International Harmonization

ICDRA: medicines agencies decide future action

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

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

Building mutual trust as a key to access

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

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

• How can regulators best contribute to public health with the resources they have?

• Should regulators assess and inspect every innovative product that is proposed for their market?

• Can and should all regulators assess and inspect generic medicines?

• Does repetitive assessment and inspection provide added value?

• How can confidence be built into scientific assessments carried out by other parties?

Moderator
Canada: Meena Ballantyne

Presentations


How to benefit from other regulators’ work. A New Zealand viewpoint. Stewart Jessamine, New Zealand.

Recommendations

WHO should:

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

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

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

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

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

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

Regulatory systems in a changing environment

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

Moderator

European Union: Thomas Lönn gren

Presentations

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

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


Recommendations

Member States should:

1. Facilitate and speed up global regulatory cooperation.

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

WHO should:

1. Continue to support and create new activities that stimulate cooperation and build trust among regulatory agencies.
Crisis management: safeguarding health

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

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

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

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

Moderators
Republic of Korea: Inkyu Kim
WHO: Bruce Plotkin

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

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


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

Responding to vaccine safety events. Karen Midthun, USA.

Recommendations

Member States should:

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

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

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

4. Play an important role in monitoring, analysing, and communication of vaccines safety.
5. Undertake passive and active surveillance after licensure including observational studies needed to detect and evaluate medicine and vaccine safety concerns.

**WHO and Member States should:**

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

**Current topics**

**Moderators**

*European Union/Council of Europe:* Susan Keitel

*Armenia:* Emil Gabrielyan

**Good Governance for Medicines**

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

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

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

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

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

Phase III: Implementation of a national GGM programme.

**Presentation**

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

**Recommendation**

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

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

**Variations**

**Presentation**

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

**Recommendation**

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

Presentation

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

Recommendations

1. Encourage better regulatory oversight.
2. Establish a prequalification system for radiopharmaceuticals.
3. Establish an international common platform (website and electronic database) for harmonized dossiers to pre-qualify radiopharmaceuticals.
4. Establish detailed mechanisms.

Involvement of consumers in medicines surveillance reporting

Presentation

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

Recommendation

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

WHO Stability Testing Guideline

Presentation

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

Recommendations

1. Finalize the revision of the guideline and apply it in Member States.
2. Provide information about the national long-term conditions to WHO.
3. WHO to make the data available on its web site.

WHO Certification Scheme

Presentation

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

Recommendations

1. Review reports of recent meetings held at WHO.
2. Give feedback to WHO for further discussion.

Adverse reactions

Presentation

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

Regulatory aspects of paediatric medicines

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

Moderator

European Union: Agnès Saint-Raymond

Presentations

Recent legislative changes regarding paediatric medicines in the European Union. Agnès Saint-Raymond, European Union.
**Clinical trials in neonates – challenges for all stakeholders?** Irja Lutsar, Estonia.

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


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

**Recommendations**

**Member States should:**

- Assist WHO to form an ICDRA paediatric working group to:
  1. Ensure global collaboration.
  - Agree on global regulatory standards.
  - Streamlining paediatric clinical trials.
  2. Implement efficient registration of children’s medicines.
    - Put children medicines as top priority.
    - Fast track strategies: e.g., hybrid applications, mutual recognition, cooperative review, waivers, etc.
  3. Develop consolidated views/advice on dosage forms and delivery devices.
    - Guideline on dosage forms.
    - Manipulations, extemporaneous formulations.
    - Increase knowledge on paediatric excipients.
  4. Devise mechanisms for ensuring transparency and exchange of information on trials, licensing, and children’s medicines (dose, adverse effects).
  5. Improve information on safety of medicines used in children and building infrastructure for pharmacovigilance.

**Other parties**

- **For industry:** continue integrating paediatric dosage forms and delivery devices early in development of new medicines.
- **For industry:** continue integrating paediatric needs, including developing countries needs in the development of new vaccines.
- **For the generic industry:** develop missing dosage forms of off-patent medicines (including necessary fixed-dose combinations).
- **To health professionals:** engage actively in sound, ethical research with children, with the aim of avoiding duplication of research.

**WHO should:**

- Convene a global paediatric working group of regulators.
- Work with civil society to mobilize and empower consumers, parents, patients’ groups and health professionals to advocate for better medicines for children.
- Develop strategies for addressing high priority needs with achievable results including: zinc for diarrhoea, *Pneumoniae* treatment, neonatal sepsis, HIV, TB, malaria treatments, and analgesics.
- Establish a drug development helpline to support new essential medicines for children.
**Vaccines and biologicals:**

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

**Member States and WHO:**

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

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

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

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

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

**Development of regulation for herbal medicines**

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

**Moderators**

*Singapore:* Shen Kuan Yee  
*Lao PDR:* Somthavy Changvisommid

**Presentations**

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

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

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

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

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

Member States should:

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

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

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

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

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

WHO should:

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

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

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

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

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

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

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

Safety and pandemic preparedness

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

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

In the case of an avian influenza pandemic the safety of vaccines administered during the pre-pandemic phase needs to be evaluated very rapidly.
Adequate storage of therapeutic agents and safe and rapid distribution channels are further challenges to be taken on.

**Moderators**

*Switzerland*: Pia Carduff-Janosa  
*Indonesia*: Lucky Slamet

**Presentations**

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

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

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

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

*Convalescent plasmas during a pandemic.*  
Jay Epstein, USA.

**Recommendations**

**WHO should:**

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

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

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

   • Develop guidance on best practices for collection and use of convalescent plasma in a flu pandemic

   • Promote pre-pandemic research on convalescent plasma

   • Encourage rapid sharing of scientific and technical knowledge from both pre-pandemic and pandemic experience

**National regulatory authorities (NRAs) should:**

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

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

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

**Regulatory approaches to proving interchangeability**

Experience has demonstrated that prescribers and other health-care professionals as well as patients are reluctant to change to generics unless there is a clear reason to do so and this reluctance is a major hurdle for the introduction of generics. Demonstrating qualitative and quantitative equality with the originator is therefore important for the introduction of generics and subsequent drop in medicines prices and health-care costs.
In light of knowledge gained in the last forty years on pharmaceuticals, scientific evidence supports the need for regulating the interchangeability of medicinal products. Many national competent authorities have issued guidelines on bioequivalence studies and on the type of medicinal product that can be exempted from *in vivo* bioequivalence studies.

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

**Moderators**

*Saudi Arabia:* Salah Bawazir

*Spain:* Carlos Lens

**Presentations**

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

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

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

*WHO biowaver guideline in regulatory practice.* Kamal Iddir, Tunisia.

**Recommendations**

*Member States should:*

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

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

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

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

**WHO should:**

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

**Strategies to fight counterfeit medicines**

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

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

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

The above principles have been the basis for the establishment of the International Medical Products Anti-Counterfeiting Taskforce (IMPACT). The Taskforce has identified five areas where action is needed in order to combat counterfeit medical products effectively. Accordingly,
five working groups have been created, covering: legislative and regulatory infrastructure, regulatory implementation, enforcement, technology, and communication.

Moderators
Nigeria: Dora Akunyili
Brazil: Bruno Rios

Presentations
National Experience in combating counterfeit medical products:
- Justina Molzon, USA
- Eishah A. Rahman, Malaysia
- Domenico Di Giorgio, Italy
- Danny Lee-Frost, United Kingdom

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

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

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

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

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

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

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

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

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

Emerging regulatory issues concerning biosimilars and biologicals
Draft WHO guidance states that, in contrast to a generics approach, the dossier for a similar biological product will need to contain information on the non-clinical and clinical data in addition to the quality data. However, the proposed guidance considers that a non-clinical and clinical package could be abbreviated; the extent of abbreviation will depend on the level of similarity to the
well established reference product with a proven record of quality, efficacy and safety.

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

**Moderators**

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

**Presentations**

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

*Regulatory considerations in Thailand.* Prapassorn Thanaphollert, Thailand.

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

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

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

**Recommendations**

**WHO should:**

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

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

**Member States should:**

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

**Emerging diseases:**

**regulating blood products**

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

**Moderators**

*USA:* Jay Epstein  
*Indonesia:* Lucky Slamet

**Presentations**

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

*Dengue outbreaks in Latin America.* Clarice Lobo, Brazil.

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

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

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

**Recommendations**

**WHO should:**

1. Take steps to further develop and strengthen national and regional blood
regulatory authorities and promote cooperation among them.

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

3. Take full account of existing assessment tools in use by NRAs by:
   • Convening a consultation of NRAs to review the draft assessment tool, and
   • Ensuring coordination with related WHO guidance documents.

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

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

Regulators contribution to access

Moderator
Hungary : Tamás Paál

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

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

Panel Discussion

Recommendations
Member States should:

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

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

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

WHO should:

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

Update on harmonization initiatives

Moderators
Tanzania: Margareth Sigonda
Canada: Mike Ward

Presentations

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

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


Recommendations

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

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

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

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

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

**Recommendations**

*Member States should:*

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

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

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

*WHO should:*

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

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

**Role of regulators in clinical trial approval**

**Moderator**

*Australia:* Rohan Hammett

**Presentations**

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

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

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

**Building regulatory capacity: best practices for the future**

**Moderators**

*India:* Debasish Panda

*Japan:* Takayuki Okubo

**Presentations**

*Building regulatory capacity.* Debasish Panda, India.

*NRA assessment/benchmark system and institutional development plan (IDP).* Rafael Perez Christia, Cuba.
Building regulatory capacity in a regulatory network: experience from twinning projects and EU worksharing. Dagmar Stará, Slovak Republic.

Recommendations

WHO should:

1. Systematically inform ministries of health of outcomes of NRA assessments.
2. Evaluate ways for improving benchmarking activities within the assessments.

Member States and NRAs should:

1. Use WHO tools for conducting self evaluation as an adequate way for improving regulatory performance.
2. Provide staff to support the WHO assessment process and take advantage of the experience resulting from this process.

GMP inspections: impact of information sharing and risk management

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

Moderators

USA: Justina Molzon

South Africa: Joey Gouws

Presentations


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

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

Recommendations

Member States should:

1. Work towards ensuring quality, efficacy and safety of drugs while making efforts to contain escalating costs of drug prices by minimizing duplication of inspection activities through:
   • Better networking.
   • Improved information sharing.
   • Enhanced collaboration.
   • Increased mutual trust/confidence.
2. Promote efficient use of inspectorate resources through use of a risk management approach in GMP inspections, especially for overseas manufacturers, by taking advantage of information available from other drug regulatory authorities.
3. Collaborate with WHO Member States and the WHO Medicines Prequalification Programme to share information about dates, purpose of inspection and major outcomes.

Manufacturers should:

1. Actively collaborate in information sharing among national, regional and international bodies involved in inspections.
2. Increase availability of non-confidential information on the web sites of interested authorities and on protected sites accessed by national authorities.

**WHO should:**

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

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

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

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

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

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

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

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

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

**Artemisinin**

**Artesunate**

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

**Nevirapine**

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

**Streptomycin**

The three groups of manufacturing methods, including the use of (genetically engineered) micro-organisms in fermentation, are frequently combined in the pharmaceutical industries.
• Recommend approaches for demonstrating process and product understanding.

• Address the complexity of different manufacturing processes and products.

• Accommodate variable approaches to development and corresponding information to be provided as described in Q8 and Q8R.

• Address enhanced approaches to manufacturing that can also create a basis for alternative approaches to control the quality of a product and for the application of innovative technologies for the manufacture of APIs (e.g. continuous manufacture).

• Address systematic approaches to drug substance development, application of quality risk management, and concepts such as design space, control strategies (including real-time release) over the lifecycle of the product.

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

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

• Information on development and manufacture of drug substances in regulatory submissions;

• Chemical and biotechnological molecular entities;

• New chemical entities opposed to generic APIs;

• Current practice versus quality by design (QbD) approach

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

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

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

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

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

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