Regulatory harmonization

16th International Conference of Drug Regulatory Authorities (ICDRA)

The 16th International Conference of Drug Regulatory Authorities (ICDRA) was held in Rio de Janeiro, Brazil, on 26–29 August 2014. The conference was hosted by the Brazilian Health Surveillance Agency ANVISA, in collaboration with WHO. The recommendations are set out on the following pages.

Government officials and regulators from more than 100 WHO Member States came together at this year’s ICDRA to discuss current challenges and strengthen collaboration. The ICDRA conferences, held every two years, have become a well-established forum for regulatory authorities, WHO and interested stakeholders to determine priorities for action in regulation of medical products.

A pre-conference titled “Ensuring Quality and Safety of Biosimilars for Patients Worldwide” was held on 24–25 August at the same venue. The ICDRA pre-conferences are open to participants from regulatory authorities, industry, academia and non-governmental and international organizations.

► WHO. International Conference of Drug Regulatory Authorities [web site]: http://www.who.int/medicines/icdra (includes links to recommendations and presentations of past ICDRA conferences)

► 16th ICDRA official web site: http://www.icdra.com.br

16th ICDRA sessions (recommendations, see pages 298–306)

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16th ICDRA recommendations

Plenary 3
The role of drug regulatory authorities in national health systems

- Strengthen the role of national regulatory authorities (NRAs) in public health protection and promotion, establishing the necessary governance and legal frameworks that will support NRAs in the exercise of this role, and establishing mechanisms to ensure effective linkages within the health, science/technology and industrial sectors, and with civil society, in order to contribute to universal health coverage.
- Strengthen the capacity of NRAs to assess and monitor the quality, safety and efficacy of medicines and medical products, ensuring effective implementation of core regulatory functions to support product registration and market authorization, as well as post-marketing surveillance, to monitor the use of the products in health services and during the complete product life cycle.
- Recognize the role of the NRA in supporting innovation and ensuring access to medical products in health systems and services by supporting regulatory processes that result in the introduction of safe new innovative medical products within health services, that guide the safe use of medical products in public health emergencies, and – in collaboration with other stakeholders – address shortages of essential medicines.

Plenary 4
Strengthening regulatory systems for medical products

- Recognize that effective regulatory systems are an essential component of health system strengthening that contribute to better public health outcomes; that regulators are an essential part of the health workforce; and that inefficient regulatory systems themselves can be a barrier to access safe, effective and quality medical products.
- Strengthen WHO’s role in strengthening regulatory systems for medical products from a public health perspective, and in supporting national drug regulatory authorities and relevant regional bodies in this area, and in particular in developing countries.
- Support the development and strengthening of national regulatory systems through the assessment of regulatory functions and system performance with WHO support, and the development and implementation of institutional development plans that will protect and promote health at the national level, and will pool and leverage regulatory capacity regionally and globally to promote access to quality, safe and efficacious and affordable medical products.
- Promote the greater participation of national regulatory authorities in existing international and regional initiatives and networks for collaboration and cooperation in accordance with WHO principles and guidelines, and increase support for and recognition of the significant role of the International Conference of Drug Regulatory Authorities in promoting the exchange of information and collaborative approaches among drug regulatory authorities, and as a resource to facilitate further development of regulatory cooperation and coherence.
### Workshop A

**Best practices in pharmacovigilance**

**Member States**
- Implement Pharmacovigilance (PV) as an integrated service that informs and improves health-systems, health resources and health-care delivery;
- integrate PV within a regulatory framework to ensure accountability and best practices in the way medicinal products are handled throughout their life cycle;
- embrace robust tools and methods for risk-based PV, to collect, manage and exploit PV information, including the detection of irrational use and quality-related aspects;
- engage all relevant stakeholders (patients, industry, authority, academia, health professionals and others) to develop and implement comprehensive PV plans; and
- in order to participate in a global PV community, be the beneficiary and the benefactor of PV information.

**WHO**
- Promote PV as an overarching integrated service that informs public health programmes and supports regulatory decisions;
- maintain and convene the global PV network and database, and support the global exchange of PV information across Member States;
- facilitate PV convergence and alignment across Member States, to allow consistent and comparable PV practices, optimal information exchange and learning; and
- develop and support the adoption of international norms, standards and tools to promote risk-based PV and for the full scope of PV (irrational use, medication errors, quality-related aspects).

### Workshop B

**How to ensure the safety of traditional and complementary medicines in national healthcare systems**

**Member States**
- Establish, strengthen and implement an effective regulation of providers of herbal medicines in respect of their qualification, in order to ensure the safety and quality of their practices;
- establish, strengthen and effectively enforce regulations on herbal medicines;
- strengthen capacity-building efforts for providers, manufactures and regulators of herbal medicines in order to improve their capacity and expertise regarding assurance of safety and quality of herbal medicines; and
- include safety monitoring on herbal medicines in pharmacovigilance systems and promote the awareness of consumers/patients on safety aspects of herbal medicines.

**WHO**
- Provide technical support to Member States in the implementation of the latest World Health Assembly resolution on traditional medicine (WHA67.18) and the WHO Traditional Medicine Strategy: 2014-2023, in particular regarding the safety of herbal medicines and of traditional and complementary medicine practices.
- Continue to provide technical support to Member States in:
  - strengthening national capacity for regulation of herbal medicines in ensuring the safety and quality of herbal medicines; and
  - sharing information regarding the safety of herbal medicines through global networking and relevant tools, including the networks of the International Regulatory Cooperation for Herbal Medicines (IRCH) and of the National Centres participating in the WHO International Drug Monitoring Programme.
**Workshop C**  
**Regulatory models for minimizing risks in blood and blood products**

**Member States**
- Member States are encouraged to add whole blood and blood components (red blood cells, platelets and fresh frozen plasma) to their national lists of essential medicines consistent with their inclusion in 2013 on the WHO Model List of Essential Medicines.
- Member States are encouraged to establish regulation of whole blood and blood components on the model of biological therapeutics* in order to:
  - protect the health and safety of blood donors; and
  - assure the quality, safety, efficacy and availability of blood for transfusion, and of plasma for further manufacturing to make essential derivatives.
- Member States are encouraged to establish regulation of whole blood, blood components and plasma derivatives within the national regulatory authority, including:
  - appropriate risk-based selection and quality assurance of test kits for donor screening; and
  - assuring bidirectional traceability of blood components between donors and patients as a foundation of haemovigilance.
- Member States are encouraged to adopt internationally recognized standards for blood collection and processing as an essential element of blood regulation.
- National standards for blood collection, processing and testing should be established and enforced by the national regulatory authority.

**WHO**
- At the request of Member States, WHO should provide assistance on:
  - capacity-building for national blood systems including a national regulatory authority;
  - establishment of appropriate legal frameworks for blood regulation and strategies for their implementation.

**Workshop D**  
**Approaches to educating regulators to meet country needs**

**WHO**
- Expedite coordination, development and launching of a global regulatory science curriculum; and
- develop and publish an inventory of accredited training centers and other training initiatives including specific areas of competency.

**Plenary 5**  
**Regulators’ role in access/availability (shortages etc.)**

**Member States**
- Explore the possibilities to promote convergence and harmonization of regulatory processes, and use joint and collaborative assessments as appropriate (with neighbouring countries or between authorities with common interest in certain products), in order to facilitate registration of medical products and increase efficiency.
- Design and implement fast-track and/or abbreviated registration processes for medical products that have already undergone rigorous evaluation in other countries e.g. by using the Collaborative procedure between national regulatory authorities in user countries and the WHO Prequalification programme for vaccines and medicines for priority diseases.
- Share experiences in design of special procedures for registration of products in case of emergencies or structural shortages, and for parallel importation.

**WHO and Member States**
- WHO and countries should:
  - collaborate in setting up a global monitoring system on medicines shortages;

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* The wording reflects recommendations as proposed and agreed during the conference; one comment was subsequently received.
– identify medicines vulnerable to supply interruption; and
– share experience in preventing and managing shortages.

► To respond to the Ebola virus disease (EVD) public health emergency of international concern, the following recommendations are made.

Member States
• Ensure there are emergency use regulatory pathways in place;
• ensure there is rapid and proactive cooperation and collaboration between regulators, and also with WHO, to help accelerate development and evaluation of investigational treatments and vaccines; and
• drive innovative clinical trial design for situations like the current EVD emergency where traditional clinical trial designs may not be feasible.

WHO
• Rapidly provide scientific information on the potential therapies and vaccines for EVD, and ensure the information is regularly updated;
• establish and lead a network of regulators globally to address the response to EVD; and
• facilitate collaborations between regulators in countries where products are being developed and those in countries where the products will be evaluated and, if found safe, used.

Plenary 6
New trends in regulating medical devices

WHO
• Continue and further strengthen international convergence/harmonization initiatives and normative work for medical devices, including IVDs, to support regulatory convergence in different jurisdictions.
• Support low- and middle-income countries (LMIC) to strengthen their regulations of medical devices, including IVDs, through provision of regulatory mechanisms that balance pre-and post-market regulatory oversight according to the risk level of the device.

Workshop E
Challenges of vaccine safety regulation and safety monitoring

Member States
• Vaccine safety concerns need to be addressed on an individual basis, and regulatory action should be tailored to the clinical setting as well as to the safety issue, the disease, and the strength of the evidence available.
• A combined effort by national regulatory authorities to support WHO in setting appropriate monitoring systems for vaccines worldwide is encouraged, especially in relation to newer vaccines.

WHO
• Multi-country collaboration on surveillance and monitoring of vaccine safety concerns should be actively pursued, to maximize the use of resources and public health protection, under the WHO umbrella.
• WHO efforts to enhance maternal immunization efforts are commended and should continue with support from all stakeholders.

Member States and WHO
• Pharmacovigilance data from multiple sources should be considered, with special emphasis and continued efforts to harmonize reporting and collection of safety data.
• Efforts to raise the quality and quantity of relevant data on vaccines use during pregnancy should continue.

Workshop F
Collaboration for ensuring the quality and safety of active pharmaceutical ingredients (APIs)

• At the request of Member States, WHO and Member States (well-resourced national regulatory authorities) should establish a system of targeted
capacity-building for ensuring the quality and safety of APIs:
– focusing on the needs and obligations of producing countries and user countries;
– emphasizing practical skills development through:
  ▪ twinning and staff placements;
  ▪ sustainable training approaches based on defined competencies (e.g., through a network of Centers of Excellence); and
  ▪ observed/collaborative/joint inspections.
• Member States should establish transparent regulatory systems, based on internationally agreed-upon standards, that will assure quality and safety of APIs produced and used in, and/or exported from their borders, ensuring that:
  – APIs and their intermediates are manufactured by regulated manufacturers; and
  – API suppliers and brokers are regulated.
• WHO and Member States should support and encourage the use of work-sharing mechanisms for ensuring the quality and safety of APIs, e.g. WHO Prequalification of APIs, Certificates of Suitability of the European Pharmacopoeia (CEP), the International Generic Drug Regulators Pilot (IGDRP), etc.
• WHO should facilitate establishment of guidance on good/risk-based regulatory practice, including identification and use of available regulatory expertise to facilitate local regulatory decisions.

Workshop G
Preventing and reducing the risk to public health from substandard/spurious/falsely-labelled/falsified/counterfeit (SSFFC) medical products

► With a view to reducing the risks to public health from SSFFC medical products, all Member States are strongly encouraged to:
• participate in the WHO Member State Mechanism on SSFFC medical products, including implementation of the agreed work plan;
• in particular, to participate in on line working groups both to:
  – establish recommendations to detect and deal with actions, activities and behaviours that result in SSFFC medical products, and
  – establish activities that fall outside of the mandate of the Member State Mechanism.
• Within the framework of the Member State Mechanism, WHO should continue to provide support and build capacity in low-income countries to tackle SSFFC medical products.

► Prevention
• National medicines regulatory authorities (NMRAs) are encouraged to develop a specific strategy to combat SSFFC medical products tailored to their national and regional needs, including but not restricted to:
  – targeted awareness campaigns for specific stakeholders; and
  – strengthening networks of key stakeholders to enable more effective collaboration, cooperation and communication.
• NMRAs utilizing track, trace and authentication technologies should share knowledge and experience with a view to strengthening supply chain integrity.
WHO and Member States should undertake research into the root causes of SSFFC medical products, including the scope, scale and harm caused to public health, health systems and Member States.

**Detection**
- All NMRAs should have access to field testing equipment and/or Quality Control Laboratories;
- all NMRAs are encouraged to carry out risk-based post market surveillance and market surveys; and
- all NMRAs are encouraged to ensure sustainable pharmacovigilance reporting systems from healthcare professionals and the public, specifically including the lack of efficacy of a medical product.

**Response**
- All NMRAs are encouraged to have developed procedures to respond to suspected SSFFC medical products, with particular attention to quarantine, seizure, sampling, analysis, recall, investigation, enforcement, information-sharing and collaborating with stakeholders.
- All NMRAs are encouraged to share information concerning incidents involving suspected SSFFC medical products with sub-regional and regional regulatory networks and WHO through rapid alert systems.
- In order to protect public health, all NMRAs should increase knowledge and understanding and influence evidence-based policy and resource allocation.

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### Workshop H

**Biosimilars**

1. **Ensure regulatory oversight throughout the life cycle of biotherapeutic products, including similar biotherapeutic products, (SBP) to assure quality, efficacy and safety of these products**

**Member States**
- Clearly define regulatory pathways for biotherapeutic products, including biosimilars, and make this information transparent and easily available (e.g. through a web site).
- Implement regulatory standards for approval of biological products that are aligned with WHO standards.
- Strengthen regulatory functions, in particular clinical evaluation and PV, including proactive collection of PV data.

**WHO**
- Update norms, standards, and tools to facilitate further development of expertise for regulatory evaluation of biologicals.
- Nomenclature for similar biotherapeutics is a complex issue for which there is no consensus yet; this is under discussion with the WHO INN Expert group, and a consultation with all Member States and stakeholders is under way.

2. **Improve efficiency of regulatory evaluation of biotherapeutic products, including SBP, in order to improve access to products of assured quality, safety and efficacy**

**Member States**
- Make effort to reduce time for evaluation without compromising quality of the review, in particular review time for the purpose of licensing or clinical trial approval.
- Facilitate the development and licensing of innovative molecules which could serve as reference products in the development of biosimilars.
- Develop information and/or work-sharing with other regulators for SBP (e.g.)
recognition of other NMRAs' conclusions; work-sharing in sub-regional or regional networks).

WHO
• Continually update information regarding WHO standards for biologicals through regional and/or inter-regional networks and initiatives.

3. WHO guidelines on biotherapeutic products and on SBP

Member States
• Implement existing WHO guidelines and subsequent updates in full, and monitor levels of implementation over time.
• If national standards differ from WHO standards, inform WHO of the rationale for this situation.

WHO
• Amend Guidelines on evaluation of SBP by providing additional information on:
  – extrapolation of indication;
  – special considerations for evaluation of monoclonal antibodies;
  – acceptance criteria and evaluation of reference biotherapeutic products (RBP) including the reliance on reference agencies;
  – the design, conduct and interpretation of data for comparability exercise.
• Facilitate implementation of existing guidelines on SBP (adopted in 2009), and subsequent updates, and on biotherapeutic products made by recombinant DNA technology (adopted in 2013).
• Develop e-learning tools for different levels (e.g. basic, advanced).
• Prepare case studies for illustrating practical application of guiding principles to different scenarios, e.g. mimic the real situation.
• Make all materials from implementation workshop (i.e. lectures, discussions, and case studies) available to all regulators.
• Develop criteria and/or tool for assessing implementation level of WHO written standards (guidelines) into regulatory practice.

4. Collaboration between regulators and other relevant stakeholders

Member States
• Involve all relevant stakeholders (e.g. manufacturers, academia, health care providers, patient associations) during development of national regulatory requirements and create opportunities for regular feedback on regulatory practices.
• Develop national initiatives for better access to biotherapeutic products, including SBPs; such initiatives may include considerations on intellectual property issues, interchangeability, and substitutability. *
• Develop programmes to educate all relevant stakeholders on the nature and intended use of biosimilars, and define the role of each stakeholder in improving access to biotherapeutic products, including biosimilars. *

WHO
• Provide a forum for information-sharing on collaborative efforts that leads to better access.

5. Regulatory convergence as a tool to increase global access to SBPs of quality, safety, and efficacy

Member States
• Make effort to align national regulatory requirements with WHO guiding principles for biotherapeutic products, including SBP.
• Define terminology for naming SBP that enables clear identification of the evaluation pathway. *
• Use the term “biosimilar” for products that were demonstrated as similar through an evaluation that is in line with the biosimilar pathway as described in WHO Guidelines on evaluation of similar biotherapeutic products, only.

WHO
• Develop tools to measure progress in regulatory convergence.

* The three points marked with asterisks reflect recommendations as proposed and to which no objections were made at the time of adoption, but which do not necessarily represent consensus since some regulators expressed different views during the meeting.
Workshop I
Current status and future vision of regulating advanced therapies

- Products containing genetically modified viable cells should be considered cell therapy medicinal products. They are biological medicinal products.
- Products containing viable cells which are used in transfusion medicine (e.g. thrombocyte, erythrocyte, granulocyte concentrates) or for haematopoietic reconstitution are not considered cell therapy medicinal products.

Member States
- Member States are encouraged to develop regulatory expertise for cell therapy medicinal products appropriate for the specific nature of these products. In this regard it is recommended to:
  - share regulatory experiences among national regulatory authorities to allow appropriate regulatory responses; and
  - promote information-sharing between academia, industry and national regulatory authorities on newest technologies including stem cell therapies.
- Development of cell therapy medicinal products in clinical trials should be facilitated prior to standard clinical use after authorization by a national regulatory authority.
- Experimental product testing by the developer should be established and enforced by the national regulatory authority.

WHO
- WHO should consider developing guidance on manufacture, non-clinical and clinical aspects of cell therapy medicinal products, taking into account existing guidelines, points to consider and recommendations, with the collaboration of leading regulatory authorities.
- At the request of Member States, WHO should organize the provision of assistance on capacity-building for the regulation of cell therapy medicinal products.
- WHO should foster international collaboration between regulatory authorities regarding information-sharing to protect patients and the public from the risks of unauthorized cell therapy medicinal products.

Workshop J
Managing decentralized Good Manufacturing Practice (GMP) systems

- It is recommended that Member States, whatever their organizational model is in the field of GMP inspections, should ensure that all inspections are done in a consistent manner and that inter-inspector variability is measured and managed.
- It is recommended that Member States, when interacting with other Member States in the field of GMP inspections, make sure that any international inspection is notified well in advance to the national inspectorate on whose territory the inspection will take place, with the aim of allowing inspectors from that country to observe the inspection, thus serving the ultimate goal of creating mutual trust and recognition between inspectorates.

Workshop K
Current challenges and transparency in clinical trials regulation

Member States
- Increase the transparency of processes, and work towards consistency of approaches to transparency for clinical trial review and approvals across countries.
- Increase collaboration and cooperation to build capacity of regulatory authorities for oversight of clinical trials;
- Ensure that appropriate regulatory pathways are in place to provide rapid but effective regulatory oversight of products to be used in public health emergencies;
- Rarely use domestic clinical trials to generate local data but use extrapolation instead; where justified, the regulator
should define the scientific question to be answered in domestic studies.

**WHO**
- Support countries in developing consistent approaches to transparency for clinical trial reviews and approvals.
- Strengthen platforms to support capacity-building initiatives for regulatory oversight of clinical trials.
- Facilitate joint reviews of multi-country clinical trial approvals.
- Establish guidelines on regulatory pathways for products to be used in public health emergencies.

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**Workshop L**

**Current topics and future developments**

**Member States**
- Promote innovative approaches to enhancing quicker access of medicinal products, without compromising safety;
- Future-proof regulatory approaches and gain insight into newer emerging products through horizon-scanning; interact with stakeholders and collaborate;
- With other national regulatory authorities, garner support for appropriate resources and funding to be better prepared in tackling the safety, quality and efficacy of these emerging products.
- Member States are encouraged to engage in multilateral cooperative networks with other regulators, which will facilitate information-sharing and provide mutual benefit for participants; and
- Member States are encouraged to join or draw benefits from multinational initiatives aimed at sharing best practices and expertise, achieving regulatory convergence of requirements as well as work-sharing, e.g. the International Generic Drug Regulators Pilot (IGDRP), the International Medical Device Regulators Forum (IMDRF) and the International Pharmaceutical Regulators Forum (IPRF).

**WHO**
- Support NMRAs in decision-making by provision of models for regulatory information-sharing and collaboration, including suitable IT instruments/tools.
- Expand existing WHO collaborative procedures for information-sharing.