

Eleventh International Conference of Drug Regulatory Authorities¹ (ICDRA)

Progress Report and Recommendations

Progress report on Tenth ICDRA (Plenary 1)

Participants recognized the progress made in many areas of medicines regulation since the Tenth ICDRA in Hong Kong in 2002. As globalization continues and has a profound impact on the development and marketing of medicines, strong international collaboration among regulatory authorities is needed to safeguard public health interests.

In view of continued regulatory problems and new challenges, participants stressed the importance of government commitment to strengthening national regulatory systems and policies and the need to intensify international collaboration to improve access to safe and effective medicines of good quality.

Regulatory aspects of access to medicines (Plenary 2)

The mission of regulatory authorities is to promote and protect public health. The lack of access to medicines remains a huge concern, whether these are essential medicines, vaccines, orphan drugs or drugs for tropical diseases. To facilitate access, regulators and

¹ Throughout this document, national regulatory authority has been chosen as the term to describe: drug regulatory authority, drug administration, medicines control authority, therapeutic products directorate or therapeutic goods agency, etc

all other stakeholders need to be actively involved in identifying difficulties and seeking solutions leading to balanced approaches to access which do not compromise public health safeguards.

Recommendations

- Regulators have a role and responsibility to facilitate access to drugs of public health importance including proposing changes to the respective regulations in order to facilitate access without compromising quality, safety and efficacy.
- When considering marketing authorization (registration) applications, regulators should give priority to medicines of high public health importance in their countries. Regulators should consider mechanisms to facilitate registration, such as reducing fees or other related costs.
- As part of the medicines approval process, regulators should carry out an appropriate risk benefit assessment to allow for adjustment to the needs and profile of the anticipated patient populations.

Strengthening of regulatory frameworks for medicinal products (Plenary 3)

The establishment of a well-functioning national regulatory system as an integral component of effective public health leads to better patient protection through provision of medicines which are safe, efficacious and of good quality. Cooperation,

communication and trust between national regulatory authorities based on common principles and harmonized approaches will strengthen the effectiveness of national regulation and international collaboration. Transparency is an important aspect of regulatory systems and helps to build public confidence, while facilitating cooperation and information exchange among regulators.

- Member States should strengthen their efforts to increase transparency of the work of national regulatory authorities. Regulatory guidelines, procedures and criteria as well as data about registered medicines should be made publicly available to all stakeholders.
- National regulatory authorities should make available to the public, in understandable language, negative and positive assessment reports (including pharmacovigilance reports).
- National regulatory authorities should provide applicants for a marketing authorization with full information on regulatory decisions and an explanation of the reason for such decisions.

Pharmacovigilance Practices (Plenary 4)

Spontaneous reporting is the mechanism used for compiling adverse drug reaction reports and regulatory authorities take important decisions based on these data.

Pharmacovigilance is a broad concept, and also includes the re-evaluation of marketed

drugs, risk management, communicating drug information, promoting rational drug use and crisis preparedness. It is becoming increasingly important to provide training in all of these activity areas and to carry out intensive monitoring of new drugs in order to evaluate the risk/benefit. Increasingly, medicines are being donated for off-label indications for specific public health needs and it is important that sufficient data is available to the national regulatory authority on safety, efficacy and quality.

Recommendations

- Member States should be encouraged to involve pharmacovigilance staff in public health risk assessment, management and communication for medicines safety activities including adverse reactions monitoring, medicines re-evaluation, drug information, rational drug use, lack of efficacy and crisis preparedness.
- Increasingly, certain medicines are approved based on special conditions, such as finalization and reporting of Phase IV studies. National regulatory authorities should collaborate on harmonizing the terms of conditional approval, and develop systems to allow sharing of information on medicines in this category.
- All sponsors and donors of medicines should provide sufficient data to allow the national drug regulatory authority to be assured that the product being donated, or recommended for use, meets appropriate standards of safety, quality and efficacy. Obligations to conduct post-marketing surveillance as a public health protection

measure should also lie with sponsors and donors, as appropriate. International agencies and aid programmes should make every effort to comply with these requirements and provide the necessary data.

- Member States should be encouraged to establish databases of clinical information suitable for epidemiological studies to examine and quantify signals of possible emerging risk.
- WHO should coordinate and develop training resources in pharmacovigilance and pharmacoepidemiology and expand its commitment to include training programmes in each of its regions.
- WHO should provide, upon request, technical advice and support to Member States on the appropriateness of post-marketing surveillance plans submitted by sponsors when a medicine is being introduced to manage a specific public health campaign in that country.
- WHO should investigate the feasibility and potential utility of creating a database of “recommendations for action” arising from evaluations made by national regulatory authorities of the periodic safety update reports (PSURs) in order to improve the usefulness of such information by making this generally available.

Pharmacopoeias in a changing regulatory environment (Workshop 1E)

Pharmacopoeial standard-setting for starting materials and finished dosage forms underpins the work of drug regulatory authorities by providing the means of ensuring the quality of medicines, particularly multisource (generic) products.

Increased collaboration and coordination at international level of pharmacopoeial bodies and all related parties is needed: (i) for the development and analysis of quality control specifications; (ii) to speed up development of pharmacopoeial specifications; (iii) to address the increasing diversity and complexity of impurity profiles and limits set at international level, especially for pharmaceutical starting materials; and (iv) to promote independent and worldwide validation of analytical methods to ensure the quality of traded and sourced products internationally.

The promotion of good quality pharmaceutical products, and the development of quality control methods - in particular to detect counterfeit drugs - is important for public health. Participants agreed on the need for international harmonization of quality control specifications, and recognized WHO's leadership role in providing normative guidance for quality control and quality assurance of medicines, particularly in the development and international harmonization of pharmacopoeial specifications for new drug entities, including antiretrovirals, anti-tuberculosis and antimalarial medicines.

Recommendations

- Member States should encourage close collaboration between regulatory authorities and pharmacopoeial secretariats/commissions.
- In collaboration with those concerned, WHO should organize an international conference on pharmacopoeial issues to exchange views and experiences among pharmacopoeial bodies and regulators.
- In collaboration with parties concerned, WHO should develop a harmonized approach to providing internationally validated specifications for medicines for neglected and emerging diseases of high public health risk.
- WHO should continue to support the establishment of international chemical reference substances (ICRS) and assist in their supply, particularly for medicines used in the treatment of diseases of high public health impact.

Regulatory assessment of combination products (Workshop 2F)

Combination products for various diseases have always been used in medical practice. Today, HIV/AIDS, tuberculosis and malaria are the major infectious diseases threatening public health and the focus of many national, regional and global initiatives. Combination therapy is considered essential for their treatment as well as for the prevention of drug resistance. Attempts to manage these diseases include the development of fixed dose combinations (FDC) of individual drugs to be administered together in one finished dosage form. Well documented clinical evidence of the efficacy and safety of the loose

combination is a key entry point for development of any FDC drug. Currently, there are no uniform principles, guidelines or international standards addressing the development and regulatory assessment of FDCs. Only a few countries have specific FDC regulatory guidelines available and irrational combinations are still common in several markets.

Recommendations

- In countries where specific guidelines do not exist regulators need to establish clear quality, safety and efficacy requirements for registering fixed dose combination medicines, particularly prescription-only drugs. Regulators should critically review the existing fixed dose combination drugs on the market and withdraw those which do not meet these requirements.
- WHO is urged to create - as a matter of urgency - model guidelines for regulatory approval of prescription-only fixed dose combination drugs with special emphasis on drugs for communicable diseases with high public health impact.

Regulators, good clinical practice and ethics (Workshop 3I)

Application of good clinical practice (GCP) guidelines assures that clinical studies on medicinal products meet scientific and ethical requirements. However, recent advances in medicine may encompass areas of clinical research not covered by existing GCP guidelines and this gap should be filled since all clinical research, including research on gene therapy and biotechnology products, should be conducted under rigorously

implemented GCP. Since data on the safety and efficacy of innovative products may be limited, it is important that national regulatory authorities strengthen mechanisms to share knowledge and experience. Given the increasing tendency to involve vulnerable subjects in research, there is a special need to strengthen the application of ethical principles in research carried out in these populations.

Recommendations

- Member States should implement good clinical practice (GCP) guidelines to assure that clinical studies follow scientific and ethical requirements. All clinical research, not only for medicinal products, needs to be regulated.
- Member States should ensure that informed consent processes, particularly for vulnerable populations and for obtaining biological samples for genetic studies, meet all GCP, national and ethical requirements.
- Member States should recognize that gene therapy is a new complex area of medicine needing rigorously implemented GCP and ethical oversight.
- WHO is requested to gather existing knowledge and experience of safety, efficacy and quality of innovative biotechnology products and share this information with Member States.

- WHO is requested to accelerate its work in regulatory capacity building for assessment of vaccines and medicines of public health importance and to explore options for providing external regulatory expert support for assessment of clinical trial applications in countries with limited resources.

Public health needs vs. the marketplace (Workshop 4J)

Development of new drugs is often driven by market forces. Some medicines for priority disease of public health impact are commercially unattractive, and this is often because they are unaffordable by poor populations. Effective mechanisms compensating for this market failure are needed to bridge the gap. Regulators, together with other stakeholders, can play an important role in supporting initiatives aimed at creating new drugs for diseases where there is no market attractiveness by motivating investment into research and development. However, there is also a regulatory capacity gap to overcome, as regulators from developing countries have limited capacity to advise on drug development or assess the safety, efficacy and quality of new drugs created for diseases exclusively prevalent in those settings.

Recommendations

- WHO is encouraged to continue cooperation with Member States, industry and other stakeholders in order to promote and facilitate development of new treatments for diseases that have little market potential, in particular for diseases prevalent in developing countries (neglected diseases). Mechanisms and incentives should be created for more proactive involvement of national regulatory authorities in all stages of research and development of these products.
- WHO should continue facilitating regulatory capacity building and networking among regulators of different countries in order to empower regulators in countries with limited resources to take informed and evidence-based decisions.
- WHO should explore the potential of creating distance learning courses for regulators.

Safety of herbal medicines (Workshop 5a)

The use of herbal medicines is increasing rapidly worldwide. Although the reasons for this may vary in different settings, the safety of herbal medicines is a common global concern. Both public and national health authorities are committed to making progress in ensuring the safe use of herbal medicines. This is a very complicated and complex issue because of differing regulatory requirements, availability and suitability of technical methods for quality control, post-marketing quality surveillance, and safety monitoring, the presence or absence of qualified practitioners and consumer education. Major issues concerning the safe use of herbal medicines are set out below.

Recommendations

- The safe use of herbal medicines requires adequate regulation. Member States should continue to adapt their national and/or regional regulatory framework, including pharmacovigilance, to the specific requirements of herbal medicines. WHO should continue to provide support including guidance and training programmes.
- Quality assurance and quality control of herbal medicines presents specific challenges. WHO should continue to provide technical guidelines, particularly for the quality control of combination products and criteria for reference substances and materials.
- Awareness amongst consumers on the benefits and limitations of herbal medicines needs to be strengthened. Member States should consider preparing a policy on consumer information and guidelines on the advertising of herbal medicines. WHO should provide general guidance to support these activities.
- Providers of traditional/complementary health care play an important role in the safe use of herbal medicines. Member States should explore appropriate mechanisms to

ensure adequate training and education of these health care providers. WHO should provide policy and technical guidance.

- Regulatory agencies should work together to make the best use of scientific resources related to herbal medicines. Sharing national experience and information is crucial. WHO should facilitate these activities e.g. by providing updated monographs on medicinal plants and technical/regulatory guidance.

Assuring quality and safety of blood products (Workshop 6B)

Blood and blood products are essential for the treatment of a number of life-threatening conditions. However, because blood may transmit infectious agents this can also cause severe harm to the recipients. During the Ninth and Tenth ICDRAs, emphasis was therefore given to procedures aimed at inactivating and removing infectious agents. In order to avoid transmission of infectious agents in a reliable manner, good manufacturing practice (GMP) has to be implemented as an essential tool of quality assurance. In addition, adherence to GMP at all levels of the process, from donor to recipient, is a prerequisite for consistent quality in the preparation of blood and blood products.

Recommendations

- WHO's policy to give high priority to the implementation of GMP in blood and plasma collection establishments is welcomed. Educational programmes and training

opportunities should be continued and strengthened. Guidance documents should be developed and/or updated.

- In order to facilitate the enforcement of GMP in both blood/plasma collection and fractionation facilities, WHO should promote “joint inspections” between several countries under the guidance of experienced inspectors.
- WHO should promote co-operation between regulatory authorities with regard to GMP compliance aimed at “mutual agreements” among Member States.
- WHO should contribute to advancing the technical expertise of regulatory authorities by enabling the creation of regional networks to facilitate their regulatory role in the area of blood and blood products.
- WHO should facilitate the formation of a global network of regulatory authorities for blood and blood products.

Human tissue: problems and challenges for regulators (Workshop 7C)

The transplantation of human cells, tissues and organs has become the treatment of choice for a wide range of both fatal and non-fatal diseases. The volume and complexity of activities relating to transplantation is growing rapidly. The ethical and safety risks of transplantation require effective regulatory oversight at national level, and international cooperation.

- Given the rapid global increase in the allogenic transplantation of cells, tissues and organs, and the associated ethical and safety risks this entails, Member States should develop and implement effective national regulation of procurement, processing and transplantation of human cells, tissues and organs.
- To facilitate this process, WHO is requested to develop clear guidelines for the quality, safety and efficacy of human cell, tissue and organ transplantation.
- To complement the regulation of human cell, tissue and organ transplantation, Member States should develop and implement effective surveillance after cell, tissue and organ transplantation.
- WHO should facilitate these surveillance activities by development of appropriate written standards and reference materials

Regulatory tools for providing drug information (Workshop 8D)

Accurate drug information is essential for the rational use of medicines. Assessment of safety, efficacy and quality of products includes also assessment of product information provided by the applicant of the marketing authorization. Although national regulatory authorities have the responsibility of validating the correctness and appropriateness of the product information, resource constraints may limit the capacity of small regulatory authorities to be able to verify the quality of information provided by the manufacturers.

- National regulatory authorities should establish and implement requirements for product information in line with the information provided in the summary of product characteristics (SPC) as part of their national drug registration process.
- At national level, product information should be harmonized for all products having the same active ingredient.
- WHO should develop guidance and new tools to control promotion and drug information.
- National regulatory authority-approved information should be the reference for providing independent information and the benchmark for controlling promotion. Approved information should be made available on the regulatory agency website.

Harmonization updates (Workshop 9G)

Harmonization of technical requirements for the registration of medicines can contribute to public health by improving access to safe, effective and good quality medicines. It can also facilitate development of a fair and transparent regulatory process, improve international collaboration, reduce duplication of work by different regulatory agencies and facilitate trade and competition. Harmonization initiatives are ongoing in all WHO regions. The major focus of many of those initiatives is to first harmonize basic regulatory requirements for generic drugs. In contrast, the International Conference of

Harmonization (ICH), an initiative set up between the European Union, Japan and USA, has been focusing on requirements to evaluate the quality, safety and efficacy of new innovative drugs, thus avoiding the necessity to duplicate many time-consuming and expensive test procedures. ICH has established a Global Cooperation Group for non-ICH harmonization initiatives to learn from ICH experience.

Recommendations

- WHO should continue to support regional and sub-regional harmonization initiatives that contribute to public health priorities. WHO should facilitate information exchange between different harmonization initiatives and report on progress made in these initiatives through its website.
- Regional harmonization initiatives should have clear public health priorities according to local needs, clear milestones to measure progress, and appropriate resources to make progress possible. Member states are encouraged to facilitate harmonization which will increase availability and accessibility of medicines.
- The ICH Global Cooperation Group should continue to serve as a forum of discussion and dialogue between ICH and non-ICH harmonization initiatives recognizing different regional needs, priorities and capacity.

Promoting good regulatory practices (Workshop 10H)

To meet the objectives of promoting and protecting public health, national regulatory authorities need to carry out their functions effectively and efficiently within a set of principles based on transparency and good governance. The issues that are necessary to promote good regulatory practices nationally and internationally include sustainability of resources, optimal structure, effective cooperation within the agency and with other agencies, transparency and accountability, competence in evaluating efficacy, safety, and quality, timeliness, independence, collaboration as a service provider, sharing information, harmonization, and mutual recognition. In many cases, regulatory authorities do not have sufficient resources to carry out these activities. Most importantly, regulatory agencies must be accountable and decision-making processes must be transparent but this needs to be balanced against the need for protecting the confidentiality of the data that has been submitted by the manufacturer. Sources of information and the decision process should be made publicly available whenever possible.

Good regulatory practices thus cover an evolutionary process, with good practices built into the systems which continuously reinforce collaboration and trust. Regulatory authorities should establish mechanisms to ensure the quality of the procedures they operate to.

Recommendations

- WHO should develop the tools and guidelines needed to help national regulatory authorities effectively implement the principles of good regulatory practices.
- Member States should encourage interagency cooperation for effective implementation of drug regulation involving national regulatory authorities, customs, judiciary, police, civil society and other relevant bodies set up to protect public health.
- National regulatory authorities should formulate a clear mission statement to reinforce effective and efficient drug regulation and customer satisfaction and make use of benchmarking to improve their performance.
- National regulatory authorities should nurture good regulatory governance (integrity, transparency, accountability, public service ethics) to establish credibility and gain confidence. The political governance responsible for national regulatory authorities should promote teamwork, overcome bureaucracy and streamline work.
- WHO should promote and provide technical assistance for the evaluation of regulatory capacity of national regulatory authorities in order to analyse the situation and to undertake necessary corrective measures.

Regulatory aspects of supply of quality medicines (Workshop 11K)

Access to quality medicines contributes to improving human health and promoting well-being. Rigorous implementation of good manufacturing practices in the production of medicines will ensure that only safe, quality products are allowed on the market.

The importance of quality has been repeatedly underlined by the occurrence in various countries of counterfeit and substandard drugs. Evidence shows an increase in production, distribution and sale worldwide of counterfeit, spurious and substandard medicines which do not comply with any quality standards. Such products are a waste of money for the people who buy them, prolong treatment periods, exacerbate the conditions being treated, increase the emergence of drug resistance and can even cause death.

Special efforts have been undertaken to raise awareness of the importance of regulatory measures covering trade in products and starting materials, including active pharmaceutical ingredients and excipients, and implementation of good manufacturing practices.

Recommendations

- Countries are encouraged to implement the new WHO good trade and distribution practices, intended to improve safety in the trade of starting materials for pharmaceutical use.

- Member States are encouraged to implement a pilot phase of the new WHO certification scheme for pharmaceutical starting materials which will give additional information on the quality assurance system used in the production of starting materials.
- WHO should continue the Pre-qualification Project of medicines for priority disease programmes, particularly HIV, malaria and tuberculosis.
- WHO should foster collaboration between manufacturers and regulators in the implementation of GMP and provide training.
- WHO should continue to develop international guidelines for registration of multisource (generic) products.

Implications of regulatory decisions for pharmacoeconomics (Workshop 12L)

The mandate of regulatory agencies is to promote and protect public health by ensuring that all medicines entering the market meet quality criteria, are safe and effective. The particular expertise of national regulatory authorities may make a valuable contribution to decisions on the cost effectiveness and rational use of medicines with regard to pharmacoeconomics and pricing. In countries with limited resources it is difficult to avoid direct involvement of national regulatory authorities in pharmacoeconomics due to their unique knowledge base.

Recommendations

- Where national regulatory agencies do not have pricing responsibilities, they should ensure that all information about safety and efficacy needed to conduct economic evaluation is made available to public bodies charged with reimbursement or pricing responsibilities.
- WHO should further support national regulatory authorities in introducing, wherever needed, elements which will contribute to pharmacoeconomic evaluation.
- WHO should carry out an analysis on the affordability of medicines, particularly in developing countries experiencing such problems. WHO should collect and make available to Member States information on various pricing options and mechanisms, examples of impact of inadvertent marketing strategies to medicines expenditure and potential public health implications of implementation of the TRIPS agreement.
- WHO should support pharmacoeconomic studies based on scientific methodology in countries and regions. Countries undertaking pharmacoeconomic studies are encouraged to present outcomes during the next ICDRA.
- Member States should study the potential of using objective measurement units such as defined daily doses (DDD) for monitoring drug utilization and using these data for

developing rational national policies for pricing and increased access to essential medicines.

Current topics (Plenary 5)

The current topics session provides an opportunity to all regulators at the ICDRA to express their views on the newly-emerging topics which have not been reflected in the conference programme. Often, the topics raised in this session lead to substantial discussion during subsequent ICDRAs.

Recommendations

- The full flexibility of the TRIPS agreement to improve access to medicines should be explored by countries. Countries should not voluntarily exceed TRIPS obligations which could limit flexibility and utility in protection of national public health interests.
- Member States should consider the potential impact of usage patents on access and affordability of medicines.
- Countries should adopt the *WHO Guidelines on Developing Measures for Combating Counterfeit Drugs*, raise public and political awareness of the problem of counterfeiting, increase national and international cooperation, data exchange

between all stakeholders, including national regulatory authorities, interested nongovernmental organizations, law enforcement agencies, industries, and relevant international organizations.

- WHO, in collaboration with other stakeholders, should develop a draft concept paper for an international convention on counterfeit drugs. WHO should convene a meeting of national regulatory authorities to discuss further the concept paper and related issues before the next ICDRA.
- The comparator product for a multisource (generic) medicine should be the first product registered in the market with a complete data file available. In case the originator is not available on the market and there is no multisource (generic) market leader, then other appropriate solutions should be considered on case by case basis.
- Doping in sports is a serious health problem and is within the remit of drug regulation. National regulatory authorities should remain vigilant and provide the necessary resources to combat such practices.