Strengthening the Regulation of Medical Products through Networking, Cooperation & Harmonization

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Current challenges in low- and middle-income countries

- In many low- and middle-income countries essential medicines are not always readily available and accessible;
- WHO estimate is that one third of the world’s population have no access to essential medicines (and more than half in some areas);
- One of the reasons of limited access is the insufficient regulatory capacity and lack of harmonized technical requirements for medicines regulation;
- Poor uptake of new and existing health solutions costs millions of lives across low-income countries;
- Lack of essential medicines contributes to disparities in health and life-expectancy between low-income and high-income countries.
Gaps in regulatory capacity

- Huge gaps between regulatory capacity in different countries in terms of:
  - Human and financial resources
  - Regulatory functions effectively performed;
  - Expertise available for fulfilling regulatory functions;
  - Availability of proper systematic training for regulators;
  - Applying quality management principles;

194 WHO Member States:

- Developed
- Variable
- Limited

≈30% of NMRAs globally have limited capacity to perform all core regulatory functions
Some summary observations:

- Guidelines and assessment procedures are not up to international standards and are often of an administrative rather than technical nature;
- Inadequate resources severely limit technical assessment of dossiers;
- In spite of resource constraints only few countries rely/refer on decisions made by other regulators (such as stringent NMRAs or by the WHO Prequalification Programme), or by other competent authorities.
Evolution of regulatory science

- Differences in general good governance principles and their application
- Differences in setup of regulatory systems on macro and micro levels remain substantial
- No clear vision or policy about HOW to set up regulatory systems in times when it is unrealistic to manage all functions in one national setting for most regulators – globalization of regulatory science
- Insufficient knowledge on what exact competencies are needed for regulators, nor any harmonized core curricula for training
Changing paradigm and realities (1)

- New products likely more complex and sophisticated demanding advanced health systems and "quality use"
  - Health systems and health providers are varying between countries
  - Are all new products equally fit for all types of health systems and health providers available?
  - Does benefit/risk assessment to take into consideration health systems in which product is to be launched?
Changing paradigm and realities (2)

• **Industry wants to be regulated**
  – To create more predictable environment for assessing quality, safety and efficacy of innovative products

• **Industry wants regulators also to be "regulated"**
  – How to create more predictable decision making about things that cannot be easily "metered"/"measured"/"quantified"?
  – Better structured quality decision making processes to lead to more predictable decisions.

Good Regulatory Practices Guideline will be an important addition
What is WHO doing that can facilitate good decision making process?

- Promoting good governance and transparency in medical products sector – **GRP process**
- Promoting and facilitating building up national regulatory systems as part of overall health systems strengthening
- Promoting functional/adequate national regulatory systems as important contributor to achieving universal health coverage and able to address public health priorities
- Supporting regulatory workforce development – Global Regulatory Curriculum
- **Promoting regulatory cooperation, convergence and harmonization**
How to reduce the time to in-country availability of essential medicines?

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Collaboration approaches

• How do NMRAs harmonize/collaborate?
  – May be between geographical neighbours but not necessarily
  – Bilaterally
    • Geographical neighbour: E.g. Malaysia-Singapore
    • Non-neighbours: E.g. Canada-Australia
  – Multilaterally
    • Regional: PAHO, ASEAN, Africa RECs
    • International: ICH, IPRF, IMDRF, IGDRP, ACSS Consortium
Views on regulatory cooperation

Convergence & harmonization

- Recognition
- Reliance
- Work-sharing
- Information-sharing

Based on treaties; "maximal benefit" but partial loss of sovereignty with regard to decision-making

Benefit for regulators; sharing of workload, but independent decisions

«Foundation», Equivalence of requirements

HIS/EMP Communications Planning
Reliance and Recognition

- Both reflect ‘taking account of” the output of other agencies
- Increasing prevalence/necessity, even with most mature/resourced agencies
- Prerequisite: regulatory system and functions that can then be the object of reliance or recognition
- Both may be unilateral or mutual
- Desirable to establish guiding principles for each
- Recognition usually requires specific regulatory authority
- Reliance usually operates within existing regulatory framework
- **NB: sovereignty maintained in both cases**

Reduction: streamline/reduce internal work
Replacement: operationally, rely on decisions
Convergence and Harmonization

**Regulatory convergence:**
- a voluntary process
- regulatory requirements become more similar or “aligned” over time
- gradual adoption of internationally recognized technical guidelines, standards and scientific principles
- common or similar practices and procedures

**Regulatory harmonization:**
- process by which technical guidelines are developed in order to be uniform across participating authorities in multiple countries
- Could also be harmonization at the legislative level (Eg. African Union Model Law Framework)

Legal framework should not impede convergence/harmonization at the technical (guidelines) level
Areas of convergence and harmonization

- Legislation & regulations – harmonization, where possible
- Clinical trials –
  - harmonization of requirements for applications to conduct CTs
  - recognition of GCP audits
  - CT registries
- Medical product registration –
  - harmonization of technical guidelines & registration requirements
  - reliance of GMP audits & dossier assessments
  - work-sharing of dossier assessments
- Post-market surveillance activities –
  - information-/work-sharing of ADR/safety assessments
  - work-sharing/reliance on product testing results
  - information-sharing on counterfeit medical products, product defects and GMP non-compliance of manufacturers
Sovereignty in regulatory cooperation

• Engaging in regulatory cooperation doesn't mean a loss of national sovereignty / autonomy

• Use of collaborative and cooperative mechanisms, (e.g., joint assessments of marketing applications or sharing of inspection reports)
  – does not necessitate collaborative decision-making
  – joint decision-making where possible, but requires the legislative basis (E.g. EU)

• In all cases the regulatory decision itself remains firmly in the hands of sovereign nations;
Why WHO supports convergence and harmonization

- Potential for savings/greater reach via generic equivalents and increased competition
- Healthcare resources can be better managed
- Improved public health outcomes

NMRAs

- Greater process transparency
- Reduced regulatory burden
- Shorter time to approval
- Greater incentive to prioritize dossier submissions
- Improved access to regional markets

Manufacturers (Local and International)

Donor Community

- Increased capacity
- More timely & cost effective evaluation processes
- Greater regulatory network, sharing of best practices & experiences
- More effective medicines control

National Government

Patients / consumers

- Quicker access to more affordable medical products of assured quality, especially for priority medicines
- Improved assurance that available medical products are safe

Higher patient reach for a given level of support
WHO's holistic approach to support regulators worldwide

• Developing evidence, maintaining knowledge and understanding of situation and needs of regulatory systems worldwide. This is done by:
  – proactively seeking information on national level, including assessing national regulatory systems upon request from Member States;
  – internationally, by participation and contribution in regional and sub-regional regulatory networks and initiatives:
    
    | ICH | AVAREF | DCVRN |
    | IPRF | ASEAN PPWG | AMRH |
    | APEC RHSC |
Regulatory convergence and harmonization in medicines registration

- Overall aim: Improve public health by increasing rapid access to safe and effective medicines of good quality for the treatment of priority diseases;
- A focus on medicines registration (MA function) as one factor in the time it takes for beneficial therapies to reach patients in need.
East African Community MRH example of collaborative process

Objective of EAC MRH:

• To harmonize medicines regulation in the EAC Partner States in order to increase the rapid availability of essential medicines in the region

Progress so far:

• All important harmonized technical guidelines and requirements developed and endorsed by EAC Ministers of Health in April 2014.
WHO-EAC joint assessment – innovative approach to accelerated approval

- **Joint activities** - one of the objectives of the EAC MRH Project
  - Three successful WHO- EAC joint assessments have been concluded
  - First pilot in 2010-2011: **2 products**
    - PQ by WHO, MA by Uganda, Tanzania, Kenya;
  - Second joint assessment in 2013-2014: **5 products**
    - PQ by WHO, MA by Uganda, Tanzania (including Zanzibar), Kenya, Rwanda and Burundi
  - Joint EAC-MRH / Swissmedic / WHO Clinical Review of two biotherapeutic products (*Avastin 100 mg and 400 mg and Herceptin 150 mg and 440 mg*), Entebbe, Uganda, 19 – 23 October 2015
    - resulted in the recommendation of **2 products** for licensing in the EAC.
Was this "exercise" useful?  
Potential expectations for the future?

- Reduced the registration timelines;
- Facilitated capacity building;
- Helped to learn how "to listen and to speak to each others";
- Trust building – among EAC regulatory experts;
- Expensive by itself but with a huge potential for future savings;
- Can be considered as one of the possible models for application in low- and middle-income countries/groupings.
WHO Project: Supporting implementation of ASEAN harmonized requirements for drug registration (SIAHR)

- Brunei;
- Cambodia;
- Indonesia;
- Lao PDR;
- Malaysia;
- Myanmar;
- Philippines;
- Singapore;
- Thailand;
- Vietnam;
Objectives of the ASEAN project

• To analyse country specific requirements and identified gaps in the implementation of ACTD & ACTR by individual AMS based on the ASEAN technical guidelines related to technical aspects of product registration

• To identify AMS strengthening needs and propose corrective measures to ensure homogeneous interpretation and implementation of the relevant guidelines

• To report the results to relevant decision-making bodies
Two kinds of findings

- Specific technical and administrative issues related to the implementation or interpretation of harmonized requirements
- Substantial issues related to insufficient communication and cooperation among NRAs with regard to the assessment of applications for marketing authorization
Specific technical and administrative issues related to implementation/interpretation

- CPP
- MaV and MiV guidelines
- GMP in PIC/S-approved sites
- Legalization of documents
- Information on excipient suppliers
- Pre-approval samples
- Regulatory status in other countries

Acceptance of either ACTD or ICH/CTD
Updates on safety information
Implementation of stability guidelines
Stability of <25°C storage condition
Rationale for CoA for APIs
Assessment duration and work load

Results are frustration for applicants and regulators
Issues related to insufficient communication and cooperation in assessment of applications

- Country visits revealed that **no cooperation or exchange of information** takes place among NRAs in relation to the assessment work.
- The existence of common formats and guidelines benefits applicants but provide no advantage for NRAs.
- Increased collaboration in the assessment of applications would provide:
  - Opportunities for learning from each other
  - Stronger basis for decisions
  - Enhanced self-confidence
  - Stronger mutual understanding and trust
  - Increased capacity to filter out low quality products
Proposals for possible action to address issues identified

Build on SIAHR project’s experience to:

• Design and implement specific activities to address the technical and administrative issues identified

• Identify priority product categories to start a pilot project of joint assessments of application dossiers to improve cooperation, strengthen technical capacity, develop mutual understanding and trust, but leaving final decision on approval to established national mechanisms
True harmonization is NOT just development of common documentation

• Appropriate legislative and regulatory requirements:
  • Legal framework to define the basis and conditions for collaboration and work sharing/acceptance of information and decisions;
  • Regulatory framework defining the practical arrangements;
  • Technical framework: applicable guidelines

• Application of these provisions:
  • Operational procedures for implementation;

• Appropriate interpretation of the requirements:
  • Competence of the personnel;
  • Capacity development, training, etc.
Success factors for convergence and harmonization initiatives (1)

• Well elaborated and clearly understood vision, mission, roles and responsibilities
• Political will and continuous support
• Effective management and administration through the secretariat and/or steering committee
• Active participation of all potential stakeholders (NMRAs, industry, development partners)
• Ownership by the NMRAs
Success factors for convergence and harmonization initiatives (2)

• To be based on the modern science and reaching the consensus
• Engagement by all parties to implement the documents developed and to follow them
• Well defined decision trees and procedures
• Adequate human and financial resources
• Transparency, effective communication and RESPONSIBILITY
Conclusions

• Regulatory capacity building, promotion of collaboration, convergence and harmonization will continue to be one of the WHO priorities;
• There is no good regulation without Good Governance (accountability, transparency, fair and equal treatment of all regulated parties etc.);
• Making medicines is no longer a "local" business and the era of locally operating regulators is coming to an end;
• The future of medicines regulation is in convergence/harmonization, collaboration and networking; regulators starting to function more as a functional network rather than individual players, and individual players focusing on where they can give the best added value;
• Harmonization means nothing if the established common guidelines are not implemented.