WHO support for medicines regulatory harmonization in Africa: focus on East African Community

The African Medicines Regulatory Harmonization (AMRH) initiative works with Regional Economic Communities (RECs) to increase access to good quality, safe and effective medicines through harmonizing medicines regulations, and expediting registration of essential medicines.

Encouraging progress has been achieved in the East African Community (EAC), where a harmonized medicines registration system is being set up. Continued advocacy and political support by the New Partnership for Africa’s Development (NEPAD) and technical support by WHO are critical for its continued success.

Medicines regulatory authorities in many countries struggle with administrative and technical bottlenecks in controlling medicines quality in their territories effectively. And as pharmaceutical production and distribution have become globalized, no regulatory authority can work in isolation any longer.

The World Health Organization (WHO) has a long history in providing medicines regulatory support to governments of its Member States. In 2008 at the 13th International Conference of the Drug Regulatory Authorities (ICDRA) – a forum bringing together regulators from around 100 WHO Member States – WHO was requested to support harmonization approaches enabling national medicines regulatory authorities (NMRAs) to use their limited resources more effectively.

The African Medicines Registration Harmonization initiative

In response to the request by its Member States, WHO initiated discussions with global partners. This led to the formation of a consortium consisting of the New Partnership for Africa’s Development (NEPAD), the Pan African Parliament (PAP), the Bill & Melinda Gates Foundation, the UK Department for International Development (DFID), the Clinton Health Access Initiative (CHAI), the Joint United Nations Programme on HIV/AIDS (UNAIDS) and the World Health Organization (WHO). In 2009 NEPAD and PAP organized a conference attended by a wide range of stakeholders, marking the emergence of the African Medicines Registration Harmonization (AMRH) initiative.

The AMRH initiative aims to promote harmonization of medicines regulation in Africa. It is a close partnership among the World Bank, NEPAD and WHO, and most of the activities involve at least two partners. WHO is the lead partner on the development of common technical standards, documents, tools and processes in line with international standards such as those of the International Conference on the Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). WHO also provides technical assistance for capacity-building and organizes joint assessment and inspection activities.

In 2010 the donor consortium decided to establish a trust fund for the AMRH finances, and an administration agreement was signed in 2011 between the World Bank and the Bill & Melinda Gates Foundation. WHO became a sub-grantee to support the implementation of the AMRH initiative.
The role of Regional Economic Communities
African countries are grouped into Regional Economic Communities (RECs), which play a crucial role in a wide range of integration activities in Africa. Accordingly they were chosen as platforms for AMRH projects, seeing that they already had commitments for medicines regulatory harmonization, and their Secretariats have the necessary infrastructure to coordinate the work. The donor consortium therefore invited the African RECs to submit project proposals for regional medicines registration harmonization.

In this preparatory phase, WHO helped to develop and review proposals, assessed regulatory systems, provided training on the Common Technical Document format for medicines registration in Francophone and Anglophone countries throughout Africa, and approached other organizations to provide technical and financial support.

The EAC Medicines Registration Harmonization project
The first REC to secure funding from the trust fund was the East African Community (EAC). WHO became a sub-grantee to support the implementation of the AMRH initiative and signed a memorandum of understanding with the EAC to support the Medicines Registration Harmonization (MRH) project.

The EAC MRH project was formally launched in March 2012 in Arusha, Tanzania, marking the beginning of the implementation phase of the AMRH initiative across Africa. The project aims to achieve a harmonized medicines registration process in its member countries – Uganda, Kenya, the United Republic of Tanzania, Rwanda and Burundi – based on common documents, processes and shared information systems. More specifically, its objectives are to:
• develop and maintain a “common documentation package” defining common technical requirements as a basis for other harmonization activities;
• build evaluator capacity to ensure adherence to agreed standards;
• streamline management systems and processes, with risk-based approaches to use available resources where it matters most;
• develop systems and processes to share regulatory information within and outside EAC countries; and
• conduct joint dossier assessments and manufacturing site inspections as a basis for national registration decisions.

NMRA assessments
Assessments of NMRA is important to identify gaps and take corrective measures. For NMRA entering into a harmonization process, they also provide an objective mechanism to evaluate progress. WHO has developed a data collection tool to assess regulatory systems. This tool was used in all five EAC countries by WHO and by the NMRA as self-assessments or mutual assessments, providing valuable inputs to the methodology and outcomes of a comprehensive situation analysis for the EAC (1).

The assessment tool was subsequently improved and consolidated to cover all relevant product areas including medicines, vaccines and medical devices. It was also adapted to match the structure of the future harmonized EAC documents, and to support implementation of the harmonized processes with built-in quality management systems. WHO will continue to refine the tool. It is planned to develop an electronic version to facilitate data capture and analysis.
Table 1. EAC / WHO prequalification joint dossier assessments

<table>
<thead>
<tr>
<th>Product</th>
<th>Review period</th>
<th>Date prequalified</th>
<th>Date registered</th>
</tr>
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<tbody>
<tr>
<td>Abacavir sulfate tablets</td>
<td>12 March 2010 – 17 July 2010</td>
<td>20 August 2010</td>
<td>Tanzania 4 October 2010</td>
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<td></td>
<td>(3 joint sessions)</td>
<td></td>
<td>Uganda 14 October 2010</td>
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<td></td>
<td></td>
<td></td>
<td>Kenya 31 March 2011</td>
</tr>
<tr>
<td>Amikacin sulfate for injection</td>
<td>12 March 2010 – 20 November 2010</td>
<td>14 January 2011</td>
<td>Uganda 7 June 2011*</td>
</tr>
<tr>
<td></td>
<td>(4 joint sessions)</td>
<td></td>
<td>Tanzania 9 June 2011**</td>
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<td></td>
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<td>Kenya **</td>
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* The products were registered after completion of legally required testing of registration samples.
** Significant delays occurred in submission of registration samples for testing; the applicant did subsequently not pursue national registration.

Joint dossier assessments
Another activity initiated by WHO before the formal launch of the EAC MRH project was the joint assessment of product dossiers that had been submitted to the NMRA of EAC countries for national registration and to WHO for prequalification. The aim was twofold: to accelerate registration of needed products and to build knowledge and experience in assessing dossiers according to unified, stringent standards.

The first joint assessment exercise, organized in 2010, resulted in prompt registration of products (Table 1). The registration times were considerably shorter than the average 18 month timeline for registration of generic products in EAC countries (1).

A second joint assessment exercise started in July 2013 with five products: misoprostol tablets, levonorgestrel tablets and three strengths of artesunate/amodiaquine fixed-dose combination tablets. Four assessment rounds have been completed at the time of writing. A fifth is planned for March 2014, with only a few issues remaining to be addressed by the applicants before the products can be jointly deemed acceptable.

In this second joint exercise, a total of 12 assessors from all six participating NMRA - the five EAC countries and Zanzibar – actively contributed to the assessment work. The contributions from all of the regulators merged in a very natural way and made for a very motivating experience. Importantly, some time was spent in the third and fourth round to clarify what steps the products – once jointly accepted – would have to complete for formal registration in each country, with a view to minimizing the time taken for these steps and working towards common, streamlined processes in the longer term.

Progress towards harmonized registration
With joint assessments and other preparatory activities already under way, the EAC MRH project got off to a good start. Four technical working groups were officially constituted in 2012, and each NMRA took technical lead in the development of regional guidelines, with the support of another NMRA (2). The working groups deal respectively with medicines evaluation and registration based on the Common Technical Document (CTD); good manufacturing practices (GMP); information management systems (IMS); and quality management system (QMS). WHO provides technical support in line with internationally recognized standards and best practice.

Significant progress has been achieved as at the end of 2013:
Draft regulatory tools and guidelines produced by the working groups have been shared as “living documents” through the EAC’s website.

EAC inspectors are participating in joint inspections organized by the WHO Prequalification of Medicines Programme.

WHO and EAC NMRAs share their inspection schedules through a WHO-administered password-protected website.

Based on a WHO assessment of existing regulatory information systems in EAC countries and best practice recommendations, business process analysis is under way to design a harmonized information management system for regulatory functions (Figure 1).

WHO as the technical lead partner has provided input into all the above-mentioned activities. It has also proposed guidelines for developing and validating the EAC regulatory documentation, has set up a regulatory knowledge base containing current, detailed bibliographies that are relevant to the EAC project, and has been issuing a quarterly newsletter for assessors and inspectors since 2011 with information on current regulatory concepts, guidance and standards.

Collaboration with other initiatives

WHO’s long-standing collaboration with global regulatory initiatives such as ICH, the Asia-Pacific Economic Cooperation (APEC) Regulatory Harmonization initiative and the International Regulatory Cooperation for Herbal Medicines (IRCH) has been useful to establish linkages between the AMRH initiative and other regulatory initiatives in different regions. This networking has facilitated the acceptance of the EAC as a member of the ICH Global Cooperation Group, which is a great achievement in its own right.

WHO also supported EAC regulators to participate in ICH meetings, in the 2012 ICDRA conference and in annual WHO technical briefing seminars.
Conclusion
The EAC Medicines Registration Harmonization project has achieved encouraging progress; and assessors and inspectors are working together with outstanding professionalism.

The main challenges, as identified by the project working groups, are twofold. Firstly, each partner state has its own laws and regulations, and the absence of a mutually recognized legal framework slows down many harmonization activities. Secondly, there is a marked difference in capacity among the NMRAs within the EAC region. Although a twinning system has been adopted – pairing each well-developed NMRA with a less advanced one – the harmonization moves at different speeds in the different countries.

Despite these challenges, the project has shown that regulators in EAC countries can implement effective, harmonized processes for review of registration submissions.

The AMRH initiative is soon to be expanded to other regional economic communities in Africa. Continued support by concerned governments and international partners are crucial for its success. Provided that such support will be forthcoming on a sustained basis, the positive experiences made in the EAC region suggest that the AMRH initiative presents good opportunities for reshaping the regulatory landscape in Africa.

References
2 Highlights from the Second Meeting of the Project Steering Committee for the EAC MRH Project, November 1-2 2012, Arusha. Meeting report.