



12th International Conference of Drug Regulatory Authorities

Recommendations



Recommendations

Access to medicines: new regulatory pathways for public health needs

1. In the assessment of products, particularly those developed for public health needs, countries should make use of new regulatory pathways provided by highly-evolved regulatory agencies in order to avoid duplication of effort. This would enable optimal use of limited resources.
2. In cooperation with well resourced regulatory agencies, WHO is urged to assist Member States to provide training on the best use of regulatory information on product approvals available in the public domain.
3. WHO should continue its efforts to prequalify active pharmaceutical ingredients for medicines for priority diseases, including HIV/AIDS, malaria and tuberculosis. Information concerning prequalified products and approved sites should continue to be made public in the form of WHO public inspection reports.
4. WHO should assist national regulatory agencies to develop innovative approaches to improve access to safe and effective essential medicines of quality which address public health needs.

Emerging diseases and crises management: regulatory challenges

1. The fight against emerging diseases requires global collaboration and multi-disciplinary effort. Member states should ensure their national regulatory agencies are closely involved in national strategic decision making processes and are engaged as key stakeholders in national contingency planning. In this context, national regulatory agencies should develop business continuity plans and may also have a role in facilitating vaccine and pharmaceutical research and development, and development of blood screening tests.

2. WHO should take a leading role in the global preparedness for pandemic infections. Central to its role as the global leading health agency, WHO should cooperate with Member States to ensure transparency of epidemiological information, co-ordinate information and technology transfer on clinical trials and research and assist Member States through developing WHO standards for pre-marketing evaluation of pharmaceuticals developed for pandemic use. It is important for national regulatory agencies to find mechanisms to share clinical trial results and epidemiological data. National regulatory agencies should not allow the threat of pandemics to compromise the principles of safety, efficacy and quality of vaccines and pharmaceuticals being considered for licensing approval.

3. National regulatory agencies should ensure that robust post-marketing surveillance systems are in place to ensure that pharmaceuticals approved during a pandemic will continue to be closely monitored and subject to further assessment of their safety, efficacy and quality. To achieve this, national regulatory agencies should work with, among others, authorities for disease surveillance and the vaccine and pharmaceutical industry as close partners.

4. During a pandemic, the demand for blood and blood products is likely to increase. On the other hand, there could be lack of blood donations because of high morbidity and mortality of prospective donors. WHO should assist Member States -when drawing up contingency plans to include measures to maintain the integrity of their blood transfusion system, the continued supply of blood and blood products, and maintain transparency and information sharing.

New challenges in safety of medicines

High-profile drug safety issues present numerous challenges for drug regulators. New ways to improve knowledge about benefit/risk assessment, methods of signal detection, and communications to health professionals and the public are continually being sought. Spontaneous adverse drug reaction reporting has long been the cornerstone of pharmacovigilance and continues to serve a vital function, but changes in public expectations and drug development are encouraging regulators to think about pharmacovigilance as early as possible in the product life cycle.

The aim of pharmacovigilance planning is to provide regulators with a proactive approach to filling in knowledge gaps, while also improving the probability of detecting important safety signals as early as possible. Ultimately, this will result in better treatment choices for patients as they and their caregivers will have better information upon which to make choices. Furthermore, the publication of various risk management guidances, the improvement of scientific methods of adverse event signal detection and better and earlier communication of drug safety concerns to health professionals and the public are being developed. In addressing challenges of obtaining quality adverse event reports, cooperation between regulatory agencies and communicating effectively with the public are foremost.

Member States should:

1. Develop ways to ensure early communication to the public when an emerging safety concern arises.
2. Give patients, healthcare professionals and consumers quick and easy access to the most up-to-date and accurate information on medicines.
3. Encourage participation in WHO activities for reporting and collecting adverse reactions to medicines and vaccines, and seek ways to enhance reporting rates.
4. Improve scientific methods of adverse event signal detection.

WHO and Member States should:

5. Encourage pharmacovigilance planning in all public health programmes wherever possible.

WHO should:

6. Encourage cooperation between regulatory authorities when a new signal emerges.

Workshop A

Herbal medicines: safety through quality

1. Quality control of herbal medicines is complicated and difficult, and high-technology could be of valuable support. However, when country

capacity is limited, continued use of dependable basic technical methods and tests is recommended.

2. Governments should provide adequate support for clinical studies, since there are few clinical studies and appropriate approaches for the assessment of efficacy. WHO should provide technical guidance of appropriate approaches for clinical studies and assessment of efficacy of herbal medicines.

3. Traditional medicine plays an important role in primary health care in many developing countries and countries should consider categorizing herbal medicines based on available knowledge and the literature. Relevant appropriate requirements should be established for the assessment of safety and efficacy for different categorized herbal medicines to reduce cost and expenditure and meet demands of accessibility and affordability.

4. A challenge for national health authorities is the lack of research information and data on herbal medicines. Sharing national information and experience, as well as setting up common accepted standards through bilateral recognition and through international and regional regulatory cooperation for herbal medicines should be considered. WHO should continue to provide support to international and regional regulatory cooperative initiatives for herbal medicines.

5. In order to ensure safe and effective use of traditional medicine, integration of traditional medicine into national health systems should be considered where appropriate.

Workshop B

Good Review Practices

1. WHO should continue supporting country efforts to improve regulatory review processes in the context of overall improvement and implementation of good regulatory practices. Special emphasis should be given to helping small regulatory authorities; existing models may need to be adapted to match the resources available.

2. Regulators should make efforts to implement good review practices in order to improve regulatory systems through the introduction of good regulatory practices. Regulators should consider the road map approach,

standardized formats for dossiers, disclosure of information, use of outside consultants, and quality management systems as useful tools for the improvement of review practices.

Workshop C

Bioequivalence: from science to practice

During recent years, the concept of bioequivalence has developed and several new regulatory approaches and guidance documents have been created. WHO has developed a comprehensive updated package of regulatory guidelines in line with former ICDRA recommendations.

1. Countries intending to implement bioequivalence requirements should consider learning from other countries' experience and take a risk based approach to implementing bioequivalence.
 2. WHO is encouraged to assist Member States by providing training for regulators and industry on the implementation of the newly adopted WHO guidelines on the establishment of interchangeability (including guidelines on registration requirements to establish interchangeability of multisource (generic) pharmaceutical products, a proposal to waive in vivo bioequivalence requirements for some of the immediate release solid dosage forms in the WHO Model List of Essential Medicines, guidelines for organizations performing in vivo bioequivalence studies and a revised list of international comparator products).
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Workshop D

Regulation of blood and blood-derived products: global challenges

Assurance of safe and adequate blood supplies nationally and regionally requires effective regulation and continuous vigilance. The preparation of blood components as well as plasma derivatives should be subject to established regulatory standards and controls. Essential elements of blood and blood product regulation include implementation and enforcement of good manufacturing practices (GMP), evaluation of blood donor screening tests, blood related drugs and medical devices, and the establishment of effective pharmacovigilance systems. In order to support development of these activities in countries with limited resources, it is

essential to strengthen international approaches to regulation and to encourage the collaboration of national regulatory agencies at both regional and global levels.

1. Effective regulatory oversight is essential to ensure the quality and safety of blood and blood products. However, this cannot be achieved in the absence of a national legal framework and policy. Countries should take an active role in updating their respective legal provisions so that the implementation and enforcement of GMP for blood establishments can be made effective. WHO should provide, upon request, technical advice to those countries wishing to update legal provisions to strengthen the regulation of blood and blood products.

2. WHO should continue to give the highest priority to strengthening educational programmes and to providing training opportunities to support implementation and enforcement of GMP in national blood and plasma establishments. Appropriate guidance documents should be developed and/or updated. Countries should take an active role to ensure the implementation and enforcement of GMP for blood and plasma establishments as a prerequisite for consistent quality in the preparation of blood and blood products

3. WHO should continue to enable/promote cooperative interaction among national and regional regulatory authorities. In particular, WHO should:

- continue to support the development of a cooperative network for leading regulatory agencies, and
- facilitate the creation of regional networks of national authorities involved in the regulation of blood and blood products in order to enhance the regulatory role and leverage technical expertise.

4. Countries should take an active role in the operation of networks and regional steering committees should be established to promote harmonization of national regulatory policies. Appropriate support should be provided to this activity by WHO.

5. WHO should promote and encourage the establishment of effective pharmacovigilance systems for blood and blood products and link these to existing pharmacovigilance systems for medicines. Countries should implement and enforce appropriate and well structured reporting mecha-

nisms for serious or unexpected adverse reactions to blood and blood products, including infectious transmissions. To enable safety investigations, countries should implement and enforce traceability with linkage from blood donor to recipient and from recipient to blood donor.

6. Regulatory authorities should encourage scientific studies to establish medical evidence in support of product labeling for clinical use. Suboptimal use of blood and blood products leads to wastage of precious products and increases the risk of side effects for recipients.

7. WHO should continue to strengthen the development of international reference materials and standards for validation and control of blood donor screening tests, especially for detection of anti-hepatitis C and anti-HIV antibodies.

8. WHO should encourage the development of risk-based regulatory strategies. Countries should consider establishing mechanisms and share information in this regard.

Workshop E

Role of regulators in control of advertising and promotion

1. Regulators should strengthen their efforts to ensure that advertising and promotion is in accordance with the approved product information and respective national regulations. To this end, regulators should collaborate closely with industry, publishers, the media and consumers. Such co-regulation of promotion must be underpinned by sound legislation and regulatory sanctions. Sanctions should be made public.

2. The global nature of the internet is difficult to regulate. Regulators need to work together to control sources of internet advertising. In addition, regulators should provide independent consumer and prescriber information on the internet to support the quality use of medicines. This information should be easy to locate and be recognizable by prescribers and consumers. WHO is requested to continue to support countries in this regard.

3. WHO should increase its efforts to disseminate and promote the WHO Ethical Criteria for Medicinal Drug Promotion, in particular the provisions to ban direct-to-consumer advertising of prescription-only medicines and

regulate free samples to medical doctors. These criteria need to be actively supported by national regulatory agencies and used as the basis for national regulations. In this regard there needs to be close alignment between the regulation of promotion of medicines, foods and cosmetics.

Workshop F

Access to treatment for severe pain: what can regulators do?

1. Regulators should make efforts to ensure that national regulatory frameworks do not impose an excessive (i.e. not prescribed by the respective international conventions) administrative and legal burden on achieving access to internationally controlled narcotic painkillers.
2. To achieve better access to narcotic painkillers, and primarily those on the Model List of Essential Medicines, regulators are encouraged to work closely with international organizations such as the International Narcotics Control Board (INCB) and WHO, as well as with national and local bodies involved in palliative care. All severe pain needs to be appropriately addressed therapeutically and especially severe pain in life-limiting illnesses (cancer, HIV/AIDS).
3. Regulators should seek proactive ways to collaborate with other national health authorities to improve access to painkillers controlled under international conventions from importation/manufacture, through secure distribution chains, rational prescribing and dispensing to patients. To cover the population in need, it is necessary to widen patient access to legitimate prescribers, taking into account the national specific situation, e.g. consideration should be given to allowing specialized palliative care nurses or clinical officers to prescribe oral morphine.
4. WHO should support countries in improving their regulatory systems in order to identify potential administrative and legal hurdles to access of narcotic painkillers and find ways to eliminate these without compromising control functions prescribed by international conventions.
5. WHO should contribute to organizing respective regional and national training courses and exchange information on effective interventions carried out by countries that have achieved improvement in making narcotic painkillers more accessible to patients in need.

Workshop G

Pharmacoeconomics and regulation

Pharmacoeconomics is a discipline established to relate and identify the benefits and costs of medicines therapies. In the public sector, the aim is to inform and support decision-making in purchasing, pricing or reimbursement of medicines and to aid in clinical choice and guidance. Some of the main challenges encountered in setting up pharmacoeconomic mechanisms include questions about the clinical data and legal/scientific issues, and availability of capacity/resources,

Member States should:

1. Strive for open access to clinical regulatory data.
2. Be transparent about the criteria used in decision-making. If pharmacoeconomics is one of them, provide clear methodological guidance.
3. Consider the need for active comparator studies and outcome data (to allow rational use of medicines) in pre-/post-authorization phases of regulatory assessment.
4. Consider the possibility to initiating/supporting independent comparative outcome studies.

WHO should:

5. Assist in high-level awareness-building.
 6. Assist in capacity building.
 7. Support regional networks.
 8. Provide guidance on basic pharmacoeconomic evaluation to the relevant national health authorities.
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Workshop H

Global challenges for regulation of vaccines and other biologicals

Biological medicines are one of the fastest growing sectors of the pharmaceutical industry. Regulation of biologicals presents special challenges due to the specificities introduced by the biological nature of the products

and processes. Problems include the inherently variable nature of the starting materials and production systems which at some stage are derived from, or use, living organisms. Certain products, such as attenuated vaccines, consist of live organisms. The test methods needed to characterize the products are biological (bioassays) and thus require special standardization efforts. Biologics research by the regulator may be necessary. Batch-related problems or accidents associated with biologicals have occurred and thus batch-by-batch regulatory review is necessary. Furthermore the complexity of biologicals is increasing and some potential applications such as gene therapy or cell and tissue therapy are at the very leading edge of scientific development. Finally, a paradigm shift is occurring where biologicals such as vaccines that will be used globally are increasingly being manufactured and first licensed in countries with the highest disease burdens. This is placing extra responsibilities on regulators in such countries, often in the context of limited regulatory resources.

1. Countries are requested to ensure that biologicals receive science-based, innovative, and special regulatory attention. Regulatory collaboration is encouraged to support regulatory research and, further, to support countries without comprehensive biologicals regulatory systems. WHO should facilitate the process through establishment of regional and global networks of regulators.
2. WHO is requested to develop global regulatory consensus and guidance for biosimilars, which are a reality in several countries and will be a major regulatory challenge in the years to come.
3. Countries are encouraged to establish regional networks of national control laboratories (NCLs) to overcome the constraints that NCLs are facing now and in the future. WHO is requested to facilitate the work of NCLs through a global review of batch release strategies.
4. Countries are requested to increase their support for the development, characterization and distribution of biological reference preparations, which are an essential tool in the regulation of biological medicines. WHO is requested to ensure sustainability of its international biological reference preparation programme.
5. Vaccines are increasingly being first trialed in countries with the highest disease burden. Countries should ensure that regulatory review of new vaccine applications includes the quality and pre-clinical, as well as clini-

cal, parts of the dossiers. WHO should extend its support for capacity building to include quality and pre-clinical evaluation.

6. New combination vaccines are increasingly being produced in developing countries and present special regulatory challenges. WHO is requested to develop guidance on the quality, safety and efficacy evaluations of combination vaccines, including advice on bridging studies when combination vaccines are used in new populations.

Workshop I

Stability: global challenges for harmonization

Efforts regionally and interregionally to harmonize stability testing conditions offer many challenges, particularly for the hot and humid zone conditions. The question has generated much debate as to proper temperature and humidity conditions in relation to predicting the proper shelf life of a medicinal product within a country.

1. Member States should identify their stability testing conditions in order to facilitate import to and export from their country. Ideally these should be based on conditions currently in use, thus avoiding creation of barriers to access to medicines
2. Member States should make information available to WHO regarding stability conditions to be used within their markets.
3. WHO should make available country information in order to facilitate accessibility by manufactures and any interested party on an international basis.
4. WHO should observe the stability situation and any future developments and continue its efforts to find harmonized conditions, in light of any major changes to the current situation in regions.
5. Any international mechanism or organization which develops guidance relevant for countries outside their own regions should ensure that those countries are made aware of these developments and are directly approached to take part in the consultation process. For the International Conference on Harmonization (ICH), the Global Cooperation Group should be stressed as a way to work with regional harmonization initiatives.

Workshop J

Counterfeit medicines: towards better structured international collaboration

The 12th ICDRA congratulates WHO for the conference organized in Rome in February 2006 following-up on the recommendations of the 11th ICDRA and endorses the Declaration of Rome.

The 12th ICDRA welcomes the establishment of the International Medical Products Anti-Counterfeiting Taskforce (IMPACT) and congratulates WHO on establishment of the IMPACT Secretariat.

The 12th ICDRA expects IMPACT to:

1. Work on the basis of terms of reference that should take into account the topics raised in the Rome Declaration and at the 12th ICDRA and should provide clear milestones and tangible results.
2. Develop concrete and pragmatic proposals on how to improve national, regional and international strategies to combat counterfeit medicines.
3. Analyse in particular how to improve the sharing of information on cases of counterfeit medicines taking into consideration existing systems, e.g. WHO Rapid Alert System.
4. Take into consideration existing activities in order to use the synergies of such activities and avoid duplication of effort.
5. The 12th ICDRA calls upon WHO to provide all necessary support to IMPACT via its Secretariat.
6. It calls upon the national and regional authorities to fully support IMPACT by providing the necessary resources during its work and by implementing its recommendations.

Workshop K

Small model drug regulatory authorities

1. Small national drug regulatory authorities (DRAs) should establish appropriate regulatory structures that correspond to the situation of the country without compromising minimum standards of safety, quality and

efficacy, and should also attune legislative and administrative practices to the resources at the DRA's disposal.

2. Regulatory activities should be prioritized to develop and build up the registration and regulatory system in a stepwise manner, but continue to expedite access of essential medicines to the country's population.
3. Small DRAs should identify appropriate best practices for implementation that can be adopted or adapted to their situations by studying reference countries and suitable benchmark authorities.
4. Small DRAs should engage proactively in international cooperation, both at regional and global levels.

WHO should:

5. Consider convening a forum of small DRAs to facilitate sharing of information and best practices, including (a) leveraging on safety, quality and efficacy information available from larger, trusted authorities; (b) identifying trusted sources of generic medicines; and (c) standardizing formats for sharing of data about registered medicines in various national jurisdictions.
6. Continue to encourage the benefits of regional networks wherein smaller regulators can work with trusted larger regional authorities in order to optimize resources and enhance regulatory capacity.

Workshop L

IPR for pharmaceuticals: improving or impeding access?

The rationale for the protection of intellectual property rights (IPR) is the creation of incentives for technological innovation. However, IP protection may limit access to technologies and products because it creates monopolies and decreases competition in the market, thereby allowing patent holders to set the prices. Neither can IPR protection (for example, as required under the TRIPS agreement), adequately address the interrelationship between incentives, IPR and innovation in pharmaceuticals. Patents on chemical compounds or molecules do not always necessarily result in priority disease drugs, or guarantee access to such drugs.

1. National regulatory agencies should contribute to ensuring the right balance between the need for innovation and equitable access, and between commercial and public health interests. To this end, they should closely collaborate with other ministries, the patent office and other national stakeholders in developing national patent legislation. However, regulatory agencies should not be involved in enforcement of patents as part of the process of regulatory decision making.

2. Countries should incorporate into their national legislation the relevant TRIPS flexibilities for export or supply of medicines of assured quality to countries with public health emergencies.

3. WHO should strengthen its capacity building to support countries in making maximum use of the TRIPS flexibilities.
