacovigilance sought to highlight current challenges, opportunities and developments. Discussion also centered on creating possibilities for improved sharing of knowledge, information and resources to support the application of global best practices in pharmacovigilance.

**Moderators**

*Esnarte Mwape, Zambia and Mary Lou Valdez, USA.*

**Presentations**

*EU new pharmacovigilance legislation and its impact on global medicines safety.*

*Peter Arlett, EMA, EU.*

*Towards better pharmacovigilance. Singapore regulator's perspective, Christine Ho, Singapore.*

*Developing pharmacovigilance in an emerging economy. Adeline Osakwe, Nigeria.*

*A vision for advancing pharmacovigilance systems. Karen Midthun, USA.*

**Recommendations****Member States and WHO should:**

- Consider broader interpretation of the pharmacovigilance definition as appropriate to the local environment.
- Develop better tools and capacity for effective:
  - ◊ Risk minimization, benefit/risk assessment.
  - ◊ Surveillance, research and decision-making.
  - ◊ Integration and cohesive systems.
- Promote a product “life-cycle pharmacovigilance” that considers safety data during:
  - ◊ Clinical trial development.
  - ◊ Postmarketing surveillance.
  - ◊ Embracing the evidence hierarchy.
- Consider and develop:
  - ◊ Additional sources of data.
  - ◊ Common nomenclature.
  - ◊ Data standards and common reporting.
  - ◊ Data sharing.
  - ◊ Appropriate use of standards.

**Plenary 6. Current topics**

This plenary session gives an opportunity for ICDRA participants to brief the audience on specific country initiatives and developments and addresses topics of common interest which have emerged either since the ICDRA was first planned or during informal discussion during the conference.

**Moderator**

*Murray Lumpkin, USA*

**Presentations**

*A global legally-binding treaty on mercury: implications for pharmaceuticals.*

*David Wood, WHO, Geneva.*

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*Addressing capacity challenges from the perspective of an emerging regulatory agency. The case of Botswana. Sinah Selelo, Botswana.*

*How to modernize ICDRAs? Lembit Rägo, WHO, Geneva.*

*Need for improvement of medicines regulation in Georgia. Tea Jikia, Georgia.*

*Serbia's legal and regulatory environment in medicines. Tatjana Sipetik, Serbia.*

## **Recommendations**

### **How to modernize ICDRAs?**

- WHO should establish a core working group to advise on action and which would:
  - ◊ Seek views from medicines regulatory authorities on any changes they would suggest for future ICDRAs.
  - ◊ Carry out consultations with all interested parties, including e-surveys.
  - ◊ Consider mechanisms for more active linkages and work between ICDRAs.

### **Workshop A. Current trends in regulating blood and cell therapies**

#### **Moderators**

*Jay Epstein, USA and Daniel Roberto Coradi de Freitas, Brazil.*

#### **Presentations**

*Blood as a medicine: summary from pre-ICDRA meeting. Ana Padilla, WHO, Geneva.*

*Regional initiative in developing countries: a road map. Retno Tyas Utami, Indonesia.*

*Plans for regulation of blood products in Zimbabwe. Gugu Mahlangu, Zimbabwe.*

*Considerations on regulation of blood cell therapies. Klaus Chichutek, Germany; Naoyuki Yasuda, Japan.*

## **Recommendations**

- Member States should take steps to assure the quality, safety and availability of blood for transfusion, including oversight through regulation, consistent with WHA 63.12 (2010).
- Member States are encouraged to establish essential medicines lists and to include whole blood and blood components for transfusion on their lists.
- WHO should take further steps to strengthen national blood regulatory systems through education and technical support of national medicines regulatory authorities. Priority should be given to:
  - ◊ Publication and training support on the *WHO Assessment Criteria for National Blood Regulatory Systems*.
  - ◊ Training on *GMP for Blood Establishments* consistent with WHO Guidelines.
  - ◊ Integration of training using available tools.
- Member States are encouraged to develop national regulatory programmes for hematopoietic progenitor cell and other advanced blood cell therapies, taking into account similarities and critical differences with respect to regulation of blood components for transfusion.

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- WHO should encourage progress towards regulation of advanced blood cell therapies through consideration of relevant best practices, including the establishment and strengthening of national blood regulatory systems.

## **Workshop B. Networking and collaboration for better regulation of herbal medicines**

### ***Moderators***

*Hiiti Sillo, Tanzania and Duc Vu, Canada.*

### ***Presentations***

*Experience of regulatory cooperation on herbal medicines: Mercosur. Laura Castanheira, Mercosur/Brazil.*

*Experience of regulatory cooperation on herbal medicines: International Regulatory Cooperation for Herbal Medicines (IRCH). Lucky Slamet, Indonesia.*

*Experience from IRCH Working Group on Vigilance and Standards of Evidence and Forum on Herbal Harmonization. Duc Vu, Canada.*

### ***WHO should:***

- Continue to promote international regulatory collaboration among WHO Member States and facilitate efforts in developing harmonization and/or regulatory convergence of national quality standards, evaluation criteria of evidence on efficacy, pharmacopoeial monographs and pharmacovigilance methodologies for herbal medicines when required, feasible and appropriate.
- Provide technical support to national regulatory capacity building/strengthening for effective and adequate regulation within a comprehensive national policy and legislative framework on health care provision and health systems, and enable national authorities to ensure efficacy, safety and quality of herbal medicines.
- Facilitate implementation of WHO technical guidelines according to circumstances and requirements with regard to:
  - ◇ Verification and establishment of analytical methods for quality control and reference standards for herbal medicines.
  - ◇ Development of pharmacopoeial monographs for herbal medicines.
  - ◇ Development and increased dissemination/communication of product information on herbal medicines to the general public and health care providers including providers of traditional and complementary medicine, to promote patient safety.

### ***Member States are encouraged to:***

- Strengthen communication and collaboration in supporting capacity building of regulation for herbal medicines in resource-limited countries.
- Join collaborative networks at sub-regional, regional and international level to share information, adopt best practices, and make use of WHO guidance documents.
- Focus on regulatory worksharing to avoid duplication.

## **Workshop C. Collaboration and capacity building for vaccines**

Vaccines are a key area for regulatory collaboration between countries and for further capacity building. Although manufactured in only 40–45 countries, a growing propor-

tion of vaccines that are used to immunize the world's population are manufactured in low- or middle-income countries. As biologicals, vaccines require appropriate regulatory oversight and this needs to be strengthened in many countries.

**Moderators**

*Laura Castanheira, Brazil and Johanna Gouws, South Africa.*

**Presentations**

*Developing a shared vision and strategy to build and sustain collaborative vaccine regulatory capacity. Lucky Slamet, Indonesia.*

*Networking for regulatory evaluation of vaccines. Catherine Parker, Canada.*

*Leveraging the prequalification process for national regulatory decision-making. Adam Mitangu Fimbo, Tanzania.*

*A global regulatory science agenda for vaccines. Karen Midthun, USA.*

**Recommendations****Member States should:**

- Consider inclusion of vaccines within the scope of existing or emerging regional regulatory collaborative networks.
- Leverage, as appropriate, the WHO prequalification process for national decision-making.
- Consider developing international networking in the area of vaccine lot release.
- Support implementation of the Global Regulatory Science Agenda (2012) for vaccines.

**WHO should:**

- Assist Member States to build the capacity of networks for regulation of vaccines.
- Promote effective networking activities for vaccines regulation, including global teleconferences.
- Invite more experts from low- or middle-income countries to participate in the WHO vaccine prequalification process.
- Communicate the priorities and benefits of the Global Regulatory Science Agenda for vaccines to Member States.

**Workshop D. Progress and challenges in regulating paediatric medicines****Moderator**

*Agnes Saint-Reymond, EMA, EU.*

**Presentations**

*Update on paediatric initiatives and on the Paediatric Medicines Regulators Network. Agnes Saint-Reymond, EMA, EU.*

*WHO Paediatric Medicines Regulators Network: country experience. Delese Darko, Ghana.*

*Regulating paediatric medicine: a viewpoint from the TGA. Jason Ferla, Australia.*

**WHO should:**

- Make the *Better Medicines for Children/Make Medicines Child Size* initiative sustainable through continuous support to national regulatory authorities and local industry with appropriate resources.
- Continue supporting and funding the network of regulatory agencies for paediatric medicines (PmRN) and its training activities (regular webinars and annual meeting).
- Continue to work on affordable and appropriate (heat and humidity resistant) paediatric formulations (e.g., guidelines).
- Provide support to market shaping to obtain affordable paediatric formulations and avoid shortages.

**Member States should:**

- Harmonize regulatory procedures for paediatric medicines to address market fragmentation.
- Share information on pharmacovigilance on paediatric medicines to make it more efficient.
- Join the PmRN network and encourage participation in training initiatives.
- Identify and address barriers to making paediatric medicines available to children.

**Workshop G. Assessing and responding to training needs of regulators****Moderator**

*Justina Molzon, USA.*

**Presentations**

*Coordinating training of regulators: the EMA experience. Emer Cooke, EU.*

*Challenges in addressing training needs for regulators. Lilit Ghazaryan, Armenia.*

*Training needs to support East African Community regulatory harmonization.*

*Fred Moin Siyoi, Kenya.*

*Training, triage and transparency. Justina Molzon, USA.*

**Recommendations****Medicines regulatory authorities should:**

- Develop a model curriculum to ensure sufficient training to implement medicines regulation effectively.
- Promote competency in evaluation of information submitted for review.
- Initiate academic training programmes on regulatory science.
- Ensure training of the next generation of regulators.
- Leverage expertise of others and tap into existing programmes in order to conserve resources.
- Focus on good review practices to promote consistency and transparency.

- Use CTD/eCTD as a common information-sharing platform.

**WHO should:**

- Encourage Member States to engage in self and external assessments of core regulatory competencies consistent with available guidelines and international models of best practices.

## **Workshop H. Responding to globalization of clinical trials**

**Moderator**

*Alar Irs, Estonia.*

**Presentations**

*Consideration of mutual recognition of clinical trials: study on ethnic factors in China, Japan and Republic of Korea. Naoyuki Yasuda, Japan.*

*Streamlining the clinical trial approval process: NRA networks, information exchange and cooperation. Laura Castanheira, Brazil.*

*European cooperation in clinical trial approval: why and how. Alar Irs, Estonia.*

### **Recommendations**

**Medicines regulatory authorities should:**

- Express views and expectations to medicines developers regarding the applicability of results of multinational trials in their settings and be encouraged to harmonize requirements with other national regulators on a regional basis to foster local clinical development of new medicines from all regions and their timely access to patients.
- Foster mechanisms to engage in dialogue with commercial and non-commercial sponsors of clinical trials to advise on the expectations of regulators regarding planning and conduct of trials.
- Establish cooperation schemes in assessing clinical trial applications and sharing assessment results to reduce duplication of work and improve coherence of regulatory decisions.

**Member States should:**

- Provide adequate resources for regulatory capacity building and collaboration in the field of clinical trial application assessments to increase patient safety and facilitate clinical development of new medicines.

**WHO should:**

- Define the minimum dataset to be presented and assessed together with the clinical trial application to facilitate worksharing.
- Advise governments on setting up efficient regulatory frameworks for clinical trial approval and surveillance.
- Develop a minimum set of data that a regulatory authority would be recommended to make available to other regulators regarding the assessment results of clinical trials.

## Workshop I. Regulatory harmonization

### **Moderator**

*Emer Cooke, EMA, EU.*

### **Presentations**

*APEC experience in developing regulatory convergence. Mike Ward, Canada.*

*Consideration of regulatory harmonization: comparison of medicines, medical devices and cosmetics. Nobumasa Nakashima, Japan.*

*Progress and challenges for East African Community medicines registration harmonization project. Hiiti Sillo, Tanzania.*

## Recommendations

### **WHO should:**

- Make efforts to support greater accessibility of information to facilitate harmonization and convergence activities.

### **WHO and medicines regulatory authorities should:**

- Seek opportunities for prospective harmonization in areas such as advanced therapies.

## Workshop J. Patient and healthcare professional involvement in medicine/medical device regulation

### **Moderators**

*Murray Lumpkin, USA and Gordon Sematiko Katende, Uganda.*

### **Presentations**

*Involving the healthcare professional and patient view in the EU.*

*Tomas Salmonson, Sweden*

*Challenges, opportunities and learning points from stakeholder engagement in medical device regulation. Raymond Chua, Singapore.*

*Update on TGA Blueprint reforms. Mark McDonald, Australia.*

*Patient and healthcare professional involvement in medicines regulation. Cordula Landgraaf, Switzerland.*

## Recommendations

### **WHO should:**

- Encourage medicines regulatory authorities to engage external stakeholders (healthcare professionals and patients) in communication and active participation in the regulation of medicines and medical devices. The choice of communication channels and methods should be dependent on local conditions.
- Encourage and provide support to medicines regulatory authorities to adjust their processes and procedures to improve quality of services by applying user friendly policies allowing stakeholder involvement in the regulation of health technologies aiming to follow and implement good review and good governance practices.

### **Medicines regulatory authorities should:**

- Improve strategies for targeted communication to patients, healthcare professionals and industry to increase overall transparency of regulatory processes and decisions.
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## **Workshop K. New tools for effective collaboration in combating SSFFC medicines**

Substandard/spurious/falsified/counterfeit medicines — SSFFCs — affect many nations across all WHO Regions. During recent years, high-level political discussions have led to establishment of the Member State Mechanism on SSFFC Medicines by the World Health Assembly in 2012. At the same time, regions and countries are continuing their own efforts to tackle the problems. The session presented an overview of some of the developments.

### ***Moderator***

*Paul Orhi, Nigeria.*

### ***Presentations***

*China's new measures for combating counterfeit drugs. Lei Chen, China.*

*West African experience in combating SSFFC medicines. Wiltshire Johnson, Sierra Leone.*

*The UK strategy for combating falsified medicines. Gerald Heddell, UK.*

## **Recommendations**

### ***Member States and WHO should:***

- Focus on the public health implications of SSFFC medical products.
- Actively support the establishment of the new Member States Mechanism within the framework of WHO to enable international collaboration to combat SSFFC medical products, through collaboration with ICDRA, regional anti-counterfeit initiatives and expert advice from other stakeholders.
- The New Member States Mechanism should enable information exchange to help in the prevention and identification of national and regional actions in cases of suspect incidents of SSFFC medical products.

### ***Member States and regions, with WHO and other partner assistance, should:***

- Strengthen their capacity and develop tools to detect, prevent and control the circulation of SSFFC medical products.
- Strengthen through capacity building and international collaboration their regulatory systems.
- Create a global monitoring system enabling exchange for information on SSFFC medical products.

## **Workshop L. Should regulators do everything?**

### **Best practices for prioritization and worksharing**

All regulators at national and regional level have limited resources and are finding it difficult to cope with increasing workloads. It is clear that more efficient use of existing resources is needed using various tools such as prioritization, collaboration and work-sharing.

**Moderator**

*Mike Ward, Canada.*

**Presentations**

*Elements for a risk-based approach in marketing authorization. Petra Dörr, Switzerland.*

*Regulatory prioritization and worksharing: a Singapore perspective. Christina Lim, Singapore.*

*Collaborative inspections involving East African Community authorities.*

*Dennis Mwesigwa, Uganda.*

*International Generic Drug Regulators Pilot Initiative. Mike Ward, Canada.*

**Member States are encouraged to:**

- Consider the application of a risk-based approach to the allocation of resources and infrastructure within national regulatory authorities that considers:
  - ◇ The continuum of risk associated with medicinal products and facilities.
  - ◇ Their national context.
  - ◇ The effective use of information and expertise from other regulatory authorities.

**WHO should:**

- Develop an analytical tool and methodology that would assist national regulatory authorities in introducing a more risk-based alignment of resources, processes and operational structure. Such a tool would complement existing national regulatory authority assessment tools.
- Engage Member States and relevant international initiatives, such as the International Generic Drug Regulators Pilot Initiative, in the design and implementation of a future model for the Programme for Prequalification of Medicines.

**Member States and WHO should:**

- Consider strategies and mechanisms to promote the exchange of staff and other joint activities as a means of building capacity, promoting regulatory convergence and establishing trust.

**Workshop M. How should medical device products be regulated?**

In many countries, the regulation of medical devices is less harmonized and has not reached the same point as medicines regulation. The challenge of regulating medical devices is further compounded by the huge complexity and variety of products and diversity of regulatory systems. However, during recent years many low- and middle-income countries have started to implement medical device regulation. In many countries, the regulatory authorities in charge of medical device regulation are often the same as those for medicines. Due to increasing interest in this area, this was the first time that an ICDRA session was devoted to the topic and updates were presented from several countries and regions followed by general discussion.

**Moderator**

*Josée Hansen, The Netherlands.*

**Presentations**

*Medical devices regulatory system in China. Chenguang Cao, China.*

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*Regulation of medical devices: Tanzanian experience. Adam Mitangu Fimbo, Tanzania.*

*Challenges in regulating medical devices: the European perspective. Josée Hansen, The Netherlands.*

## **Recommendations**

- Medical devices should be regulated to protect public health and promote their proper use.
- Nomenclature systems for medical devices should be harmonized for better understanding by regulators and to better protect public health.
- WHO should encourage collaboration between medicines regulatory authorities with well established regulatory systems for medical devices and countries with less developed systems.

## **Workshop N. Role of regulators in addressing availability**

Together with other governmental institutions, regulators also have a responsibility to facilitate availability of needed medicines. Unfortunately, many needed medicines are not available to the patient for a variety of reasons. The role and practices of regulators in addressing availability varies considerably from country to country and under different circumstances. Consequently, there is a lot to learn from each other. Promoting best practices and better collaboration among regulators in addressing the problem of availability can certainly offer solutions.

### **Moderators**

*Kristin Raudsepp, Estonia and Sonam Dorji, Bhutan.*

### **Presentations**

*Challenges with drug shortages in a small island state: Barbados experience.*

*Maryam Karga-Hinds, Barbados.*

*Addressing drug shortages: Australian experience. Jason Ferla, Australia.*

*Challenges of ensuring availability of quality essential medicines. Sonam Dorji, Bhutan.*

### **Medicines regulatory authorities should:**

- Consider developing an on-line list of shortages of medicines and actively communicate this information to healthcare professionals.
- Utilize the provisions in their available legislation to avoid shortage and availability problems as far as possible.

### **Member States should:**

- Provide a legal framework to foresee crisis situations and develop emergency plans to ensure that the population is protected from severe shortage and unforeseen sudden unavailability of medicines.
- Define the role and obligations of manufacturers to prevent challenges regarding the availability and shortage of medicines so that patients do not lack the necessary treatment.

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**WHO should:**

- Expand the safety alert system to enable exchange of information among MRAs when challenges regarding the availability and shortage of medicines arise which may have repercussions on other countries and internationally.
  - Encourage and facilitate information sharing and networking on biosimilar evaluation status to benefit small- and middle-resourced medicines regulatory authorities.
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**Pre-ICDRA meeting.  
Quality of medicines in a globalized world:  
focus on active pharmaceutical ingredients**

This two-day meeting covered in-depth issues related to the quality of active pharmaceutical ingredients (APIs). Many highly technical presentations were made during the three plenaries and ten workshops dedicated to topics such as how quality can be assessed, what measures need to be taken to ensure manufacture in compliance with good manufacturing practices (GMP), or how to procure safely whilst making best use of worksharing opportunities between regulatory authorities. Other topics ranged from new regional legislative initiatives to ensure API quality; need for assessment of API quality as part of marketing authorization; use of established worksharing schemes to reduce duplication, and ways of securing API supply chain security. In addition, innovative issues were discussed and included: considering blood as an API for blood products, specific challenges related to starting materials of herbal medicines, and harmonization of pharmacopoeias.

**Plenary 1. The importance of starting materials for quality medicines**

Ensuring starting material quality for medicines is high on the agenda for both regulators and industry. In an era of globalization and diminishing resources, collaboration among regulatory authorities is fundamental to safeguarding public health. Agreement on common standards and exchange of information are important measures to be taken, while open dialogue between stakeholders must be promoted in combination with effective collaboration and networking among regulatory authorities.

**Moderators:**

*Susanne Keitel, EDQM/European Council, EU and Xinyu Weng, SFDA, China.*

**Presentations**

*The challenges of globalization for the quality of medicines. Susanne Keitel, EDQM/European Council.*

*Viewpoints from industry associations. George France, IFPMA; Julie Maréchal-Jamil, EGA-IGPA; Barbara Steinhoff, WSMI.*

*API manufacturer's viewpoint. Prashant Deshpande, CIPLA, India.*

**Recommendations**

To achieve consistent and effective regulation of active pharmaceutical ingredients (APIs) it is recommended that:

1. All organizations involved in the API supply chain collaborate in communication and cooperative activities designed to achieve a common understanding of:
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- Applicable standards.
- Responsibilities in relation to the quality of APIs.

2. The regulation of APIs should:

- Be science- and knowledge-based.
- Be appropriate and proportional.
- Be based on harmonized API standards.
- Avoid unnecessary duplication of regulatory activities.

## **Plenary 2. Challenges of ensuring the quality of APIs**

Although the supply of APIs has become increasingly global, their sourcing is concentrated in few regions and countries. Regulators from both well-resourced and resource-limited settings are facing equal challenges in ensuring the quality of APIs. The solution requires a holistic approach to ensuring API quality, including increased information exchange, collaboration and convergence of regulatory approaches.

### ***Moderators:***

*Johanna Gouws, MCC, South Africa and Deusdedit Mubangizi, WHO, Geneva.*

### ***Presentations***

*API regulation in China: progress and challenges. Xinyu Weng, SFDA, China.*

*The new EU rules for APIs: how to get prepared. Stefan Fuehring, European Commission, EU.*

*Challenges of assuring API quality in resource limited settings. Deusdedit Mubangizi, WHO, Geneva.*

*Indonesian experience in controlling API quality. Antoia Retno Tyas Utami, NADFC, Indonesia.*

## **Recommendations**

1. Dialogue and multilateral initiatives should be established between regulators to increase cooperation, convergence, harmonization, transparency and to build trust.
2. Capacity building activities in resource-limited settings should collaborate with, and leverage, relevant organizational expert assessment (for example WHO, EDQM, PIC/S and stringent regulatory authorities) to build API regulation capacity and ensure access to quality-assured APIs. In particular, capacity building initiatives should focus on building practical experience and knowledge during training.

## **Workshop 1. Blood as an API**

The regulation of blood products is complex and currently lags behind other areas of medicines regulation, particularly in terms of equal distribution of regulatory capacity. Discussion focused on the need for strengthening national blood regulatory systems as a key component of making safe, quality blood products available, together with the potential for treating blood and blood products as essential medicines.

### ***Moderators***

*Jay Epstein, CBER/FDA, USA and Paul Strengers, IPFA, The Netherlands.*

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**Presentations**

*Blood and blood components as essential medicines. Jay Epstein, CBER/FDA, USA*

*The WHO Model List of Essential Medicines. Ana Padilla, WHO, Geneva.*

*Regulatory frameworks for blood and blood components. Catherine Parker, Health Canada; Petra Dörr, Swissmedic, Switzerland; Naoyuki Yasuda, MHWL, Japan.*

**Recommendations**

1. Workshop participants endorsed the concept of whole blood and blood components as essential medicines.
2. Interested parties are encouraged to participate in applications for listing of whole blood and blood components (e.g., red blood-cell concentrates) on the WHO Model List of Essential Medicines through timely communication to WHO.
3. WHO is encouraged to make known any applications for listing of whole blood and blood components as Essential Medicines through the WHO Regional Offices.
4. In considering listing of whole blood and red blood-cell concentrates as essential medicines, WHO should note the need to:
  - Establish and strengthen national blood regulatory systems through education and technical support to regulators of medicines.
  - Promote establishment of adequate blood system infrastructures.
  - Assist Member States to avoid potential unintended consequences to existing blood systems.

**Workshop 2. Strategies to prevent counterfeit/falsified APIs**

During the session it was emphasized that it can be very difficult to detect if an API included in a finished dosage form, is falsified/counterfeit. Moreover, APIs can reach a large number of patients as they are usually included in more than one single dose unit. APIs, including those being falsified/counterfeited, can spread easily to several continents in the various stages of production, i.e., as batches of starting materials, intermediates and as a finished dosage form.

Counterfeit/falsified APIs will penetrate more easily into markets that have less stringent regulatory measures and less surveillance capacity in place. Communication and information sharing is therefore very important as, increasingly, strict measures in some countries may lead to redirection of falsified/counterfeit APIs and excipients to other less secure destinations. Among the existing tools that may help in preventing and detecting falsified/counterfeit APIs are the following: new screening technologies (such as NIR and Raman spectroscopy), certification schemes, reporting systems and pharmacovigilance reports.

**Moderator**

*Gerald Heddell, MHRA, United Kingdom*

**Presentations**

*Strategies for fighting falsified/counterfeit starting materials for medicinal products: a regulator's perspective. Lisa Bernstein, FDA, USA.*

*Preventing counterfeit/ falsified APIs – the European API manufacturer's view. Marieke van Dalen, MSD/APIC, The Netherlands.*

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*Preventing counterfeit/ falsified APIs: a viewpoint from the Netherlands. Marcel Moester, Healthcare Inspectorate, The Netherlands.*

## **Recommendations**

### **Regulatory authorities should:**

1. Tighten national and regional oversight of APIs and excipients through control measures throughout the legitimate supply chain.

### **National authorities and manufacturers should:**

2. Strengthen communication and information sharing. Action should take the form of:

- Global intelligence and data gathering
- Capacity building through collaborative training programmes.
- Global cooperation by convergence of standards towards worksharing opportunities.

3. Increase enforcement action.

### **National authorities and WHO should:**

4. Strengthen activities to increase consumer awareness of the dangers posed when purchasing medicines outside of the legitimate supply chain.

5. Develop new tools and technologies to enable quality control laboratories to detect falsified/counterfeit APIs and through:

- Harmonization of technologies.
- Certification.
- Reporting systems.
- Pharmacovigilance.

## **Workshop 3. The importance of assessing API quality as part of marketing authorization**

The API supply chain is complex and effective regulation is needed at both national and international levels. The importance of assessing API quality as part of the marketing authorization was emphasized during the workshop. However, many regulators may lack the specific technical capacity required and remain heavily dependent on work carried out by regulators in other agencies. Harmonizing assessment capacity will require a high level of networking and information sharing among regulators.

### **Moderator**

*Maryam Mehmandoust, ANSM, France*

### **Presentations**

*API assessment from Japanese experience. Naoyuki Yasuda, MHLW, Japan.*

*News on regulatory requirements regarding API quality to be documented in CTD module 3. Jutta Reidl, Swissmedic, Switzerland.*

*Challenges in assessing APIs as part of marketing authorization. Antonia Retno, Tyas Utami, NADFC, Indonesia*

## Recommendations

1. Regulators should collaborate on the identification of available API information and explore how to share the information effectively, including recognition of outcomes of inspections conducted by stringent regulatory authorities.
2. Regulators should establish appropriate procedures to obtain critical technical information relating to APIs that is required for the assessment of dossiers.
3. Existing capacity of medicines regulatory authorities, including technical expertise required for API quality assessment, should be benchmarked to allow the development of appropriate capacity building programmes.
4. The feasibility of developing API regulatory networks should be assessed. The activities of such networks could include information sharing and training in the conduct of assessments and inspections.

### Workshop 4. Collaboration in GMP inspection of API manufacturers

At the present time, it is becoming increasingly evident that cooperative and collaborative arrangements between regulators is the key to effective regulation of APIs. An essential element of monitoring ongoing compliance with quality standards is the conduct of GMP inspections, which may be complicated by the geographical distribution of API and FPP manufacturers.

#### **Moderators**

*David Cockburn, EMA, EU, and Marcel Moester, Healthcare Inspectorate, The Netherlands.*

#### **Presentations**

*Regulation of APIs in the Brazilian market. Jacqueline Condack Barcelos, ANVISA, Brazil.*

*GMP inspection collaboration: past, present and future. David Cockburn, EMA, EU. Optimization of inspections process – industry perspective. Stefan Rönninger, Hoffmann-La Roche/IFPMA, Switzerland.*

## Recommendations

1. Regulators should continue to explore mechanisms for enhancing access to regulatory information by national authorities in resource-limited settings. This should include outcomes of inspections by stringent regulatory authorities, for instance EudraGMP.
  2. Regulators should harmonize inspection processes, such as:
    - Applying a risk-based approach to the design of GMP inspection programmes.
    - Use of common inspection report formats.
    - Avoiding duplication by relying on stringent regulatory authority GMP certificates.
  3. WHO, in collaboration with other concerned parties, should explore methods to leverage existing capacity building and training initiatives, such as those of PIC/S.
  4. Although ICH Q7 is a key resource, a convergence of interpretation of this guidance by different regulators is needed. Reference to resources should be made, such as WHO's respective explanatory notes.
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## **Workshop 5. Collaboration in assessing API documentation**

In the current global medicines market, API manufacturers often supply to several finished pharmaceutical product (FPP) manufacturers. This provides opportunities for collaboration between regulators both regionally and internationally.

### **Moderator**

*Helen Bruguera, EDQM/Council of Europe*

### **Presentations**

*Collaboration in assessing API documentation: the certification procedure.*

*Helen Bruguera, EDQM/Council of Europe.*

*Collaboration in assessing API documentation: a European regulator perspective.*

*Maryam Mehmandoust, ANSM, France.*

*Opportunities for generic medicines industry in more collaborative approaches to assessing API documentation. Jan Moors, TEVA.*

## **Recommendations**

1. Regulators should create greater transparency, harmonization and access to existing API assessment information to avoid duplication of regulatory efforts.
2. National authorities in resource-limited settings are encouraged to take advantage of the existing EDQM certificate of suitability (CEP) procedure and the WHO prequalification of APIs scheme to reduce workload and that of industry whilst ensuring high quality APIs.
3. All stakeholders involved in API manufacture and the supply chain are encouraged to continue collaboration towards achieving consistent and effective regulation of APIs. This requires dialogue between regulators, between industry and between regulators and industry.

## **Workshop 6. Building capacity and ensuring supply of APIs**

A complex API supply chain requires effective regulation at national, regional and international levels. For this to be achieved, a high level of networking and information sharing is needed between regulators as well as communication and cooperation within industry, and between industry and regulators. API quality assurance is a global issue that requires regulatory authorities of highly-resourced countries to contribute to capacity building aimed at addressing regulatory gaps.

### **Moderators**

*Louise Dery, Health Canada and Harry Rothenfluh, WHO.*

### **Presentations**

*Assuring quality of APIs in Ukraine. Denys Gurak, Ukraine.*

*Capacity building in API supply: Japanese experience. Hiroshi Kato, Pharmaceuticals and Medical Devices Agency, Japan.*

## **Recommendations**

1. Regulators should continue to harmonize standards and regulatory processes, such as GMP inspections, and pursue opportunities for cooperation, building of mutual trust and worksharing.
2. National authorities in resource limited settings should be encouraged to take advantage of existing training and capacity building programmes such as those of

PIC/S, the WHO Prequalification of Medicines Programme and those offered by other stringent regulatory authorities.

3. Capacity building activities by WHO and stringent regulatory authorities should:

- Focus on addressing regulatory gaps in quality assessment, toxicological evaluation, GMP compliance, laboratory testing, etc.
- Be designed to provide hands-on experience.
- Be competency based and meet the needs of those being trained.

4. Regulators should develop a consistent approach for sharing regulatory information and making information about regulatory outcomes publicly available.

### **Workshop 7. Specific challenges for herbal medicines**

Challenges for herbal medicines in ensuring the quality and safety of starting materials centre on a lack of harmonized regulatory approaches, standards and testing methodologies. Discussion focused on opportunities for achieving better regulatory convergence.

#### **Moderator**

*Hubertus Cranz, AESGP*

#### **Presentations**

*IRCH working progress on quality of herbal medicines. Yixin Chen, SFDA, China.*

*GMP in the production of herbal medicinal products: a pragmatic approach.*

*Barbara Steinhoff, AESGP.*

*The challenges faced when developing herbal monographs. Samantha Atkinson, MHRA, United Kingdom.*

*Challenges when introducing new analytical assay methods to established monographs. Michael Wierer, EDQM/Council of Europe.*

1. WHO should strengthen and coordinate international regulatory collaboration among member countries to support and develop, when possible, harmonization or regulatory convergence of quality standards, evidence on efficacy and safety surveillance methodologies for herbal medicines.

2. WHO should support regulatory capacity building in countries to develop adequate regulations, in combination with national policy on health care practices and health systems to ensure the safety and quality of herbal medicines.

3. WHO should facilitate the development of testing methodologies for reference standards, herbal monographs, and to enhance patient safety by increasing communication of product information to the public and healthcare providers including alternative and traditional medicine providers.

### **Workshop 8. Supply chain integrity of APIs**

Ensuring supply chain integrity is important for both finished products and APIs. The API supply chain has its own specificity which needs to be considered when planning and applying control measures. Exchange of best practices and information are crucial to the building and maintenance of secure supply chain integrity.

**Moderators**

*Kim Dayman-Rutkus, Health Canada and Stefan Fuehring, European Commission, EU.*

**Presentations**

*The threat of medicines supply from global sourcing of APIs. Gerald Heddell, MHRA, United Kingdom.*

*APEC roadmap on global supply chain integrity. Lisa Bernstein, FDA, USA*  
*Industry challenges to secure supply chain integrity in the global environment.*  
*George France, Novartis/IFPMA*

*Challenges of maintaining supply chain integrity of APIs: a generic industry perspective. Igor Lifshitz, TEVA, Israel.*

**Recommendations**

## 1. Regulators should:

- Collaborate to achieve convergence of standards and engage with manufacturers to ensure a common understanding of requirements.
- Cooperate in regulatory practice, including applying a risk-based approach, in order to avoid duplication of effort.

2. Manufacturers and regulators should be aware of risks to API supply chains and work towards minimization of these risks. More intensive communication and synergy should be established within existing initiatives.

3. Effective quality auditing by finished product manufacturers is crucial to assure compliance of the API supply chain with required standards and can contribute to prevention of supply crises.

4. Regulatory initiatives and collaboration to assure quality of APIs should be strategic, practical and designed to avoid duplication. Any increase of regulation should be balanced by training and capacity building. Existing multinational and international initiatives should continue to play a key role.

5. When assessing risks to the API supply chain, regulators should consider the complexity of the environment, including frequent site and ownership transfers, cross-contamination, change control, design of production lines, reporting culture, investigation skills and environmental issues.

6. The API industry needs to adopt an innovative approach and benchmark against other industries. Industry may consider strengthening information-sharing of audit findings which may be relevant for other actors.

**Workshop 9. Collaboration and harmonization of pharmacopoeias**

Pharmacopoeias are embedded in their respective national or regional regulatory environment. Retrospective harmonization has proven difficult to achieve. Prospective harmonization may be easier but presents certain challenges after the initial work has been done, as the maintenance process over time and the establishment of the related reference standards and logistics need to be viewed within a long-term perspective. Complete pharmacopoeial harmonization is only possible once regulatory systems

have also been harmonized. Developments in science and medical practice, globalization and the presence of adulterated products require pharmacopoeias to constantly adjust. Convergence and reinforced collaboration among pharmacopoeial committees and regulators, supported by adequate interaction with industry, will assist in facing new challenges and resource constraints.

Quality control laboratories may increasingly encounter medical products with unexpected impurities or added substances. Close collaboration with regulators and manufacturers will be essential in such crisis situations.

**Moderators**

*Susanne Keitel, EDQM/Council of Europe and Gugu Mahlangu, Zimbabwe.*

**Presentations**

*International cooperation among world pharmacopoeias: focus on recent events.*

*Sabine Kopp, WHO, Geneva.*

*Towards good pharmacopoeial practices: an industry view on harmonization.*

*J. Mark Wiggins, MSD-Merck/IFPMA, Switzerland.*

*Harmonization of pharmacopoeias: a generic industry perspective. Manish Gangrade, Cipla, India.*

**Recommendations**

1. The pharmacopoeias should use opportunities for collaboration and worksharing globally, regionally, and interregionally.
2. WHO should provide a neutral platform for discussion among pharmacopoeias and the development of good pharmacopoeial practice as a basis for further collaboration, worksharing, convergence and ultimately prospective harmonization. Ideally, this undertaking would be further facilitated by harmonization of regulatory requirements.

**Workshop 10. Prequalification of APIs**

The WHO Prequalification of Medicines Programme (PQP) facilitates access to quality medicines through assessment of products and inspection of manufacturing sites. Since good quality APIs are vital to the production of good quality medicines also needed for disease treatment programmes, PQP has implemented a scheme to prequalify APIs. A list of prequalified APIs provides UN agencies, medicines regulatory authorities and other interested parties with information on APIs that have been found to meet WHO-recommended quality standards.

**Moderators:** *Hiiti Sillio, Tanzania and Valerie Faillat-Proux, Sanofi/IFPMA, Switzerland.*

**Presentations**

*WHO API prequalification: success and challenges. Antony Fake, WHO, Geneva.*

*WHO API prequalification and site inspections. Deusdedit Mubangizi, WHO, Geneva.*

*Assessor experience with WHO API prequalification. Maryam Mehamdoust, ANSM, France.*

*Prequalification of APIs: viewpoint from a manufacturer. Navneet Anand, IPCA, India.*

*The API PQP: a new tool for drug quality, industrial feedback, experience and perspective as participant and user. Valerie Faillat-Proux, Sanofi/IFPMA, Switzerland.*

## Recommendations

1. WHO, national regulators and industry should continue to support the WHO API prequalification scheme to:

- Ensure availability of APIs of known quality and GMP of manufacturers of essential medicines.
- Assist national regulatory decision-making processes in resource-limited settings.
- Build capacity in resource-limited settings by involvement in the WHO API prequalification scheme.

2. WHO and medicines regulators should collaborate further to avoid duplication of effort, increase harmonization and encourage industry participation in the WHO API prequalification.

3. A collaborative approach to inspection and assessment of APIs used during WHO API prequalification is recommended to medicines regulatory authorities to facilitate:

- Tapping into international skills.
- Ensuring transparency.
- Facilitating ownership of outcomes.
- Contributing to capacity building.
- Sharing the workload and avoiding duplicative inspections.

4. Existing tools of information sharing should be developed further and promoted to facilitate collaboration.

## Plenary 3. Best practices and collaboration in regulation of APIs

### **Moderators**

*Susanne Keitel, EDQM/Council of Europe, EU and Harry Rothenfluh, WHO.*

### **Presentations**

*Regulators and industry: tentative identification of joint priorities to address API quality challenges. Georges France, Novartis/IFPMA, Switzerland and Isabelle Clamou, EFPIA*

### **Panel discussion**

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### **General discussion**

*Pre-ICDRA recommendations for presentation at Plenary 3, 15th ICDRA.*

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# WHO Programme for International Drug Monitoring

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## Strategy for promoting best pharmacovigilance practices in resource-limited settings

A 2008 WHO-led assessment of pharmacovigilance activities in 55 low- and middle-income countries (1) confirmed that countries in resource-limited settings face a number of challenges in pharmacovigilance related to:

- Limited experience with newer medicines.
- Overburdened healthcare systems.
- Poor medicines regulation.
- The presence of informal medicines markets.
- Inadequate adverse events databases.
- Inadequate or limited access to information.
- Significant resource constraints.

The United Nations Millennium Development Goals represent a historic commitment to a time-frame for addressing some of the world's greatest development challenges. Millennium Development Goal number eight specifically relates to providing access to affordable essential medicines as a fundamental human right (2). However, efforts to improve access to medicines have not met with a proportionate attention to development of pharmacovigilance systems. This is a concern because access to new medicines is being increased in those very settings that currently have little or no capacity for pharmacovigilance.

For the most part, efforts in advancing pharmacovigilance in the developed and developing parts of the world have progressed in parallel fashion with little overlap. The role of WHO in consolidating these efforts is of primary importance.

### Global challenges in medicines safety

#### Norms and standards

Systems are in place to develop and promote the use of global norms and standards. While harmonized definitions and terminologies for pharmacovigilance exist, additional work is needed to define a broader framework for gathering data on the safety, efficacy and rational use of medicines. Equally, data management

systems that facilitate data-sharing and usage by all stakeholders in pharmacovigilance are essential.

#### Regulatory and policy aspects

Once a safety issue has been identified and validated it must be communicated to medicines regulatory authorities (MRAs) for appropriate action. In developed countries, data collected in pharmacovigilance systems are most commonly used for medicines regulatory activities

such as updating product information or suspending or withdrawing a product from the market. But this is not the case in many developing countries — presumably because the information is considered inadequate to trigger or support regulatory decisions. However, a majority of these countries share pharmacovigilance information with public health programmes, drug information centres and health professionals or drugs and therapeutics committees. Pharmacovigilance information is less commonly used when elaborating essential medicines lists, therapeutic guidelines or in providing information to the public.

### **Methodological issues**

National pharmacovigilance systems rely heavily on spontaneous reporting of adverse reactions by health professionals and manufacturers and, in some settings, by patients. Spontaneous reporting systems are the easiest to establish and the cheapest to run and have proven their value in the early identification of products that need to be recalled and in capturing risks that were not identified during clinical trials. However, because of low and irregular reporting, it is difficult to determine the actual number of individuals experiencing an adverse reaction to the medicine. Additional methods are needed to establish quantitative aspects of medicines safety, identify specific risk factors and high-risk groups and provide valid clinical characteristics of problems associated with specific medicines.

### **Risk management**

Recent market withdrawals of medicines with high market penetration (3, 4), uncertainty about the safety of antidepressants in children and adolescents (5) — and the confusion over reports of cardiac events associated with rosiglitazone (6) — have intensified questioning about safety issues. The pharmaceutical industry is required by stringent regulatory agencies to provide full details of risk management plans prior to product approval with clear

pharmacovigilance plans that identify, characterize and/or quantify risks and delineate risk minimization activities (7). However, very little has been done to adapt these measures for patient safety in the developing world.

### **Missing stakeholders**

In most countries, only healthcare professionals are currently encouraged to report adverse drug reactions. Yet it has been repeatedly demonstrated that healthcare professionals only forward a small number of reports they receive (8). Worldwide, efforts are being made to include consumer organizations in the national pharmacovigilance network. Early results of these efforts indicate that new dimensions of medicine-related problems can be identified and described sooner by patients themselves (9). However, if consumer reporting is to be optimized, methodology and best practice must be internationally agreed and promoted.

Worldwide, the use of traditional medicines has grown. However, few countries include practitioners of traditional medicines in their pharmacovigilance network (1), thus missing out on valuable information from this group of health professionals.

### **Preventable harms and irrational use of medicines**

Ongoing morbidity and mortality from adverse drug reactions remains high and represents a significant yet preventable burden on national health systems (10). Dear doctor letters sent by manufacturers to provide information on potential adverse drug reactions (ADRs) to a specific product and how to avoid them, and safety advisories issued by MRAs and manufacturers to health professionals regarding specific products, have limited impact on prescribing practices. We need to understand why preventable ADRs continue to occur and to develop other methods to mitigate or avoid them.

### **Patient care and case management**

In order to prevent, diagnose and manage relatively rare ADRs, health professionals need information that is up-to-date, well-collated, analysed, validated, and presented in a system that is easy to navigate and process. While databases such as the Cochrane Collaboration and the National Institute for Health and Clinical Excellence (NICE) are good resources, they are not comprehensive or readily accessible to a busy health professional.

### **Dependence, adverse events due to poor quality medicines**

Abuse liability assessment is complex and requires specific, relevant data. Calls have already been made for better use of pharmacovigilance data in this area (11). The data could also contribute to the identification of poor quality and substandard medicines.

### **Communications in pharmacovigilance**

The controversies surrounding the withdrawal of rofecoxib (12) and reports of psychosis with SSRIs (13) highlight the current need for effective, timely and transparent sharing of medicines safety information. Communicating risk-benefit assessment is a huge challenge that involves presenting understandable, coherent information in a responsible and timely fashion, both within professional circles and to the general public.

### **Pharmacovigilance training and capacity building**

The lack of staff trained in pharmacovigilance seems to be the most serious limiting factor for the development of pharmacovigilance in low- and middle-income countries (1). Competencies in cross-cutting scientific areas are normally required in carrying out pharmacovigilance functions. While very few academic institutions offer formal education in pharmacovigilance, several international agencies are stepping in with various

training programmes and activities to support pharmacovigilance in countries. These efforts need to be harmonized to ensure global standards and best practices in pharmacovigilance.

### **Under-reporting, poor quality reports and signal detection**

The primary function of pharmacovigilance is to provide early warning signals of hitherto unknown ADRs. The Bayesian Confidence Propagation Neural Network (BCPNN) and other statistical methods have a high early predictive value and can greatly enhance traditional signal detection procedures. However, the usefulness of these methods relies on the amount and quality of the data available (14, 15). Since pharmacovigilance has not been part of the basic training of practising health workers, considerable efforts are needed to promote the importance of pharmacovigilance and to instil a reporting culture in this group. Under-reporting can seriously compromise the usefulness of pharmacovigilance data.

### **High burden diseases and global health initiatives**

In the developing world, malaria, HIV/AIDS and tuberculosis treatment programmes and immunization programmes have received a lot of attention as components of the Millennium Development Goals. Initiatives such as the Global Fund for HIV, TB and Malaria have dramatically improved access to good quality medicines and reduced the cost of treatment for these diseases. However, efforts have fallen short in not including any pharmacovigilance component or measures for strengthening regulatory systems (16). Between 2003 and 2008, access to antiretroviral medicines in low- and middle-income countries rose ten-fold (17). Yet very little information is available on ADRs in these settings. It is vital to gather data on adverse drug reactions in resource-limited settings, since different populations with different co-morbidities are being treated, compared to treated

### **The WHO Pharmacovigilance Strategy**

- Develops measures that build on the established experience and strength of the Programme and its international network.
- Exploits the current global interest, awareness and favourable atmosphere for pharmacovigilance in general.
- Aggressively addresses the weaknesses in current practices for more effective delivery of Programme goals.
- Strikes new partnerships and alliances to mitigate the many threats and challenges facing the development of pharmacovigilance, particularly in resource-limited settings.

populations in resource-rich countries. These data are essential for the development of policy and country or regional treatment guidelines and to provide better information for patient management.

### **WHO Pharmacovigilance Strategy**

The WHO Programme for International Drug Monitoring (the Programme) aims to address these challenges through a comprehensive and global WHO Pharmacovigilance Strategy that leverages available pharmacovigilance expertise in the developed world to respond to the pharmacovigilance needs of low- and middle-income countries. The specific objective is to build systems that promote the best use of medicines by identifying, minimizing and managing the risks with these products. The long term objective is to advance best practices in pharmacovigilance as a global, cross-cutting theme in both developed and developing settings.

#### **Strategic Partners**

The Programme came into existence in 1968 following two resolutions of the World Health Assembly (WHA 17.39 and WHA 19.35) that requested WHO to develop methods for monitoring adverse reactions to medicines. In 1978, an agreement was reached with the Swedish Government to transfer opera-

tional activities of the Programme to a Collaborating Centre in Uppsala while retaining responsibility for policy aspects, coordination, and dissemination of information at WHO, Geneva.

The Programme brings together all relevant stakeholders to develop and enact a pharmacovigilance strategy for the safety and safe use of medicines worldwide. These stakeholders include:

- Member countries participating in the Programme.
- The WHO Medicines Safety Team at Headquarters, and the six WHO regions and country offices.
- The WHO Collaborating Centre for International Drug Monitoring/Uppsala Monitoring Centre (UMC), Sweden.
- The WHO Collaborating Centre for Training and Advocacy in Pharmacovigilance, in Accra, Ghana.
- The WHO Collaborating Centre for Pharmacovigilance and Patient Safety in Rabat, Morocco.
- The WHO Collaborating Centre for Drug Statistics Methodology in Oslo, Norway.

In addition, the Pharmacovigilance Strategy benefits from direct input from various other programmes within WHO: Medi-

cines Regulatory Support, the Medicines Prequalification Programme, various public health programmes dealing with HIV, TB, malaria, vaccines, neglected tropical diseases, and the WHO Family of Classifications (FIC), the WHO Patient Safety Programme, etc.

Different technical agencies are invited to assist in the implementation of the pharmacovigilance strategy at national and regional levels. These include Management Sciences for Health (MSH), Systems for Improved Access to Pharmaceuticals and Services (SIAPS)/USAID and professional organizations such as ISoP, FIP, ISPE, etc., as well as academia, nongovernmental organizations and national information centres.

Industry input is channeled through institutions such as the Council for International Organizations of Medical Sciences (CIOMS), the International Conference on Harmonization (ICH) and the International Federation of Pharmaceutical Manufacturers Associations (IFPMA).

The Programme also benefits from the expertise of stringent regulatory authorities, individual consultants and other expert networks. Overall guidance and expert advice are provided by the WHO Advisory Committee on Safety of Medicinal Products (ACSoMP).

### **Strategic choices: prioritizing the challenges**

Given the breadth of challenges and available resources, the approach for advancing the Pharmacovigilance Strategy will continue to be priority-driven, implementing activities in a phased, step-wise manner. Establishing norms and standards for pharmacovigilance will have the highest priority for high burden diseases in selected countries. A strategic approach will be to ensure that at least minimum pharmacovigilance systems, structures and processes are in place in countries before planning for advanced activities such as medication

errors, monitoring events due to poor quality medicines, or drug resistance.

## **Strategic activities**

### **Norms, standards and guidelines**

Over the years, partners within the Programme have been working together to develop and promote norms and standards for best practice and innovation in the collection, storage, analysis and communication of pharmacovigilance data. These collaborative efforts will continue with a focus on, but not limited to, priority diseases (HIV, TB and malaria), special populations (children, women and the elderly), consumers, and new medicines. The resulting publications, handbooks and guidelines will be made available to Member States and those interested in medicines and patient safety.

### **Classifications, terminologies and definitions**

The WHO Collaborating Centre for Drug Statistics Methodology is responsible for the Anatomical Therapeutic and Chemical (ATC) classification and Defined Daily Dosage (DDD) system. An international working group oversees the work which provides important tools to allow the classification of medicines and measurement of drug utilization across and within countries.

The activities of CIOMS cover a broad range of drug safety topics via working groups. Senior scientists from regulatory authorities, the pharmaceutical industry and academia form part of working groups that have developed tools such as the international reporting forms for adverse drug reactions (CIOMS I reporting form), terminologies and definitions of adverse drug reactions. These efforts will be continued, particularly in the context of the expanding scope of pharmacovigilance towards harmonized standards and comparable data. The Programme will collaborate with the FIC and the Department of Traditional and Complementary Medicines (TRM) to produce an interna-

tional standard terminology and classification system for uniform data collection, monitoring, and evaluation of traditional medicines.

### Exchange of information

From WHO HQ, the Programme has established a network of designated national medicines information officers to manage the regular exchange of information between Member States on the safety and efficacy of pharmaceutical products. This practice will continue with information disseminated through publication of the *WHO Pharmaceuticals Newsletter* (18) and by distribution of one-page *Alerts* (19) on an ad hoc basis.

Relevant restrictive regulatory decisions will be published in the *United Nations Consolidated List of Products Whose Consumption and/or Sale Have Been Banned, Withdrawn, Severely Restricted or not Approved by Governments*. WHO will also continue to publish updates to this list in *Pharmaceuticals: Restrictions in use and availability*. WHO Regional mechanisms for exchanging and analysing information, including bulletins, journals, etc., will be exploited further to make information available more quickly, widely, and in an open and transparent manner. Specific methods of communication or cooperation of proven usefulness, such as e-mail groups, communities of practice, regional observatories and web platforms will be encouraged and pursued.

### Training and capacity building

WHO, together with its collaborating centres and other technical partners, will continue to organize courses and training programmes to build and strengthen pharmacovigilance capacity in various countries.

The following additional activities will be advocated to improve efficiency:

- Integrating pharmacovigilance into the curriculum.

- Developing a comprehensive training module that countries can adapt and use.
- Working with countries to apply pharmacovigilance within a regulatory framework.
- Increasing support to countries by developing and maintaining a database of pharmacovigilance experts.
- Developing specific modules and training activities for pharmacovigilance for inclusion in public health programmes.
- Developing online courses for e-learning and self-training in pharmacovigilance.
- Establishing centres of excellence to provide training in key pharmacovigilance methodologies and research areas.
- Advancing twinning arrangements and exchange programmes in pharmacovigilance between countries.
- Organizing quality translations of key documents and guidelines into all UN official languages.

### Minimizing preventable harms from medicinal products

Capturing comprehensive data as a source of learning is the basis for identifying areas of change and promoting recommendations for minimizing preventable adverse drug reactions. The Programme will work with partners such as the World Alliance for Patient Safety to promote an extended role for pharmacovigilance centres, unveil medication errors reported as adverse drug reactions, understand systemic failures responsible for adverse drug reactions, and propose corrective solutions to minimize adverse events due to medicines.

### Regulatory aspects

The Programme will propose measures to ensure that pharmacovigilance will con-

tribute to regulatory decision-making and in turn will be strengthened by association. Partners will organize training programmes to build pharmacovigilance capacity in regulatory agencies. In particular, the training programmes will strengthen regulatory capacity to assess pharmacovigilance systems and risk management plans and will create an enabling environment within countries for industries to fulfil their pharmacovigilance obligations. Many small-sized countries receive less than 100 individual case safety reports per year — a number too small to assist in signal detection or inform local regulatory decisions. The Programme will address this issue by bringing together smaller countries with similar demographics, genetic background, nutritional status and co-morbidities to consolidate their data for common regulatory decision-making.

### **Access to data and responsible communication**

The WHO Collaborating Centre for International Drug Monitoring at the Uppsala Monitoring Centre (UMC) manages the WHO global database of individual case safety reports (20). Every effort is made to ensure that the database is populated with the best quality data from countries, whilst adhering to applicable country laws and regulations, so that the Programme can fulfil its mandate of detecting signals and providing global information on drug safety. As regards initiatives such as EudraVigilance (the European Union Pharmacovigilance database), WHO will continue to work with the European Medicines Agency (EMA) for the optimal transmission of reports to the WHO global database.

The Programme will share the results of signal assessments with national authorities. Assessments will also be made public through WHO bulletins, newsletters and scientific journals for broader dissemination and knowledge sharing.

### **Additional methods and data sources to complement spontaneous reporting**

The Programme will develop methods of scientific rigour that can complement spontaneous reporting. Cohort event monitoring (CEM) and targeted spontaneous reporting (TSR) are two such methods that have been developed and will be promoted. Other sources of data — registries, population databases, electronic health-care records, etc., — will also be exploited as useful sources of pharmacovigilance information to support signal detection and global information exchange.

### **Broader use of existing pharmacovigilance data**

Existing WHO Adverse Drug Reaction Terms (WHO-ART) such as drug abuse, drug dependence, or withdrawal syndrome, provide a good starting point for detecting dependence liability in therapeutic use. Ascertaining whether the reaction terms 'treatment ineffective' and 'therapeutic effect decreased' could serve as surrogate markers for identifying medicines of poor quality will be explored. The UMC is also engaged in identifying indicators of dependence liability and therapeutic inefficacy in the WHO ADR database. Such investigations will be supported further to inform the work of various expert committees in WHO (for example, the Expert Committee on Drug Dependence, Expert Committee on the Selection and Use of Essential Medicines) and other programmes such as the WHO Quality Assurance of Medicines Programme.

### **Public health programmes**

The Programme will continue working with various disease treatment programmes to introduce the principles of pharmacovigilance to the treatment of priority diseases (HIV, TB and malaria), as well as neglected diseases (leishmaniasis, lymphatic filariasis, schisto-

somiasis and Chagas). The use of CEM and TSR will be promoted for safety data within these programmes, and to identify issues concerning operative procedures and actual implementation of the guidelines (21).

### **Global health initiatives and minimum pharmacovigilance requirements**

WHO will work with various stakeholders (including the Global Fund and UNITAID) to ensure that treatment programmes supported by these initiatives will include at least the minimum pharmacovigilance components (22). A pharmacovigilance tool kit (23) has also been developed to facilitate the technical implementation of pharmacovigilance within these programmes. The WHO Collaborating Centre for Advocacy and Training in Pharmacovigilance, Accra, Ghana, will have a leading role in both maintaining the tool kit and in assisting countries in the implementation of minimum pharmacovigilance requirements. Additional technical agencies such as SIAPS and regional partners will also be brought in to facilitate global implementation.

### **Electronic transfer and data management systems**

According to ICH standards, individual case safety reports have to be 'E2b compatible' where E2b defines the format for the electronic transfer of individual case safety reports (ICSRs). In view of this, and in support of countries that do not have a data management system of their own, the UMC has developed a data management tool (VigiFlow™) which allows a seamless online submission of ICSRs that include all E2b fields. VigiFlow™ also allows national centres to manage their data locally, thereby eliminating the need for additional software for national database management. WHO will work with the UMC to promote use of this data management tool as a cost effective way of setting up national databases

in resource limited settings. The tool is available free of cost to any country that will use it solely for submitting reports to the WHO database. A nominal fee will be charged if the tool is also used to set up and manage a national database. The proceeds will then be used to develop the tool further and for creating newer versions and upgrades that will then be provided free of charge to subscribing countries.

Many countries have self-designed databases for managing their data. WHO will work with these countries to determine additional solutions to support E2b standards of reporting. Additional tools will be developed as needed to support newer methods such as CEM, reporting in a pandemic, consumer reporting, or off-line reporting solutions for countries with little or no internet connectivity. For example, in 2009, amidst concerns of a predicted influenza pandemic and in preparation for a possible surge of adverse events following immunization (AEFI) reports, the UMC developed PaniFlow®, a tool for reporting adverse events related to pandemic influenza vaccines. The tool has been offered to all WHO Member States.

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# Safety and Efficacy Issues

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## Dalfampridine: risk of seizure

**United States of America** — The Food and Drug Administration (FDA) is reporting a risk of seizures in patients with multiple sclerosis (MS) who are starting dalfampridine (Ampyra®). The majority of seizures happened within days to weeks after starting the recommended dose and occurred in patients having no history of seizures.

Although the mechanism of action in MS patients is not fully understood, studies in animals show increased neuronal activity in response to the drug. In addition, the drug label has been updated to clarify recommendations that kidney function should be checked in patients before starting dalfampridine. Additionally, patients who miss a dose should not take extra doses—an extra dose can increase seizure risk.

**Reference:** *FDA Drug Safety Communication*, 23 July 2012 at <http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm313055.htm>

## Sildenafil: not for pulmonary hypertension in children

**United States of America** — The Food and Drug Administration (FDA) is recommending that sildenafil (Revatio®) not be prescribed to children aged 1–17 years of age for pulmonary arterial hypertension (PAH). This recommendation is based on a recent long-term clinical paediatric trial showing that: (i) children taking a high dose of sildenafil had a higher risk of death than children taking a low dose and (ii) the low doses of sildenafil are not effective in improving exercise ability (1). Most deaths were caused by pulmonary hypertension and heart failure.

Sildenafil is a phosphodiesterase-5 inhibitor used to treat pulmonary arterial hypertension. It is also marketed in the prescription product Viagra®, for adult male erectile dysfunction.

Sildenafil is not approved for the treatment of PAH in children, and in light of this new clinical trial information, off-label use of the drug in paediatric patients is not recommended. Sildenafil is approved to improve exercise ability and delay clinical worsening of PAH in adult patients. The current Revatio® label recommends avoiding doses higher than 20 mg three times a day. The effect of Revatio® on the risk of death with long-term use in adults is unknown (2).

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## Interaction: proton pump inhibitors and methotrexate

**Canada** — The labelling for methotrexate and proton pump inhibitors (PPIs) is being updated to include information on a potential interaction between these products.

Methotrexate is used in the treatment of cancer and autoimmune diseases and proton pump inhibitors are acid reducers used in the treatment of heartburn or acid indigestion.

The use of these two products at the same time by patients may increase the amount of methotrexate in the blood leading to side effects. The possible risks include kidney failure, low red blood cell count, inflammation of the digestive tract, irregular heartbeat, muscle pain, infections, and diarrhoea. While a definite association between PPI use and an increase in methotrexate has not been confirmed, there have been a number of studies suggesting a possible interaction.

PPIs, in general, should be prescribed at the lowest dose and for the shortest duration of therapy appropriate to the condition being treated.

The following PPIs are available in Canada:

Dexlansoprazole; esomeprazole; omeprazole; losec; lansoprazole; pantoprazole; pantoprazole/magnesium, and rabeprazole. PPIs are also available in combination with other drugs.

**Reference:** *Information Update*, 2012–157, 19 October 2012 at [http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/\\_2012/2012\\_157-eng.php](http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2012/2012_157-eng.php)

### **Fingolimod: cardiovascular monitoring**

**Canada** — Healthcare professionals have been advised of stronger recommendations regarding first-dose cardiovascular monitoring and use in patients with pre-existing cardiovascular conditions of fingolimod (Gilenya®), a drug indicated for the treatment of relapsing-remitting multiple sclerosis.

Isolated delayed-onset cardiovascular events, including transient asystole and unexplained death, have occurred within 24 hours of the first dose of fingolimod. Health Canada has completed its review, which included a number of international reports of deaths, several of which were considered possibly associated with fin-

golimod. No deaths have been reported in Canada.

Fifty-four Canadian case reports of serious cardiovascular adverse events, possibly associated with fingolimod, have been reported between March 2011 and January 2012. The majority of these cases have occurred within 6 hours of the first dose and consisted of bradycardia, hypertension, hypotension and dizziness/malaise/palpitations.

Initiation of fingolimod treatment results in reversible heart rate decrease and has also been associated with atrio-ventricular conduction delays and isolated cases of serious cardiovascular events and unexplained death.

An electrocardiogram (ECG) should be performed and blood pressure measured prior to and 6 hours after the first dose. All patients should be monitored for signs and symptoms of bradyarrhythmia, with hourly pulse and blood pressure measurement for at least 6 hours after the first dose.

**Reference:** Communication from Novartis Pharmaceuticals Canada Inc. dated 21 August 2012 at [http://www.hc-sc.gc.ca/dhp-mps/me-deff/advisories-avis/prof/\\_2012/gilenya\\_hpc-cps-eng.php](http://www.hc-sc.gc.ca/dhp-mps/me-deff/advisories-avis/prof/_2012/gilenya_hpc-cps-eng.php)

### **Pramipexole: risk of heart failure**

**United States of America** — The Food and Drug Administration (FDA) is reporting a possible increased risk of heart failure with pramipexole (Mirapex®), a drug used to treat Parkinson disease and restless legs syndrome. Results of recent studies suggest a potential risk of heart failure that needs further review of available data.

Pramipexole is a dopamine agonist used to treat the signs and symptoms of Parkinson disease and moderate to severe symptoms of primary restless legs syndrome. It works by acting in place of

dopamine, produced by specific areas of the brain that control movement.

The FDA has evaluated a pooled analysis of randomized clinical trials and found that heart failure was more frequent with Mirapex® than with placebo; however, these results were not statistically significant. FDA also evaluated two epidemiologic studies that suggested an increased risk of new onset of heart failure with Mirapex use (1, 2). Study limitations make it difficult to determine whether excess heart failure was related to Mirapex® use or other influencing factors.

Because of the study limitations, the FDA is not able to determine whether Mirapex® increases the risk of heart failure and will update the public when more information is available.

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## Lyme disease test kits: limitations

**Canada** — As of June 2012, Health Canada has received one incident report of false-negative serologic test results for 24 patients that may have delayed treatment. Timely recognition of Lyme disease

and treatment are imperative to facilitate recovery and prevent long-term sequelae.

Lyme disease test kits are class II in vitro diagnostic devices intended for the detection of antibodies to *Borrelia burgdorferi* in human serum, plasma or cerebrospinal fluid.

The first tier consists of an enzyme immunoassay, such as an enzyme-linked immunosorbent assay (ELISA), or an indirect immunofluorescent assay. If the result of first-tier testing is negative, the sample is reported to be negative for antibodies to *B. burgdorferi* and is not tested further. If the result is positive or indeterminate, second-tier testing with a standardized Western blot is then performed. Even when the conventional two-tiered testing approach is used, the sensitivity and specificity of the combined test results can be less than optimal.

The currently available Lyme disease test kits have been found to have limitations of sensitivity and specificity, particularly when used on patients with acute infection, which is usually easily treated with antibiotics.

In a comprehensive study of 280 serum samples from well-characterized Lyme disease patients, the sensitivity of the two-tiered approach was as low as 38% for the sera of patients who had erythema migrans during the acute phase and 67% during their convalescence after antimicrobial treatment. In late Lyme disease, the sensitivity increased to 87% for the sera of patients with early neuroborreliosis and to 97% for the sera of patients with Lyme arthritis.

Serologic test results are supplemental to the clinical diagnosis of Lyme disease and should not be the primary basis for making diagnostic or treatment decisions.

*Extracted from Canadian Adverse Reaction Newsletter, Volume 22, Number 4, October 2012.*

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## Anti-androgens: hepatotoxicity

**Canada** — Anti-androgens are a class of drugs used in androgen deprivation therapy for the treatment of advanced or metastatic prostate cancer. They are classified into two groups: nonsteroidal anti-androgens (flutamide, bicalutamide and nilutamide) and steroidal anti-androgens (cyproterone acetate).

Both groups work by competing with circulating androgens for receptor sites within the prostate cell, thus promoting apoptosis and inhibiting prostate cancer growth. Steroidal anti-androgens have the added ability of suppressing the production of testosterone. Depending on the

drug, anti-androgens are indicated for use in monotherapy, or in combination with radiotherapy, luteinizing hormone-releasing hormone analogues or orchiectomy for complete androgen blockade.

Although the risk of hepatotoxicity and hepatic failure is currently labelled in the Canadian product monographs for flutamide, a recent safety review conducted by Health Canada suggested that hepatotoxicity remains an important safety concern.

As of 31 March 2012, Health Canada has received 25 case reports of hepatotoxicity in men aged 60–98 years old that were suspected of being associated with anti-androgens, 24 of which were serious. The most common adverse reactions included jaundice, increased liver enzyme levels, nausea, hepatic necrosis, ascites and hepatitis.

The risk of hepatotoxicity with the use of anti-androgens has also been described in the clinical literature. Although both steroidal and nonsteroidal anti-androgens have been associated with hepatotoxicity, the frequency of these adverse reactions, and their clinical features, appear to differ from one drug to another.

*Extracted from Canadian Adverse Reaction Newsletter, Volume 22, Number 4, October 2012.*

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## Agomelatine: hepatotoxicity and liver failure

**United Kingdom** — There have been several serious cases of hepatotoxicity reported with agomelatine (Valdoxan®, Thymanax®). These include six reports worldwide of hepatic failure. The existing recommendations to perform liver function tests in all patients receiving agomelatine at treatment initiation and during treatment have been extended to include testing when the dose is increased.

Agomelatine should be immediately discontinued if patients present with symptoms or signs of potential liver injury, or if an increase in serum transaminases in liver function tests exceeds three times the upper limit of normal. Patients should be informed of the symptoms of potential liver injury and advised to stop taking agomelatine immediately and seek urgent medical advice if these symptoms appear.

Agomelatine is an antidepressant indicated for the treatment of major depressive episodes in adults. Agomelatine is a melatonin MT1 and MT2 receptor agonist, and antagonist at the serotonin 5-HT<sub>2C</sub> receptor, thereby increasing levels of dopamine and noradrenaline in areas of the brain involved in mood control.

Following several reports of liver injury, including hepatic failure, all available data on elevated transaminases and hepatotoxicity with agomelatine use have been reviewed.

Prescribers are advised to monitor liver function frequently and are warned about the risk of hepatitis and elevated transaminase levels. Agomelatine is contraindicated in patients with hepatic impairment (cirrhosis or active liver disease).

**Reference:** *Drug Safety Update*, Volume 6, Issue 3, October 2012 at <http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON199558>

### **Hypotonic saline in children: fatal hyponatraemia**

**United Kingdom** — Four children have died of cerebral oedema caused by very low levels of serum sodium after receiving intravenous hypotonic saline (0.18% saline/4% glucose solution) in hospital. This solution is now contraindicated in children except under expert medical supervision in paediatric specialist settings – such as renal, cardiac, liver, high dependency and intensive care units.

Intravenous hypotonic saline (0.18% saline/4% glucose infusion solution) is given to maintain normal fluid and electrolyte requirements or to replenish substantial deficits or continuing losses.

Following the restart of a public inquiry, primarily into the deaths of three children in the UK who died of cerebral oedema secondary to hyponatraemia after administration of intravenous hypotonic saline, the Commission on Human Medicines (CHM) has recently reviewed all data on the benefits and risks of this solution when used in children.

There have been over 50 reported permanent neurological injuries or deaths in children worldwide as a result of iatrogenic hyponatraemia associated with the use of hypotonic intravenous fluids, often in previously healthy children undergoing routine elective surgery. In addition, several published studies and reviews have demonstrated hyponatraemia after administration of hypotonic intravenous fluids such as 0.18% saline/4% glucose (1–4). On the basis of the evidence from the review, the CHM concluded that the use of 0.18% saline/4% glucose should be contraindicated in all but a limited group of children treated by experts in

paediatric specialist settings, such as renal, cardiac, liver, high dependency, and intensive care units.

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### **Denosumab: fatal hypocalcaemia**

**United Kingdom** — Cases of severe symptomatic hypocalcaemia have occurred in patients receiving denosumab 120 mg (Xgeva®) or 60 mg (Prolia®). Some of these cases were fatal in those receiving the 120 mg dose.

Pre-existing hypocalcaemia must be corrected prior to initiating denosumab, and supplementation of calcium and vitamin D is required in all patients receiving the 120 mg dose unless hypocalcaemia is present. Although hypocalcaemia most commonly occurs within the first six months of treatment, it may occur at any time.

Denosumab 120 mg solution for injection (Xgeva®) is given once every four weeks for the prevention of skeletal related events (pathological fracture, radiation to bone, spinal cord compression or surgery to bone) in adults with bone metastases from solid tumours.

Denosumab 60 mg solution for injection (Prolia®) is given once every six months for the treatment of osteoporosis in postmenopausal women at increased risk of fractures, and for the treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk.

Signs and symptoms of hypocalcaemia include altered mental status, tetany, seizures and QTc prolongation. Hypocalcaemia with denosumab most commonly occurs within the first six months of dosing, but it can occur at any time during treatment

**Reference:** *Drug Safety Update*, Volume 6, Issue 3, October 2012 at <http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON199560>

### Axitinib: prescriber review

**Australia** — Recently marketed, axitinib (Inlyta®) is another addition to the group of tyrosine kinase inhibitors — sorafenib, sunitinib and pazopanib — for renal cell carcinoma. Its anti-angiogenic effects stem from its inhibition of the vascular endothelial growth factor receptors (1–3).

Early trials of axitinib in patients with refractory metastatic disease were promising (1,2). In a more recent open-label randomized phase III trial of 723 patients, axitinib (5 mg twice daily) was compared with sorafenib (400 mg twice daily). At enrolment, patients had progressive disease despite previous treatment with sunitinib, bevacizumab plus interferon alfa, temsirolimus or cytokines.

The safety of axitinib seems to be comparable to sorafenib. Adverse reactions were very common, with over half of the patients in the trial having their axitinib dose reduced or interrupted because of an event. Diarrhoea, hypertension, fatigue, decreased appetite, nausea, dysphonia and hand-foot syndrome were

the most common. Thrombocytopenia, lymphopenia, creatinine elevation, hypocalcaemia and lipase elevation were also common. Axitinib can affect thyroid and liver function so these should be measured at baseline and regularly during treatment.

High blood pressure is a problem with axitinib and should be controlled with antihypertensives. In persistent cases, the axitinib dose may need to be reduced, or interrupted then restarted at a lower dose when blood pressure has normalised. Proteinuria occurs with axitinib and should be monitored before and during treatment.

Axitinib is metabolized mainly by cytochrome P450 (CYP) 3A4, but also by CYP1A2, CYP2C19 and UGT1A1 so there is a potential for drug interactions. Concomitant use of strong CYP3A4 inhibitors or inducers may affect axitinib concentrations.

The prognosis for patients with advanced renal cell carcinoma is poor. Axitinib provides another option for those who have relapsed despite previous treatment. Although it may temporarily reduce disease progression, it does not seem to prolong overall survival any more than sorafenib. It is not known how axitinib will compare to other treatments for this disease.

*Extracted from the Australian Prescriber, Volume 35, Number 5, 2012 at <http://www.australianprescriber.com>*

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### Velaglucerase alfa: prescriber review

**Australia** — Gaucher disease is one of the lysosomal storage diseases. A genetic disorder results in a lack of glucocerebrosidase. This enzyme deficiency leads to accumulation of glucocerebroside in macrophages, with enlargement of the liver and spleen. There can be bone involvement, anaemia and thrombocytopenia.

Enzyme replacement therapy has been available since the 1990s, first with alglucerase and later with the genetically engineered imiglucerase. While imiglucerase was produced from Chinese hamster ovary cells, velaglucerase alfa is produced from human fibroblast cell lines. It has the same amino acid sequence as natural glucocerebrosidase.

As Gaucher disease is relatively rare (only about 400 patients in Australia), the clinical trials of velaglucerase have been small. In a trial of adults with no recent use of imiglucerase, 12 symptomatic patients were given intravenous infusions of velaglucerase every other week for up to nine months. There were improvements in their haemoglobin and platelet counts. Liver and spleen volumes reduced. These improvements were sustained in nine patients who entered an extension study for an additional 39 months (1).

A phase III study randomized 34 patients to be treated with velaglucerase 60 units/kg or imiglucerase for nine months. Patient haemoglobin concentration was the primary outcome. Mean haemoglobin increased and there was also an increase in mean platelet counts and decreases in liver and spleen volumes.

These results showed that the efficacy of velaglucerase is not inferior to that of imiglucerase.

A shortage of imiglucerase in 2009 led to patient treatments being reduced. Some of the effects of reduced treatment were reversed in a group of 32 patients who were switched to velaglucerase. However, imaging in ten of these patients detected an increase in liver volume in five patients after six months of velaglucerase (2).

The safety data for velaglucerase came from 94 adults and children. Reactions to the infusion were the most common problem. These included headache, fever, nausea, dizziness and altered blood pressure. Adverse events which were more frequent than with imiglucerase included headache, fever, diarrhoea, hypertension and arthralgia. Patients may also complain of bone pain or back pain. No data are available concerning the use of velaglucerase in pregnancy or lactation.

*Extracted from the Australian Prescriber, Volume 35, Number 5, 2012 at <http://www.australianprescriber.com>*

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### Cyclizine lactate: prescriber review

**Australia** — Cyclizine, an antihistamine, is already being used (tablets and injectable solution) as an antiemetic after

surgery in Australia. However, the solution for injection (Valoid®) has only recently been approved by the Therapeutic Goods Administration.

A Cochrane review of antiemetics analysed 10 studies of parenteral cyclizine (1). The trials were mainly in women having surgery (caesarean, laparoscopy), except for one study in boys. An analysis of these studies found that cyclizine decreased the risk of nausea by 65% and vomiting by 55%, compared to placebo. Overall, cyclizine's antiemetic effect was comparable to ondansetron. However in the study of boys having surgery for hypospadias, cyclizine was no better than placebo (2).

In a trial not included in the review, cyclizine was compared to droperidol in patients administering their own analgesia after surgery. Thirty women were randomized to receive cyclizine or droperidol during surgery and then after, intravenously, with patient-controlled morphine. Nausea scores were comparable between treatments, with three patients in each group needing extra antiemetics (3).

Cyclizine has also been used in combination with other antiemetics. Before anaesthesia, 960 women undergoing day surgery were given intravenous cyclizine 50 mg, intravenous granisetron 1 mg, or both. Postoperative nausea and vomiting were less common with combination treatment than with cyclizine or granisetron alone (4).

Drowsiness is common with cyclizine and it may have additive effects with alcohol and other drugs that cause nervous system depression such as hypnotics, sedatives and anaesthetics. Other adverse effects include dizziness, dry mouth, constipation, blurred vision, headache, somnolence, dyskinesia, tremor, convulsions, transient speech disorders and injection-site reactions. Disorientation, restlessness, agitation, insomnia and hallucinations have also been reported. Temporary paralysis has

occasionally occurred in patients with underlying neuromuscular disorders.

Because of its anticholinergic effects, cyclizine may precipitate urinary retention and incipient glaucoma. Monitoring is recommended in patients with glaucoma, obstructive disease of the intestine, liver disease, epilepsy and prostatic hypertrophy. As cyclizine may cause thickening of bronchial secretions, it should be used with caution in patients with asthma or chronic obstructive pulmonary disease. This drug may increase the adverse effects of other anticholinergic drugs.

Cyclizine is contraindicated in patients with severe heart failure. It is a category B3 drug and its use in pregnancy and lactation is not recommended.

This drug is effective for preventing post-operative nausea and vomiting, and is comparable to other antiemetics such as ondansetron, granisetron and droperidol. Cyclizine is not recommended for children and there have been no studies in older people.

*Extracted from the Australian Prescriber, Volume 35, Number 5, 2012 at <http://www.australianprescriber.com>*

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## Cardiovascular safety of NSAIDs

**European Union** — The European Medicines Agency (EMA) has finalized a review of recently published information on the cardiovascular safety of nonsteroidal anti-inflammatory drugs (NSAIDs).

The Agency's Committee for Medicinal Products for Human Use (CHMP) has concluded that evidence from newly available published data sources, including meta-analysis of clinical trials and observational studies, and the results of an EU-funded independent research project, the 'Safety of nonsteroidal anti-inflammatory drugs' (SOS) project, on the cardiovascular safety of this class of medicines confirm findings from previous reviews, conducted in 2005 and 2006.

Most of the data related to the three most widely used NSAIDs – diclofenac, ibuprofen and naproxen. In relation to naproxen and ibuprofen, the CHMP was of the opinion that the current treatment advice adequately reflects the knowledge regarding the safety and efficacy of these medicines.

For diclofenac, the latest evidence appears to show a consistent but small increase in the risk of cardiovascular side effects compared with other NSAIDs, similar to the risks of COX-2 inhibitors, another class of painkillers.

**Reference:** *European Medicines Agency Press Release, EMA/CHMP/667707/2012.* 19 October 2012 at <http://www.ema.europa.eu>

## Antibiotics and liver Injury

**New Zealand** — Prescribers are advised of the risk of liver injury associated with antibiotic treatment. Early recognition is essential as withdrawal of the causative antibiotic is the most effective treatment (1). Specialist advice should be sought in all cases of severe liver injury and in patients who fail to improve despite withdrawal of the antibiotic.

Drug-induced liver injury (DILI) can be classified as hepatocellular, cholestatic or mixed depending on the specific liver function test abnormalities that occur. As with other liver diseases, DILI can present with jaundice, malaise, abdominal pain, unexplained nausea and anorexia.

Antibiotics are a common cause of DILI, probably because of the high rate of exposure in the community. Most cases are idiosyncratic and are therefore rare, unpredictable (from the pharmacology of the antibiotic) and largely dose-independent (1, 2).

Genetic variability is considered to be the most important risk factor, although specific genetic markers have not yet been elucidated for most antibiotics (1). Other potential risk factors include: previous hepatotoxic reaction to a specific antibiotic; female sex; increasing age, and co-morbid illnesses.

An important exception are tetracyclines, where high doses seem to be a predictor of liver injury (2).

Treatment consists primarily of withdrawal of the causative antibiotic and supportive care if required. Most cases are mild and self-limiting (1). However, rare cases of acute liver failure and death have been reported (1). Chronic liver disease is a very rare complication but is more likely to develop if the antibiotic is continued despite evidence of liver injury.

The Centre for Adverse Reactions Monitoring (CARM) has received a total of 360 reports of liver injury associated with the use of non-tuberculosis antibiotics since January 2000. Seven reports (2%) involved a fatality. The majority of CARM reports of liver injury were associated with  $\beta$ -lactam penicillins. Amoxicillin/clavulanic acid, flucloxacillin and erythromycin were the antibiotics most often implicated in the development of liver injury in New Zealand.

Extracted from *Prescriber Update*, Vol. 33, No. 3, September 2012 at <http://www.medsafe.govt.nz/profs/PUArticles>

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## Statins: risk of diabetes mellitus?

**New Zealand** — Statins (HMG-CoA reductase inhibitors) are one of the most widely prescribed classes of medicinal products in New Zealand. PHARMAC estimates that over 1.7 million statin prescriptions were written for over 400,000 patients during 2011.

Recent publications have suggested that there may be an association of new-onset type 2 diabetes mellitus (T2DM) with the use of statins (1, 2). The Medicines Adverse Reactions Committee (MARC) has reviewed relevant studies and concluded that there is a small, but statistically significant association, particularly in patients already at risk of T2DM. Nevertheless, the MARC considered that the benefits of statin treatment clearly outweigh any risk of developing new-onset T2DM.

A total of six meta-analyses were reviewed by the MARC. The studies all had limitations and suggest that other individual risk factors may also contribute to the association. The risk factors included: raised fasting glucose level; body mass index greater than 30kg/m<sup>2</sup>; raised triglycerides, and history of hypertension.

There was insufficient data to exclude an effect with any individual statin or to support a dose-dependent relationship.

Healthcare professionals should be aware of the association of new-onset T2DM with the use of statins and are advised to monitor at risk patients according to best practice guidelines.

Extracted from *Prescriber Update*, Vol. 33, No. 3, September 2012 at <http://www.medsafe.govt.nz/profs/PUArticles>

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## Antimalarials: assessing resistance risk

The Medicines for Malaria Venture has developed a framework to evaluate the risk of resistance for the antimalarial compounds in its portfolio. A paper based on this work *A framework for assessing the risk of resistance for antimalarials in development* has been published in the *Malaria Journal* at <http://www.malariajournal.com/>

A cross-resistance test using a panel of multidrug-resistant strains of the parasite will check for pre-existing resistance liability. This will ensure that none of MMV's compounds are cross-resistant with other drugs.

The framework also includes selection experiments in the laboratory that measure how easy it is for the parasite to develop resistance, in other words, the likelihood of the occurrence of mutations that confer resistance. This is achieved by measuring the minimal inoculum for resistance — the minimum number of parasites from which a resistant one is

likely to be selected by drug pressure. Although this is already being done, the framework offers a standard, systematic method.

This new framework could also be used by other malaria researchers to test their compounds for potential resistance, measure the genetic ability of parasites to develop resistance and the intensity of the resistance.

**Reference:** *MMV Press Release*, 22 August 2012 at <http://www.mmv.org>

### **Simvastatin: increased risk of myopathy/rhabdomyolysis**

**Canada** — Healthcare professionals have been informed of new safety recommendations on dosage related to the increased risk of myopathy/rhabdomyolysis, particularly with the 80 mg dose of simvastatin (Zocor®, and generics).

An increased risk of myopathy/rhabdomyolysis within the recommended dose range for simvastatin can also be seen with concomitant administration of certain medications. Simvastatin is indicated in patients at high risk of coronary events.

Concomitant use of the recommended dosage of simvastatin with certain drugs and grapefruit juice increases the risk of myopathy/rhabdomyolysis. Patients currently tolerating the 80 mg dose of simvastatin who need an interacting drug that is either contraindicated, such as potent inhibitors of CYP3A4, cyclosporine, danazol, and gemfibrozil, or associated with an increase of plasma level of simvastatin should be switched to an alternative statin with less potential for a drug-drug interaction.

**Reference:** Communication from Merck Canada Inc. dated 7 November 2012 at [http://hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/\\_2012/zocor\\_hpc-cps-eng.php](http://hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/_2012/zocor_hpc-cps-eng.php)

*Spontaneous monitoring systems are useful in detecting signals of relatively rare, serious or 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

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## **New task force for antibacterial drug development**

**United States of America** — The Food and Drug Administration has announced the formation of an internal task force to support development of new antibacterial drugs, a critical public health goal and priority for the agency.

As part of its work, the Antibacterial Drug Development Task Force will assist in developing and revising guidance related to antibacterial drug development, as required by the Generating Antibiotic Incentives Now (GAIN) Title of the Food and Drug Administration Safety and Innovation Act (FDASIA).

Research and development for new antibacterial drugs has been in decline in recent decades and the number of new FDA-approved antibacterial drugs has been falling steadily since the 1980s. During this time, the persistent and sometimes indiscriminate use of existing antibacterial drugs worldwide has resulted in antibacterial drug resistance or antibiotic resistance.

More than 70% of the bacteria that cause hospital-associated infections are resistant to at least one type of commonly used antibacterial drug.

The task force plans to:

- Explore novel scientific approaches to facilitate antibacterial drug development, including broader use of clinical pharmacology data, statistical methods, innovative clinical trial designs, additional available data sources, and advancement of alternative measures to evaluate clinical effectiveness of potential new therapies.
- Identify issues related to unmet medical needs for antibacterial drugs, reasons for the lack of a robust pipeline for antibacterial drug development, and new approaches for weighing the risks, benefits, and uncertainties of potential new antibacterial drugs.
- Evaluate existing FDA guidance related to antibacterial drug development, determine if revision or elaboration is needed, and identify areas where future guidance would be helpful, as set out in the GAIN Title of FDASIA.
- Use existing collaborative agreements to work with think tanks and other thought leaders to explore various approaches that could enable antibacterial drug development, including innovative study designs and statistical analytical methods.

**Reference:** *FDA News Release*, 12 September 2012 at <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm320643.htm>

## **NIBSC: new MHRA centre**

**United Kingdom** — On 1 April 2013 the National Institute for Biological Standards and Control (NIBSC), currently part of the Health Protection Agency (HPA), will officially become a new centre of the Medicines and Healthcare products Regulatory Agency (MHRA) alongside the Clinical Practice Research Datalink (CPRD).

The MHRA and NIBSC already work closely together and have common interests in managing risks associated with biological medicines, facilitating development of new medicines safely and effectively, and maintaining UK expertise

and ability to contribute to assuring the quality and safety of medicines in Europe and beyond.

These developments will create a new organization that is a world leader in supporting science and research and the regulation of medicines and medical devices, and will strengthen support provided to the UK's medicine's industry.

**Reference:** Medicines and Healthcare products Regulatory Agency at <http://www.mhra.gov.uk/NewsCentre/CON203876>

### **New Pakistan drug regulatory authority**

**Pakistan** — The Drug Regulatory Authority of Pakistan (DRAP) bill was enacted by the Government of Pakistan on 12 November 2012. The bill had earlier been approved by the National Assembly and Senate after being moved by the Minister for National Regulation and Services. DRAP is envisaged as regulating the manufacturing, import, export, storage, distribution and sale of therapeutic goods in line with the Drugs Act 1976.

The World Health Organization has provided support to Pakistan. Many missions were commissioned to review various aspects of the pharmaceutical regulations. The mission formulated and recommended the detailed framework that endeavors to strengthen the national medicines regulatory system. Pharmaceutical manufacturers have been advised of the technical guidance provided by WHO and the WHO Prequalification of Medicines Programme.

There was long awaited need to establish a national medicines regulatory authority to implement internationally recognized standards in the regulation of pharmaceuticals. The tragic incidence in Lahore, where more than 160 cardiac patients died due to contaminated medicines, put more emphasis on the establishment of a regulatory authority in Pakistan.

Under the Drug Act 1976, Pakistan was the first country in Asia to implement good manufacturing practices. Currently, there is a shortage of trained human resources across public and private sectors for pharmaceutical procurement, management and dispensation. Irrational use of medicines continues to increase health care costs. With enactment of the DRAP, the role of pharmacists is officially recognized.

It is hoped that the new DRAP Act 2012 can serve as a tool to fill the gaps and also allow the huge Pakistani pharmaceutical sector to play a role in improving access to safe medicine of good quality, at affordable cost. A copy of the DRAP Act is available at [http://ppapak.org.pk/drap2012\[1\].pdf](http://ppapak.org.pk/drap2012[1].pdf)

**Reference:** Pakistan Pharmacists Association (PPA), 17 November 2012 at <http://ppapak.org.pk>

### **EU clinical trial regulation: public consultation**

**United Kingdom** — The European Commission proposes to simplify the rules for the conduct of clinical trials and harmonize the way trials are conducted in the European Union. The proposed Regulation will replace the Clinical Trials Directive 2001/20/EC which has been the subject of significant concern amongst commercial and academic researchers since its introduction in 2004.

It is widely acknowledged that the Directive has reduced the attractiveness of the EU for conducting clinical trials on medicines. The Directive brought in unnecessary administrative and regulatory burdens, lacked clarity in some aspects and some Member States have introduced additional requirements when implementing the Directive which limit harmonization, create delays and increase costs for researchers.

The number of clinical trials conducted in the European Union fell by 25% between

2007 and 2011. In the UK, the number of commercial trials fell by 22% over the same period. Although this decline cannot be attributed solely to the Directive, it did have an effect on the cost and feasibility of conducting clinical trials.

The Medicines and Healthcare products Agency (MHRA) is consulting on the European Commission's proposal for a Clinical Trial Regulation and are keen to hear the views of interested parties. Responses can be sent by e-mail to [clinical.trials@mhra.gsi.gov.uk](mailto:clinical.trials@mhra.gsi.gov.uk).

**Reference:** Medicines and Healthcare products Agency, 5 November 2012, at <http://www.mhra.gov.uk/Publications/Consultations/Medicinesconsultations/MLXs/CON202300>

### **Pegloticase approved for chronic tophaceous gout**

**European Union** — On 18 October 2012, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorization for pegloticase (Krystexxa®), 8 mg/ml, concentrate for solution for infusion indicated for the treatment of severe debilitating chronic tophaceous gout in adult patients who may also have erosive joint involvement and who have failed to normalize serum uric acid with xanthine-oxidase inhibitors at the maximum medically appropriate dose or for whom these medicines are contraindicated.

The active substance of Krystexxa® is pegloticase, an 'other antigout preparation' (M04AK02) and is a polyethylene-glycol-modified recombinant mammalian uricase of the therapeutic class 'bio-uricolytic agents that reduce serum uric acid'.

The benefits with Krystexxa® are its ability to reduce serum uric acid to an undetectable level in patients who have failed to respond to conventional urate-lowering therapy (xanthine-oxidase

inhibitors or uricosuric agents). The most common side-effects are infusion reactions/anaphylactic reactions and serious cardiac events, and gout flares have been identified.

**Reference:** European Medicines Agency at <http://www.ema.europa.eu/ema/index.jsp>

### **Tofacitinib: approved for rheumatoid arthritis**

**United States of America** — The Food and Drug Administration has approved tofacitinib (Xeljanz®) to treat adults with moderate to severe active rheumatoid arthritis who have had an inadequate response to, or who are intolerant of, methotrexate.

The use of Xeljanz® was associated with an increased risk of serious infections, including opportunistic infections, tuberculosis, cancers and lymphoma. Treatment is also associated with increases in cholesterol and liver enzyme tests and decreases in blood counts.

The FDA has approved Xeljanz® with a Risk Evaluation and Mitigation Strategy (REMS). The most common adverse reactions in clinical trials were upper respiratory tract infections, headache, diarrhoea, and inflammation of the nasal passage and the upper part of the pharynx.

**Reference:** FDA News Release, 6 November 2012 at <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm327152.htm?source=govdelivery>

### **Rivaroxaban: extended indication approved for blood clotting**

**United States of America** — The Food and Drug Administration has expanded the approved use of rivaroxaban (Xarelto®) to include treating deep vein thrombosis (DVT) or pulmonary embolism (PE), and to reduce the risk of recurrent DVT and PE following initial treatment.

Xarelto® is already FDA-approved to reduce the risk of DVTs and PEs from occurring after knee or hip replacement surgery, and to reduce the risk of stroke in non-valvular atrial fibrillation.

The major side effect observed is bleeding, similar to other anti-clotting drugs.

**Reference:** *FDA News Release*, 2 November 2012 at <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/>

### **Omacetaxine mepesuccinate: approved for chronic myelogenous leukaemia**

**United States of America** — The Food and Drug Administration has approved omacetaxine mepesuccinate (Synribo®) to treat adults with chronic myelogenous leukemia (CML), a blood and bone marrow disease.

On 4 September 2012, the FDA approved bosutinib (Bosulif®) to treat patients with chronic, accelerated or blast phase Philadelphia chromosome positive CML who are resistant to or who cannot tolerate other therapies.

The most common side effects reported during clinical studies include thrombocytopenia, anaemia, neutropenia, febrile neutropenia, diarrhoea, nausea, weakness and fatigue, injection site reaction, and lymphopenia.

**Reference:** *FDA News Release*, 26 October 2012 at <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm325895.htm>

### **Perampanel: approved for partial onset seizures**

**United States of America** — The Food and Drug Administration has approved perampanel (Fycompa®) to treat partial onset seizures in patients with epilepsy aged 12 years and older.

The most common adverse reactions reported by patients receiving Fycompa® in clinical trials include: dizziness, drowsiness, fatigue, irritability, falls, upper respiratory tract infection, weight increase, vertigo, ataxia, gait disturbance, balance disorder, anxiety, blurred vision, dysarthria, asthenia, aggression, and hypersomnia.

The Fycompa® label has a boxed warning on the risk of serious neuropsychiatric events, including irritability, aggression, anger, anxiety, paranoia, euphoric mood, agitation, and mental status changes. Some of these events were reported as serious and life-threatening. Violent thoughts or threatening behavior were also observed in a few patients.

Fycompa® will be dispensed with a patient Medication Guide that provides important instructions on its use and drug safety information.

**Reference:** *FDA News Release*, 22 October 2012 at <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm325038.htm>

### **Regorafenib: approved for colorectal cancer**

**United States of America** — The Food and Drug Administration has approved regorafenib (Stivarga®) to treat patients with metastatic colorectal cancer.

Stivarga® is a multikinase inhibitor that blocks several enzymes that promote cancer growth. The drug was reviewed under the FDA's priority review programme that provides an expedited six-month review for drugs that offer major advances in treatment or that provide treatment when no adequate therapy exists.

Colorectal cancer is the third most common cancer in men and in women and the third leading cause of cancer death in men and in women in the United States.

Stivarga® is being approved with a boxed warning indicating that severe and fatal liver toxicity occurred during clinical studies. The most common side effects reported include weakness or fatigue, loss of appetite, palmar-plantar erythrodysesthesia, diarrhoea, mucositis, weight loss, infection, high blood pressure, and dysphonia.

**Reference:** *FDA News Release*, 27 September 2012 at <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm321271.htm>

### **Teriflunomide: approved for multiple sclerosis**

**United States of America** — The Food and Drug Administration has approved teriflunomide (Aubagio®), a once-a-day tablet for the treatment of adults with relapsing forms of multiple sclerosis (MS).

For most people with MS, relapse is initially followed by remissions. However, over time, recovery periods may be incomplete, leading to progressive decline.

The most common side effects of Aubagio® in clinical trials include diarrhoea, abnormal liver tests, nausea, and hair loss.

The Aubagio® label contains a boxed warning to alert prescribers and patients to the risk of liver problems, including death, and a risk of birth defects. Physicians should carry out blood tests to check liver function before initiation and periodically during treatment. Aubagio® is labelled as pregnancy category X, which means women of childbearing age must have a negative pregnancy test before starting the drug and use effective birth control during treatment.

Aubagio® will be dispensed with a patient Medication Guide that provides important instructions on its use and drug safety information.

**Reference:** *FDA News Release*, 12 September 2012 at <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm319277.htm>

### **Ocriplasmin: approved for vitreomacular adhesion**

**United States of America** — The Food and Drug Administration has approved ocriplasmin (Jetrea®), the first drug to treat symptomatic vitreomacular adhesion.

The most common side effects reported in patients treated with Jetrea® include eye floaters, bleeding of the conjunctiva, eye pain, photopsia, blurred vision, unclear vision, vision loss, retinal edema, and macular edema.

**Reference:** *FDA News Release*, 18 October 2012 at <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm324369.htm>

### **Florbetapir 18F: approved for neuritic plaque density imaging**

**European Union** — The European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) has recommended marketing authorization for florbetapir 18F (Amyvid®) as a diagnostic agent in patients who are being evaluated for Alzheimer Disease (AD) or other causes of cognitive decline.

Amyvid® is a radiopharmaceutical agent used in positron emission tomography (PET) imaging which can highlight amyloid protein plaques in the brain.

Alzheimer disease is the most common cause of dementia in the elderly, affecting up to 5.1 million people in the European Union. Accurate diagnosis of AD has been hampered to date by the lack of diagnostic tests. The current gold standard for confirming a clinical diagnosis of AD is post-mortem autopsy.

A negative Amyvid® PET scan can rule out the presence of AD, and is expected to reduce the frequency of false positive diagnosis. However, a positive Amyvid® scan is consistent with, but does not independently establish, the diagnosis of AD since  $\beta$ -amyloid neuritic plaque deposition may also be present in the brain of asymptomatic elderly and some neurodegenerative dementias, including Parkinson disease dementia and Lewy body dementia.

Common adverse reactions include headache and taste alterations.

**Reference:** *European Medicines Agency Press Release, EMA/CHMP/670812/2012.* 19 October 2012 at <http://www.ema.europa.eu>

### **Insulin degludec: approved for diabetes mellitus**

**European Union** — The European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) has recommended marketing authorization for insulin degludec, a new basal analogue insulin for the treatment of diabetes mellitus in adults. It is introduced in a pre-filled pen in two formulations — 100 units/ml and 200 units/ml.

This is the first insulin approved in Europe at a higher strength than the EU-wide standard of 100 units/ml, for many years the only strength of insulin available across the EU. It will be marketed under the trade name Tresiba®. The approval of a 200 units/ml insulin, allowing doses up to 160 units in a single injection, is expected to respond to the growing need for higher-dose insulin.

To reduce the risk of medication errors, the 200 units/ml strength is only presented in a pre-filled pen, both strengths are dialled-in units, the pack design of the two strengths has been clearly differentiated and an educational programme has been agreed.

**Reference:** *European Medicines Agency Press Release, EMA/CHMP/675745/2012.* 19 October 2012 at <http://www.ema.europa.eu>

### **Linaclotide: approved for irritable bowel syndrome**

**European Union** — The European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) has recommended authorization of linaclotide (Constella®) for adults with moderate to severe irritable bowel syndrome with constipation, a common subtype of the disease. Linaclotide is a new, synthetic 14-amino-acid peptide, which works by increasing the secretion of fluid in the intestine and accelerating the movement of material through the gut. It is taken by mouth once a day at least 30 minutes before a meal.

The CHMP based its recommendation on the results of two main clinical studies showing superiority of linaclotide over placebo in terms of improving symptoms after 12 weeks. These effects were sustained for at least six months. However, it noted that around half of the patients in the main studies did not respond to linaclotide sufficiently, leading to the recommendation that prescribers should assess patients regularly and reconsider treatment if there is no improvement in symptoms after four weeks.

The most common side effect in clinical trials was diarrhoea, which was reported in a fifth of the patients taking the medicine. The Agency is recommending that patients with severe or prolonged diarrhoea should be monitored closely when taking linaclotide and that it should be used with caution in patients prone to water or electrolyte-balance disturbances.

**Reference:** *European Medicines Agency Press Release, EMA/CHMP/611096/2012.* 21 September 2012 at <http://www.ema.europa.eu>

## Meningitis B Vaccine approved for *Neisseria meningitidis*

**European Union** — The European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) has recommended the granting of a marketing authorization for Bexsero®, a new vaccine intended for the immunization of individuals over two months of age against invasive meningococcal disease caused by *Neisseria meningitidis* group B.

There is currently no authorized vaccine available in the European Union for bacterial meningitis caused by *Neisseria meningitidis* group B. Each year, approximately 1.2 million cases of invasive meningococcal disease are recorded worldwide, of which 7000 occur in Europe. Over 90% of cases of meningococcal meningitis and septicaemia are caused by five of the 13 meningococcal serogroups, specifically groups A, B, C, W135 and Y. In Europe, group B is the most prevalent meningococcal serogroup. Whereas there are authorized vaccines to protect against meningococcal disease caused by groups A, C, W135 and Y, there is currently none available that provides broad coverage against group B meningococcal disease.

**Reference:** *European Medicines Agency Press Release*, EMA/CHMP/728052/2012. 16 November 2012 at <http://www.ema.europa.eu>

## Bromelain-based debriding agent approved for burn wounds

**European Union** — The European Medicines Agency (EMA) has recommended approval of a concentrate of proteolytic enzymes enriched in bromelain (NexoBrid®), an orphan-designated medicine, for removal of eschar in adult patients with deep partial- and/or full-thickness thermal burn. Eschar is the dried-out, thick, leathery, black necrotic tissue that covers severe burn wounds. Its removal is essential to initiate the wound healing

process and prevent further complications such as infections in burn victims.

Data from clinical studies have shown that, compared to standard of care, NexoBrid® reduces the time to successful eschar removal and the need for excisional surgery in patients with severe burn wounds. The studies have also shown that wounds not treated optimally after debridement with NexoBrid® can be associated with longer time to complete wound closure.

**Reference:** *European Medicines Agency Press Release*, EMA/CHMP/406865/2012. 21 September 2012 at <http://www.ema.europa.eu>

## Drug-eluting stent approved for peripheral arterial disease

**United States of America** — The Food and Drug Administration has approved the Zilver PTX Drug-Eluting Peripheral Stent (Zilver PTX Stent), the first drug-eluting stent indicated to re-open a femoropopliteal artery narrowed or blocked as a result of peripheral artery disease (PAD).

The Zilver PTX Stent includes a self-expanding metal stent that keeps an artery open coated on its outer surface with paclitaxel. In clinical studies, the most common major adverse event was restenosis requiring additional treatment to re-establish adequate flow in the artery.

The device is contraindicated in patients with stenoses that cannot be dilated to permit passage of the catheter or proper placement of the stent, patients who cannot receive recommended drug therapy due to bleeding disorders, or women who are pregnant, breastfeeding, or plan to become pregnant in the next five years.

**Reference:** *FDA News Release*, 15 November 2012 at <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm327068.htm>

### **Human insulin products: marketing authorization application withdrawal**

**European Union** — The European Medicines Agency (EMA) has been notified by the manufacturer of its decision to withdraw its application for a centralized marketing authorization for the human insulin medicines Solumarv®, Isomarv® and Combimarv® (human insulin), all as 100 international units (IU)/ml solution for injection. They were intended to be used for the treatment of patients with diabetes mellitus who require insulin for the maintenance of glucose homeostasis.

The company stated that it has decided to withdraw the application to have sufficient time to repeat and submit bioequivalence T1D [type-1 diabetes] pharmacokinetic/pharmacodynamic data on each clamp study in order to comply with the planned new insulin guideline.

**Reference:** *European Medicines Agency Press Release*. 27 November 2012 at [http://www.ema.europa.eu/ema/index.jsp?curl=pages/news\\_and\\_events/news/2012/11/news\\_detail\\_001665.jsp&mid=WC0b01ac058004d5c1](http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2012/11/news_detail_001665.jsp&mid=WC0b01ac058004d5c1)

### **Ridaforolimus: marketing authorization application withdrawal**

**European Union** — The European Medicines Agency (EMA) has been notified by the manufacturer of its decision to withdraw its application for a centralized marketing authorization for the medicine ridaforolimus (Jenzyl®), 10-mg tablets. Ridaforolimus was intended to be used for the treatment of patients with metastatic soft-tissue sarcoma or bone sarcoma as a maintenance therapy.

The company stated that it has decided to withdraw the application since the CHMP considers that the data provided do not allow the Committee to conclude on a positive benefit-risk balance.

**Reference:** *European Medicines Agency Press Release*. 30 November 2012 at [http://www.ema.europa.eu/ema/index.jsp?curl=pages/news\\_and\\_events/news/2012/11/news\\_detail\\_001667.jsp&mid=WC0b01ac058004d5c1](http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2012/11/news_detail_001667.jsp&mid=WC0b01ac058004d5c1)

# Recent Publications, Information and Events

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## Evaluation of psychotropic substances

The Thirty-fifth WHO Expert Committee on Drug Dependence met in Hammamet, Tunisia, 4–8 June 2012. This was the first meeting where the *Guidance on the WHO review of psychoactive substances for international control*, adopted by the WHO Executive Board in January 2010, was applied.

The report of this meeting contains a summary of the Committee's evaluations. Eleven substances were evaluated, two of which were critical reviews:  $\gamma$ -hydroxybutyric acid (GHB) and ketamine. GHB was recommended to be rescheduled from Schedule IV to Schedule II of the Convention on Psychotropic Substances.

The report also discusses the nine substances that were pre-reviewed: dextromethorphan, tapentadol, N-benzylpiperazine (BZP), 1-(3-trifluoromethylphenyl)piperazine (TFMPP), 1-(3-chlorophenyl)piperazine (mCPP), 1-(4-methoxyphenyl)piperazine (MeOPP), 1-(3,4-methylenedioxybenzyl)piperazine (MDBP),  $\gamma$ -butyrolactone (GBL), and 1,4-butanediol (1,4-BD). Of these, tapentadol, BZP, GBL and 1,4-BD were recommended for critical review.

Issues identified for consideration at future Expert Committee meetings are listed in the report. Also discussed were: the use of terms, use of pharmacovigilance data for the assessment of abuse and dependency potential, balancing medical availability and prevention of abuse of medicines manufactured from controlled substances, and improving the process for substance evaluation.

The printed version of the report is available from the WHO Bookshop in English and French (<http://apps.who.int/bookorders>) and is currently available online at <http://www.who.int/medicines>

**Reference:** World Health Organization. *WHO Access and Control Newsletter*, Number 14, November 2012. <http://www.who.int/medicines>

## Pharmacovigilance: towards a safer use of medicines

*Practical topics in pharmacovigilance* is a handbook addressed to practitioners with the aim of highlighting the importance of early adverse drug reaction identification in clinical practice. The book describes practical challenges facing physicians and how to deal with them.

Information and reviews address various subjects: clinically-significant drug-drug interactions — including those involving herbals and food — and interactions that can cause hospitalization due to bleeding, falls, electrolyte disturbances and cardiovascular symptoms. The handbook also contains practical information on the role of pharmacogenetics, hypersensitivity reactions and drug-induced Q-T interval prolongation.

A description of activities within the Argentinian Food and Drug Administration (ANMAT) and the structure and functions of the national pharmacovigilance system are also provided. Finally, it gives complete and practical guidance on better communication of pharmacovigilance issues. All chapters are fully referenced and the book includes easy-to-read tables.

**Reference:** *Practical topics in pharmacovigilance*. Eds. Raquel Herrero Comoglio and Luis

Alesso in collaboration with ANMAT and the Uppsala Monitoring Centre. ISSN 978-987-28104-1-2. Sociedad Argentina de Farmacovigilancia at <http://www.safv.org.ar>

## Drug-resistant tuberculosis report

Medecins Sans Frontières and the International Union Against Tuberculosis and Lung Disease have released the second edition of *DR-TB Drugs Under the Microscope*, a report examining prices, sources and issues surrounding medicines used for treatment of drug-resistant TB (DR-TB). With new, faster tools diagnosing more people than ever before, DR-TB is a growing epidemic requiring an immediate treatment response.

The report also looks at recent progress on drugs in the pipeline, with two completely new compounds (bedaquiline and delamanid) due for approval soon. How these drugs will be used in treatment regimens will be critical in managing DR-TB treatment in the future — whether they are added to existing regimes or new ones are devised. The report also looks at the issues surrounding access to DR-TB drugs, with a focus on linezolid and clofazimine.

**Reference:** Medecins Sans Frontières – Access Campaign. *Press Release*. DR-TB Drugs Under the Microscope (second edition) at <http://msfaccess.org/content/dr-tb-drugs-under-microscope-2nd-edition>

## Helminth infection research

Research gaps and challenges have been identified in a new report on helminth infections, *Helminth infections research priorities identified*, published by the Disease Reference Group on Helminth Infections of the Special Programme for Research and Training in Tropical Diseases (TDR).

Helminths are a broad range of organisms that include intestinal parasitic worms. They are the most common infections worldwide when transmitted

by soil, and affect the poorest and most deprived communities. More than 1.5 billion people, or 24% of the world's population are infected, with the greatest numbers occurring in sub-Saharan Africa, the Americas, China and east Asia.

The current strategy to control infections is through periodic deworming of at-risk people living in endemic areas. The research priorities identified are focused on improving this control through five major core themes:

- Intervention.
- Epidemiology and surveillance.
- Environmental and social ecology.
- Data and modelling.
- Fundamental biology.

The report also outlines the need for appropriate health research policies and building research capacity in disease-endemic countries where the infections occur.

The Disease Reference Group on Helminth Infections is part of an independent think tank of international experts, established by TDR to identify key research priorities. The mandate was to evaluate information on research and challenges in helminthiasis of public health importance, including onchocerciasis, lymphatic filariasis, soil-transmitted helminthiasis, schistosomiasis, food-borne trematodiasis and taeniasis/cysticercosis.

This is one of ten disease and thematic reference group reports that have come out of the TDR think tank contributing to the development of the *Global Report for Research on Infectious Diseases of Poverty*.

**Reference:** Helminth infections research priorities identified. *TDR news item*. 16 October 2012 at [http://www.who.int/tdr/news/2012/helminth\\_infections2/en/index.html](http://www.who.int/tdr/news/2012/helminth_infections2/en/index.html)

## **Malaria and dengue control: genetically modified mosquitoes**

A public online consultation is now being held concerning the draft guidance framework to provide quality standards for assessing the safety and efficacy of genetically modified (GM) mosquitoes for malaria and dengue control.

So far, trials of GM mosquitoes have been conducted in enclosed spaces, such as large cages, or under controlled field conditions. Once published, the guidance document is intended to help those planning and conducting all phases of testing.

The main method currently under discussion seeks to suppress the number of wild mosquitoes by changing the males genetically so that their offspring do not survive to adulthood after release in the field.

Another method, which is still under development, is to genetically change mosquitoes so that they no longer transmit malaria parasites and dengue pathogens.

The guidance framework development process has been led by two organizations: TDR, the Special Programme for Research and Training in Tropical Diseases and the Foundation for the National Institutes of Health (FNIH) in the United States. Drafting and review were undertaken through collaboration with more than 40 experts worldwide. It has gone through a series of reviews by health experts in developing and developed countries, as well as experts from other fields including molecular biology, ecology, regulatory requirements, and ethical, social and cultural issues. This is its first public consultation.

TDR has been working for several years to develop a pool of scientists well trained in the assessment and management of biosafety for human health and the environment in relation to the potential use of GM mosquitoes for the control of

vector-borne diseases. Courses in bio-safety have been held in regional training centres in Africa, Asia and Latin America for 148 participants from 51 countries between 2008 and 2010.

**Reference:** Special Programme for Research and Training in Tropical Diseases. Guidance Framework for testing genetically modified mosquitoes. *TDR news item*. 29 October 2012. [http://www.who.int/tdr/news/2012/guidance\\_framework/en/index.html](http://www.who.int/tdr/news/2012/guidance_framework/en/index.html)

## **Patent opposition database**

A new online resource for civil society and patient groups in developing countries to challenge unwarranted medicines patents has been launched by Médecins Sans Frontières (MSF). The Patent Opposition Database comes as many developing countries face dramatically high medicines prices because patents block the production of lower-cost generic versions. MSF relies on affordable medicines for its medical work in more than 60 countries; in the case of HIV treatment, over 80 per cent of medicines used in developing countries are generics.

A 'patent opposition' — a legal challenge to prevent or overturn the granting of an unwarranted patent — is allowed under international trade rules as a way to keep checks and balances on pharmaceutical patenting. In countries where they are allowed, like Brazil, India or Thailand, patent oppositions have successfully prevented undeserved patent monopolies from being granted and allowed generic competition to bring the price of medicines down.

Successful examples include the opposition by Indian groups to a patent application in India on the HIV fixed-dose-combination zidovudine/lamivudine, on the grounds that it was not a 'new invention', but simply the combination of two existing drugs. This combination is now widely used in HIV treatment in developing countries.

A pre-grant opposition filed by the Cancer Patient Aid Association was also the spur for the rejection of a patent application on the salt form of imatinib, on the basis that the medicine was merely a new form of an old medicine.

The Patent Opposition Database aims to guide civil society groups through the process of challenging an unjustified patent. It will allow organizations to forge new alliances and share vital specialist knowledge, as a patent application can often be challenged in different countries on the same basis. It contains a searchable listing of 45 patent oppositions relating to key medicines and over 200 other supporting documents that will aid in the building of future patent oppositions.

**Reference:** *Médecins Sans Frontières (MSF) Press Release*, 2 October 2012 at <http://www.patentoppositions.org>

### Clinical management of dengue

*The Handbook for clinical management of dengue* has been produced to help healthcare practitioners at all levels manage dengue. Aspects of managing severe cases of dengue are also described for practitioners at higher levels of health care. Additional and more specific guidance on the various areas related to clinical management of dengue (from other sources in WHO and elsewhere) are cited in the reference sections. This handbook is not intended to replace national treatment training materials and guidelines, but it aims to assist in the development of such materials produced at a local, national or regional level.

This publication complements the 2009 edition of *Dengue: Guidelines for diagnosis, treatment, prevention and control*.

**Reference:** Special Programme for Research and Training in Tropical Diseases. *The Handbook for clinical management of dengue*. 2012. [http://www.who.int/medicines/areas/quality\\_safety/35thecddmeet/en/index.html](http://www.who.int/medicines/areas/quality_safety/35thecddmeet/en/index.html)

### Infectious diseases: new peer-reviewed journal freely available online

*Infectious Diseases of Poverty* is an open access, peer-reviewed journal publishing topics and methods that address essential public health questions. These include various aspects of the biology of pathogens and vectors, diagnosis and detection, treatment and case management, epidemiology and modeling, zoonotic hosts and animal reservoirs, control strategies and implementation, new technologies and application. Transdisciplinary or multisectoral effects on health systems, ecohealth, environmental management, and innovative technology are also considered.

The inaugural issue is themed *Health Systems Research for Infectious Diseases of Poverty*. Twelve articles have been selected to discuss treatment strategies, disease surveillance and interventions, as well as innovative programmes which provide a link between policy level and academic research.

Research submitted to *Infectious Diseases of Poverty* will follow an efficient online submission process, a rapid, high quality peer-review service, and immediate publication upon acceptance. There are no colour charges or limits on the number of figures or embedded movies.

The published version of articles will be immediately placed in PubMed Central and other freely accessible full text repositories. Publication costs are currently supported by the National Institute of Parasitic Diseases and the Chinese Centre for Disease Control and Prevention, so authors do not need to pay an article-processing charge.

**Reference:** *Infectious Diseases of Poverty* at <http://www.idjournal.com/about/>

# ATC/DDD Classification

## ATC/DDD Classification (Temporary)

The following anatomical therapeutic chemical (ATC) codes, defined daily doses (DDDs) and alterations were agreed by the WHO International Working Group for Drug Statistics Methodology in October 2012. Comments or objections to the decisions should be forwarded to the WHO Collaborating Centre for Drug Statistics Methodology at [whocc@fhi.no](mailto:whocc@fhi.no). The new ATC codes and DDDs will be considered final and be included in the January 2014 issue of the ATC Index. The inclusion of a substance in the lists does not imply any recommendation for use in medicine or pharmacy.

ATC level	INN Common name	ATC code
<i>New ATC 5th level codes:</i>		
	afibercept	L01XX44
	amlodipine and diuretics	C08GA02
	bedaquiline	J04AK05
	canagliflozin	A10BX11
	candesartan and amlodipine	C09DB07
	cineole	R05CA13
	cridanimod	L03AX18
	dabrafenib	L01XE23
	dimethyl fumarate	N07XX09
	dolutegravir	J05AX12
	ethacizine	C01BC09
	gemigliptin	A10BH06
	indacaterol and glycopyrronium bromide	R03AL04
	ipidacrine	N06DA05
	laquinimod	N07XX10
	levofloxacin, combinations with other antibacterials	J01RA05
	lixisenatide	A10BX10
	lorcaserin	A08AA11
	mebicar	N06BX21
	meldonium	C01EB22
	mercaptamine	S01XA21
	metformin and repaglinide	A10BD14
	olodaterol	R03AC19
	perindopril, amlodipine and indapamide	C09BX01
	phenibut	N06BX19
	ponatinib	L01XE24
	radium ( <sup>223</sup> Ra) dichloride	V10XX03

ATC level	INN Common name	ATC code
	rosuvastatin and acetylsalicylic acid	C10BX05
	rosuvastatin and ezetimibe	C10BA06
	sequifenadine	R06AX32
	technetium ( <sup>99m</sup> Tc) etarfolatide	V09IA08
	teriflunomide	L04AA31
	trametinib	L01XE25
	trastuzumab emtansine	L01XC14
	ulipristal	G03XB02
	vilanterol and fluticasone furoate	R03AK10
	vilanterol and umeclidinium bromide	R03AL03
	vintafolide	L01CA06

**New ATC level codes (other than 5th levels):**

ACE inhibitors, other combinations	C09BX
Adrenergics in combination with anticholinergics	R03AL <sup>1</sup>

**Change of ATC codes:**

INN Common name	Previous ATC	New ATC
ferric oxide dextran complexes	B03AC06	B03AC <sup>2</sup>
ferric oxide polymaltose complexes	B03AC01	B03AC <sup>2</sup>
ferric sodium gluconate complex	B03AC07	B03AC <sup>2</sup>
ferric sorbitol gluconic acid complex	B03AC05	B03AC <sup>2</sup>
fibrinogen, human	B02BC10	B02BC30 <sup>3</sup>
iron-sorbitol-citric acid complex	B03AC03	B03AC <sup>2</sup>
saccharated iron oxide	B03AC02	B03AC <sup>2</sup>

**Change of ATC code and/or ATC level name:**

Previous	New
R03AK03 fenoterol and other drugs for obstructive airway diseases	R03AL01 fenoterol and ipratropium bromide
R03AK04 <sup>4</sup> salbutamol and other drugs for obstructive airway diseases	R03AK04 salbutamol and sodium cromoglicate R03AL02 salbutamol and ipratropium bromide
R03AK07 <sup>4</sup> formoterol and other drugs for obstructive airway diseases	R03AK07 formoterol and budesonide R03AK08 formoterol and beclometasone R03AK09 formoterol and mometasone

**Change of ATC level names:**

Previous	New	ATC code
Adrenergics and other drugs for obstructive airway diseases	Adrenergics in combination with corticosteroids or other drugs, excl. anticholinergics	R03AK

**Change of ATC level names (continued):**

Previous	New	ATC code
Iron trivalent, parenteral preparations salmeterol and other drugs for obstructive airway diseases	Iron, parenteral preparations salmeterol and fluticasone	B03AC R03AK06
thyrotropin	thyrotropin alfa	H01AB01

<sup>1</sup> Split of ATC 4th level R03AK, separate 4th level for combinations with anticholinergics

<sup>2</sup> ATC 5th levels deleted, all products classified on the 4th level only (B03AC Iron, parenteral preparations)

<sup>3</sup> Combinations previously classified in B02BC10 should be altered to B02BC30 combinations (existing code)

<sup>4</sup> Separate ATC 5th levels for the various combinations (split of code). New ATC 4th level (R03AL) for combinations with anticholinergics

**New DDDs:**

	DDD	unit	Adm.R	ATC code
colecalfiferol	20	mcg	O	A11CC05
gemigliptin	50	mg	O	A10BH06
ivacaftor	0.3g	O	R	07AX02
pasireotide	1.2	mg	P	H01CB05
thyrotropin alfa	0.9	mg	P	H01AB01

# ATC/DDD Classification

## ATC/DDD Classification (Final)

The following anatomical therapeutic chemical (ATC) classifications, defined daily doses (DDDs) and alterations were agreed by the WHO International Working Group for Drug Statistics Methodology in October 2012. They have been included in the January 2013 version of the ATC Index. The inclusion of a substance in the lists does not imply any recommendation for use in medicine or pharmacy. The WHO Collaborating Centre for Drug Statistics Methodology can be contacted at [whocc@fhi.no](mailto:whocc@fhi.no).

### New ATC 5th level codes:

ATC level	INN Common name	ATC code
	eberconazole	D01AC17
	fluticasone, combinations	R01AD58
	glycerol phenylbutyrate	A16AX09
	limbal stems cells, autologous	S01XA19
	linaclotide	A06AX04
	lipegfilgrastim	L03AA14
	lurasidone	N05AE05
	masitinib	L01XE22
	metformin and alogliptin	A10BD13
	peginesatide	B03XA04
	pertuzumab	L01XC13
	poliomyelitis oral, bivalent, live attenuated	J07BF04
	quifenadine	R06AX31
	regorafenib	L01XE21
	tamsulosin and solifenacin	G04CA53
	tofacitinib	L04AA29
	trenonacog alfa	B02BD12
	vismodegib	L01XX43

### Change of ATC codes:

INN Common name	Previous ATC	New ATC
prucalopride	A03AE04	A06AX05
tegaserod	A03AE02	A06AX06

### Change of ATC level names:

Previous	New	ATC code
Drugs for functional bowel disorders	Drugs for functional gastrointestinal disorders	A03A
Drugs acting on serotonin receptors	Serotonin receptor antagonists	A03AE

**Change of ATC level names (continued):**

Previous	New	ATC code
Other drugs for functional bowel disorders	Other drugs for functional gastro-intestinal disorders	A03AX
Laxatives	Drugs for constipation	A06
Laxatives	Drugs for constipation	A06A
Bulk producers	Bulk-forming laxatives	A06AC
Other laxatives	Other drugs for constipation	A06AX
tetrachlorodecaoxide	sodium chlorite	D03AX11
etynodiol and estrogen	etynodiol and ethinylestradiol	G03AA01
quingestanol and estrogen	quingestanol and ethinyl-estradiol	G03AA02
lynestrenol and estrogen	lynestrenol and ethinylestradiol	G03AA03
megestrol and estrogen	megestrol and ethinylestradiol	G03AA04
norethisterone and estrogen	norethisterone and ethinyl-estradiol	G03AA05
norgestrel and estrogen	norgestrel and ethinylestradiol	G03AA06
levonorgestrel and estrogen	levonorgestrel and ethinyl-estradiol	G03AA07
medroxyprogesterone and estrogen	medroxyprogesterone and ethinylestradiol	G03AA08
desogestrel and estrogen	desogestrel and ethinylestradiol	G03AA09
gestodene and estrogen	gestodene and ethinylestradiol	G03AA10
norgestimate and estrogen	norgestimate and ethinyl-estradiol	G03AA11
drospirenone and estrogen	drospirenone and ethinyl-estradiol	G03AA12
norelgestromin and estrogen	norelgestromin and ethinyl-estradiol	G03AA13
nomegestrol and estrogen	nomegestrol and estradiol	G03AA14
chlormadinone and estrogen	chlormadinone and ethinyl-estradiol	G03AA15
megestrol and estrogen	megestrol and ethinylestradiol	G03AB01
lynestrenol and estrogen	lynestrenol and ethinylestradiol	G03AB02
levonorgestrel and estrogen	levonorgestrel and ethinyl-estradiol	G03AB03
norethisterone and estrogen	norethisterone and ethinyl-estradiol	G03AB04
desogestrel and estrogen	desogestrel and ethinylestradiol	G03AB05
gestodene and estrogen	gestodene and ethinylestradiol	G03AB06
chlormadinone and estrogen	chlormadinone and ethinyl-estradiol	G03AB07
dienogest and estrogen	dienogest and estradiol	G03AB08
reproterol and other drugs for obstructive airway diseases	reproterol and sodium cromoglicate	R03AK05
Other urologicals, incl. antispasmodics	Urologicals	G04B
Urinary antispasmodics	Drugs for urinary frequency and incontinence	G04BD
Tests for renal function	Tests for renal function and ureteral injuries	V04CH

**New DDDs:**

	<b>DDD</b>	<b>unit</b>	<b>Adm.R</b>	<b>ATC code</b>
dexmedetomidine	1	mg	P	N05CM18
droperidol	2.5	mg	P	N05AD08
leuprorelin	60	mcg	Depot implant	L02AE02
linagliptin	5	mg	O	A10BH05
pirfenidone	2.4	g	O	L04AX05
rilpivirine	25	mg	O	J05AG05

**Herbal medicinal products\*****New ATC 5th level codes:**

<b>ATC level</b>	<b>Common name</b>	<b>ATC code</b>
	Hederae heliis folium	R05CA12

\* Assessed and approved by regulatory authorities based on dossiers including efficacy, safety, and quality data (e.g. the well-established use procedure in EU).