International Regulatory Harmonization

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


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


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


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.
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 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.


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


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.
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.
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 worksharing.
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.

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

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 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.
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.

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
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:
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:

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.

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.
Presentations

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

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


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.
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**
- 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.

**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
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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/IPFMA
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 if 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**
Assessor experience with WHO API prequalification. Maryam Mehmandoust, 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

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

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