Regulatory harmonization initiatives: update

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In a broad sense harmonization means harmonization of technical requirements for medicines regulation, i.e., legislations, guidelines, procedures, etc.

- These requirements relate to the quality, safety and efficacy of the medicinal products;

- These requirements differ in complexity, from one type of marketing authorization application to another.
What we do mean under Harmonization?

- True harmonization goes further than just development of common documentation;

- It requires effective *communication* and *collaboration* aimed at *building capacity and trust* (e.g., information sharing, recognition and joint working);

- In combination, these activities can lead to similar or collaborative approaches to drug registration;

- Paving the way for *mutual recognition* and/or *centralized registration* (if desired) in the longer-term future.
What we do not mean under Harmonization?

Harmonization **doesn't** mean a loss of national sovereignty / autonomy (and certainly not in the early stages)

- **Common documentation** stipulates the requirements for registration;
- **Better communication enables countries** to choose which information they will use;
- **Collaborative mechanisms**, such as joint assessments or inspections, **does not imply collaborative decision-making**!

In all cases the registration decision itself stays firmly in the hands of sovereign nations
How it started?

- The five European Nordic Countries (Denmark, Norway, Sweden, Finland and Iceland) formed **The Nordic Council on Medicines** (NLN) in 1975. It was a great success of cooperation and supported the development of modern medicines regulations in these countries and beyond…

  - The Nordic Council was closed down in 2002, since all countries started participating in the EU procedures coordinated by the European Medicines Agency in London.

- In **the European Community** harmonization of regulatory requirements started in the 1980s, when the EC (now the European Union) moved towards the development of a single market for pharmaceuticals.
Internationalization

- At the same time in the 1980s bilateral discussions between Europe, Japan and the US on possibilities for harmonization started.

- At the WHO International Conference of Drug Regulatory Authorities (ICDRA), in Paris, in 1989, specific plans for action began to materialize. Soon afterwards, the authorities of Europe, Japan and US approached IFPMA to discuss a joint regulatory-industry initiative on international harmonization.

- The birth of what is known today as ICH took place at a meeting in April 1990, hosted by the EFPIA in Brussels.
ICH Background

- Unique harmonization project involving the regulators and research-based industries of US, EU and Japan
  - WHO, Canada, and EFTA are observers

- Well-defined objectives:
  - to improve efficiency of new drug development and registration process
  - To promote public health, prevent duplication of clinical trials in humans and minimise the use of animal testing without compromising safety and effectiveness

- Accomplished through the development and implementation of harmonised guidelines and standards
Existing harmonization initiatives (1)

International initiatives:

- The International Conference on Harmonization (ICH)

- International Conference of Drug Regulatory Authorities (ICDRA), biennially convened by the WHO since 1980.
Existing harmonization initiatives (2)

Regional initiatives of regulators actively involved in harmonization include (but are not limited to):

- Andean Community;
- APEC
  - Asia-Pacific Economic Cooperation (21 member economies)
- ASEAN
  - Association of the Southeast Asian Nations (10 economies)
- GCC
  - Gulf Cooperation Council (6 Gulf states)
Regional initiatives of regulators actively involved in harmonization include (but are not limited to):

- Mercosur
- PANDRH
  - Pan American Network for Drug Regulatory Harmonization
- SADC
  - Southern African Development Community (14 countries)
- EAC
  - East African Community (5 countries)
Harmonization creates a common language for regulators

- Harmonization of technical requirements creates a "common language" for regulators
- To speak the language fluently constant training is needed
- Only based on "common language" effective communication and collaboration can be built
- Only based on effective communication and collaboration mutual trust and avoiding duplication can be achieved
Lessons learnt from various regulatory harmonization initiatives: strengths

- **Political support** for clear long term objectives and incentives for achieving them (creating common market, faster market access etc.)
- **Strong commitment** from major concerned stakeholders (regulators and regulated parties) for producing results
- **Effective governance** structure with authority supported by
- Well resourced **effective secretariat**
- **Clear "business model"** – processes and procedures clearly defined and followed, including for **updates** and **implementation**
- **Adequate human and financial resources** made available
- **Transparency and effective communication** to and with affected stakeholders (patients, medical community and academia, special interest groups etc.)
Lessons learnt from various regulatory harmonization initiatives: weaknesses

- Lack of continuous political support
- Badly defined objectives with no "reality check" for implementation
- No clear incentives for concerned stakeholders to move the agenda
- No effective governance with authority
- Weak or badly functioning secretariat
- No clear or inadequate "business model", no mechanisms to ensure timely updates and final implementation
- Relative lack of human and financial resources
- Lack of transparency and poor communication
What WHO is doing to support regulators

- Developing evidence - assessments of regulatory systems worldwide (more than 50 NMRAs assessed in all 6 regions);
- Providing direct technical support (capacity building, tools and guidance) to regions and countries;
- Stimulating / initiating collaboration between regulators from various countries on various regulatory activities;
- Promoting and facilitating communication among national/regional regulatory systems using ICDRA, specific network meetings (e.g. WHO Annual Pharmacovigilance Centres meetings, and International Regulatory Cooperation for Herbal Medicines (IRCH));
- Promoting regulatory collaboration and harmonization.
Where we are with medicines regulatory systems today?

Some summary observations:

- Guidelines and assessment procedures are not up to international standards and are often of an administrative rather than technical nature;
- Wide-ranging exemption clauses exist which are not justified by a risk assessment, for example for public sector imports or donations;
- Inadequate resources severely limited technical assessment of dossiers;
- In spite of resource constraints only few countries relied on decisions made by other regulators (such as stringent NMRAs or by the WHO Prequalification Programme);
- Regulatory decisions by other competent authorities were not widely considered.
26 country study in Africa - post-marketing surveillance and market control

FIGURE 9: MARKET CONTROL MECHANISMS

- Quality monitoring
- Anti-counterfeiting programme
- Recall procedure
- Pharmacovigilance
- Control of promotion

Legend:
- Yes
- Exists, inadequate
- No
- No information
26 country study in Africa – registration (marketing authorization)
WHO work with regulators (1)

- Global and regional, *ad hoc* and planned - Experts from regulatory authorities for various WHO activities – taking place almost daily

- Regular, Global:
  
  - Discussions and planning through Governing Bodies – World Health Assembly and Executive Board
    - Recent Intergovernmental WG on Substandard, Spurious, Falsely labelled, Falsified, Counterfeit (SFFC) medicines
  - Biennial International Conferences of Drug Regulatory Authorities (ICDRA) hosted by national regulators

WHO work with regulators (2)

- Regulators networks on Global (HQ) level:
  - Blood Regulators Network
  - Paediatric Regulators Network

- Work with regulators on Regional and country level
  - WHO secretariat for some regional harmonization initiatives (e.g. PANDRH – PAHO/AMRO); all regional offices work with regulators but principles and intensity varies
  - Regions supporting with WHO staff in countries harmonization – e.g. AMRHI in AFRO
  - WHO collaborating centres for specific tasks (e.g. WHO CC for Biological Standardization in CBER/US FDA)

- More structured collaboration – a dream?
  - Various *ad hoc* and joint projects with a variety of partners
  - Confidentiality arrangements for certain areas of work on HQ level
Role of WHO in regulatory capacity building in Africa

WHO has contributed more than any other organization in building regulatory capacity in the continent with numerous activities and will continue to do so:

- Assessment of national MRAs
- Higher level general advise and help in policy setting
- General and highly technical training courses
- Involvement of regulators in real assessments and inspection (medicines prequalification programme)
- Assisting national quality control laboratories
- Assisting in setting up pharmacovigilance systems
- Facilitating information sharing
- Creating regulators networks
- ...
Sharing regulatory information is a key to faster access to medicines

- WHO is working with regulators and other partners to find out how best to build confidence in regulatory decisions taken by other regulators, including:
  - how to facilitate exchange of consolidated information about assessments and inspections
  - without challenging their sovereignty.

- Establishment of African Medicines Regulatory Harmonization Initiative
Regulatory harmonization in Africa

- Africa – a continent of huge diversity and complex unity, with numerous Regional Economic Communities (REC);

- ... overlaps and politically complicated environment.
African Medicines Registration Harmonization Initiative (AMRHI)

- Process started with the informal consultations in ICDRA Meeting, September 2008, Bern, Switzerland;
- In response to the growing recognition of the potential benefits of harmonizing medicines registration in Africa, a WHO concept paper was developed to describe a proposed approach to supporting drug registration harmonization within and across African regional groupings.

WHO Drug Information, Volume 22, Number 3, 2008
African Medicines Registration Harmonization Initiative (AMRHI)

- Further discussions and orientation in the meeting in Johannesburg, South Africa, 24-26 February 2009, organized jointly by BMGF, NEPAD, William J. Clinton Foundation and the WHO.

The purpose of the meeting was:

- to explore the possibilities of supporting medicine registration harmonization, as an initial first step to broader regulatory harmonization within African Regional Economic Communities (RECs) and organizations, and

- to initiate a strategic approach to develop project proposals for mobilizing the necessary financial and technical resources to support RECs undertaking medicine registration harmonization.
African Medicines Registration Harmonization Initiative (AMRHI)

- Donor partners, NEPAD and WHO confirmed their interest in supporting the RECs, including necessary actions to support national implementation, strengthen national regulatory agencies and promote inter-REC and continental exchange of information, coordination and technical consistency.

- Their strategic approach was *to invite summary project proposals from committed RECs* and seek financial and technical support for the most sound and promising proposals among them.
Consortium of key partners established to accelerate and ensure regulatory harmonization in Africa

Consortium Partners

Other Stakeholders

Regional Economic Communities and Organizations (RECs)

Unanimous consensus emerged: now is the right time to push for regulatory harmonization in Africa
Also enlisting support from likely in-kind donors

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<th>Stakeholders likely to provide support</th>
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<tr>
<td>Bill &amp; Melinda Gates Foundation</td>
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<td>Norway</td>
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<td>Canada</td>
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<th>Other stakeholders interested in AMRH</th>
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<tr>
<td>United Nations Population Fund (UNFPA)</td>
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<td>UNITAID</td>
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<td>USAID</td>
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<td>Switzerland</td>
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<th>Monetary contributions</th>
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<td>PHARMA</td>
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<td>IPA</td>
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<td>UPMA</td>
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<th>In-kind contributions</th>
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<td>World Health Organization</td>
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<td>Clinton Health Access Initiative</td>
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<td>SAGMA</td>
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<td>WAPMA</td>
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<td>Australian Government Department of Health and Agering</td>
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<td>Therapeutic Goods Administration</td>
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In addition RECs and member countries will be contributing to harmonization plans.
African Medicines Registration Harmonization Initiative (AMRHI)

steps in the implementation of the project:

- **By 31st May 2009** RECs were invited to submit to WHO and NEPAD a summary project proposal in support of regional medicine registration harmonization. A draft format and a suggested scope and outline are available. NEPAD and WHO are willing to give limited technical support to the development of such regional proposals.

- **April - May 2009**: Submission of summary project proposals;

- **June 2009**: Review of proposals and feedback to RECs;

- **July - October 2009**: Selected RECs to submit their full project proposals to NEPAD & WHO;

- **November-December 2009**: Review of full project proposals by Project consortium and submission to interested Donors;

- **January - June 2010**: World Bank joined the process as a Multi-Donor Trust Fund Holder

- **Early 2011**: The process started in East African Community
Regional Example: Eastern African Community (EAC): Medicine Registration Harmonization project launched on 30 March 2012

EAST AFRICAN COMMUNITY
Press Release

Launch of the East African Community Medicines Registration Harmonization Project
Assuring Access to Quality, Effective and Safe Medicines in the Region

Arusha, 30th March 2012

Today 30th March 2012, The East African Community Officially Launches the Medicines Registration Harmonization (EAC - MRH) Project. This Project seeks to promote the African Medicines Regulatory Harmonization (AMRH) Programme across the globe as a key contributor to public health; through ensuring rapid access to good quality, safe and effective medicines for priority health diseases. The EAC – MRH project is supported by the
Progress in EAC

- Four technical Working groups are up and running:
  - TWG on Medicines Evaluation and Registration;
  - TWG on Good Manufacturing Practices (GMP);
  - The TWG on Information management systems (IMS)
  - The TWG on Quality Management System (QMS);

- A number of guidelines and guidance documents have been developed and are currently in the process of discussion for adoption
Roughly 85% of Sub-Saharan Africa covered by proposals already completed or in process

### REC progress

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<th>Completed or in-process RECs</th>
<th>Countries covered</th>
<th>Total members*</th>
<th>% pop covered</th>
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<tr>
<td>EAC &amp; OCEAC</td>
<td>12 (20%)</td>
<td>11</td>
<td>17%</td>
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<tr>
<td>EAC, OCEAC, ECOWAS</td>
<td>26 (46%)</td>
<td>26</td>
<td>45%</td>
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<tr>
<td>EAC, OCEAC, ECOWAS, SADC</td>
<td>41 (74%)</td>
<td>41</td>
<td>72%</td>
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*Tanzania in both EAC and SADC (but will go with EAC); UEMOA/ECOWAS are working out overlap

We are pushing forward those RECs that are ready while continuing to work with the remaining regions

Source: BCG analysis
Main roles of partners

WHO
- Provide technical assistance to develop harmonized approaches for registration and GMP inspection, and for development of Quality Management and Information Management systems
- Support capacity building and training

NEPAD
- Advocacy to create positive political climate for regulatory harmonization at continental and regional levels
- Assist RECs in developing project proposals
- Facilitate prompt resolution of implementation bottlenecks at REC and country levels working with partners
Main roles of partners

Regional Economic Communities
- Prepare and implement plans for regulatory harmonization
- Establish regional platforms for information sharing and learning
- Coordinate capacity building activities to bring all NMRAs together.
- Facilitate harmonized policy making

World Bank
- Advocacy for resource mobilization
- Implementation support
- Fiduciary oversight
- Documentation and dissemination of lessons
Challenges for WHO

- The environment in which WHO operates has changed
- Resource base has changed
  - From organizational budget to project based management depending on donors
  - Supporting regulatory activities on HQ level – virtually no WHO budget, only specified funds
- Has still competitive advantages over other organizations/arrangements
  - WHO is highly recognized by developing countries
  - Infrastructure reaching out to all countries through its regional and country offices
  - Has well established mechanisms such as ICDRA forum
Conclusions (1)

- The future is in regulatory harmonization, either first in more focused or in more broad meaning, eventually both.

- Due to sophistication of science, new amount of information and data to be assessed there is no alternative for better and more efficient communication and collaboration.

- The price for the failure of regulators to act will always be paid by the patients …
Conclusions (2)

- WHO has promoted regulatory collaboration and harmonization long time and will continue to do so being open to new ideas and change.
- WHO is still one of the most important parties giving help to less resourced regulators.
- WHO is currently going through reform process.
- This can be both opportunity and challenge.
Thank you!