WHO updates on Regulatory System Strengthening and Prequalification activities

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Regulatory Systems Strengthening
Carmen Rodriguez
Vaccines assessment PQT
Essential Medicines and Health Products
The New Regulatory Reality

- National Regulatory Authorities are on the critical path to innovation and access to safe and effective medical products.
- Degree to which NRAs fulfill their mandates in an effective, efficient and transparent manner has a direct impact on innovation, access and public health.
- Increasingly, NRAs must consider more modern and intelligent models of regulation that consider resource constraints, increasingly complex technologies, globalization and public expectations.
Regulatory convergence foundation for regulatory collaboration

• Convergence and harmonization efforts should in theory diminish duplication, creating a "common language" for decision-making and facilitating cooperation, work-sharing and eventually reliance or recognition

• Convergence/harmonization **required but not sufficient:**
  -> set up conditions for enhanced collaboration and new regulatory paradigms
Levels of Cooperation

- **Recognition (mutual or unilateral)**
- **Work-sharing/Reliance: “Good Cooperation Practices”**
- **Harmonization/Convergence**
WHO’s role in promoting access to quality medical products

- WHO has long supported regulators in fulfilling their mandates through:
  - Developing norms and standards
  - Promoting regulatory convergence and harmonization
  - Training and capacity building
  - Supporting information and work sharing initiatives

- Experience to date has helped characterize the benefits, challenges and potential evolution of such initiatives in accelerating in-country regulatory decisions
An Apparent Dilemma

- WHO supports the strengthening of regulatory systems in accordance with numerous WHA resolutions
- WHO also promotes access to essential medical products as one of the key enablers of health and equality
- The challenge: Strengthening the capacity of regulatory authorities to regulate in a manner that is consistent with timely access to priority medicines
Considerations

- Weak regulatory systems do not serve interests of consumers, patients, industry nor the health care system.

- At the same time, as countries develop regulatory capacity it is important that regulatory systems be science based, respect international standards and best practices, and adopt an approach that focuses on what cannot be done by others while leveraging the work of other trusted NRAs and regulatory networks for the rest.
## Global Regulatory Scenarios

<table>
<thead>
<tr>
<th>NRA Maturity Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Well resourced SRA</td>
<td>Robust registration system: ‘Full service” regulator. Serve as a reference for emerging systems.</td>
</tr>
</tbody>
</table>
| Functional- formal system | - Technical registration system in place, however may be challenged to balance responsibilities with resources and expertise.  
  - Should consider collaborative approaches and reliance whenever possible to effectively meet these challenges. |
| Administrative system | Administrative registration system: rely on and adopt decisions of other NRAs. |
| No formal system | No registration system: rely when possible on UN procurement of PQ’ed products, or accept products already approved in SRA countries. |
An Effective Approach to Regulation

- Some elements of regulatory oversight can be shared
  - Evaluation of quality, efficacy and safety

- Other elements of regulatory oversight must be local
  - Licensing decision
  - Local manufacturing oversight
  - Pharmacovigilance
  - Appropriate distribution controls (stability and cold chain)
  - Product security (protection against counterfeiting and adulteration)

- Regulatory framework should also be flexible, providing for expedited or waiving of registration in the case of public health emergencies
Flexibility

- Regulatory oversight must be risk-based to achieve a balance between appropriate controls and timely access to medical products

- Circumstances will arise where accelerated access is warranted
  - Emergencies of Public Health Concern
  - Drug shortages
  - Innovations in treatment of critical illness

- A spectrum of risk-based options could include waivers, accelerated evaluation pathways or provisions to accept expert recommendations
WHO working to accelerate access to quality medicines

Some examples:

- Regulatory system strengthening
- Good Regulatory Practices
- Networks
- Facilitated reviews
WHO NRA Assessment Visits: 1997

The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

Data Source: World Health Organization, Immunization Vaccines and Biologicals (IVB). Updated as of 2 May 2011

Map Production: Public Health Information and Geographic Information Systems (GIS) World Health Organization in collaboration with P&B Consulting

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WHO NRA 5 Step Capacity Building

1. Benchmarking
   Development of NRA assessment tool
   - Revision of indicators & assessment process (Every 2-3 years)
   - Harmonization of tools

2. Assessment of NRA
   - Re-assessment Every 2-7 years
   - Self assessment for planning formal assessment

3. Development of Institutional Development Plan (IDP)
   - With or without a road map for prequalification of products

4. Providing technical support, Training/Learning, networking,
   - WHO support through:
     - Global Learning Opportunities (GLO)
     - Technical Support
     - In-country training

5. Monitoring progress and impact
   - WHO electronic platform to monitor NRAs information and assessment reports, IDP, training, etc.

Minimal capacity met, Vaccine: eligibility for PQ
Regulatory functions depending on vaccine source
(The old functionality model)

<table>
<thead>
<tr>
<th>Regulatory functions</th>
<th>Vaccine source</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>UN agency</td>
</tr>
<tr>
<td>Regulation System</td>
<td>✓</td>
</tr>
<tr>
<td>Licensing</td>
<td>✓</td>
</tr>
<tr>
<td>AEFI monitoring</td>
<td>✓</td>
</tr>
<tr>
<td>Lot Release</td>
<td>Functions assured by NRA of producing country and WHO PQ system</td>
</tr>
<tr>
<td>Access to laboratory inspections</td>
<td>✓</td>
</tr>
<tr>
<td>Authorization of clinical trials</td>
<td>✓</td>
</tr>
</tbody>
</table>

*WHO/EMP/RHT/RSS/Country Regulatory Strengthening (CRS) Group*
**Proposed matrix for correlation between medical products sourcing, maturity levels of different regulatory functions and minimal capacity**

**MINIMAL and/or OPTIMAL CAPACITY**

<table>
<thead>
<tr>
<th>Vaccine producing</th>
<th>Medicine producing</th>
<th>Medicine Non-Producing</th>
<th>Vaccine Self-procuring</th>
<th>Vaccine UN Supplied</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y/N</td>
<td>ML</td>
<td>Y/N</td>
<td>ML</td>
<td>Y/N</td>
</tr>
<tr>
<td><strong>RS</strong></td>
<td>(Y)</td>
<td>3</td>
<td>(Y)</td>
<td>3</td>
</tr>
<tr>
<td><strong>MA</strong></td>
<td>(Y)</td>
<td>3</td>
<td>(Y)</td>
<td>3</td>
</tr>
<tr>
<td><strong>VL</strong></td>
<td>(Y)</td>
<td>3</td>
<td>(Y)</td>
<td>3</td>
</tr>
<tr>
<td><strong>MC</strong></td>
<td>(Y)</td>
<td>3</td>
<td>(Y)</td>
<td>3</td>
</tr>
<tr>
<td><strong>LI</strong></td>
<td>(Y)</td>
<td>3</td>
<td>(Y)</td>
<td>3</td>
</tr>
<tr>
<td><strong>RI</strong></td>
<td>(Y)</td>
<td>3</td>
<td>(Y)</td>
<td>3</td>
</tr>
<tr>
<td><strong>LA</strong></td>
<td>(Y)</td>
<td>3</td>
<td>(Y)</td>
<td>3</td>
</tr>
<tr>
<td><strong>CT</strong></td>
<td>(Y)</td>
<td>3</td>
<td>(Y)</td>
<td>3</td>
</tr>
<tr>
<td><strong>LR</strong></td>
<td>(Y)</td>
<td>3</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

**ML:** Maturity Level  
**RS:** National Regulatory System  
**MA:** Registration and Marketing Authorization  
**VL:** Vigilance  
**MC:** Market Surveillance and Control  
**LI:** Licensing Premises  
**RI:** Regulatory Inspection  
**LA:** Laboratory Access and Testing  
**CT:** Clinical Trials Oversight  
**LR:** National Lot Release  

\(a\): apply for GDP and may be GCP  
\(b\): in CT going on for vaccine/medicine  
\(Y\): Yes (recommended)  
\(N\): No (not recommended) unless private sector procures significant volume of vaccine
AVAREF-African Vaccine Regulatory Forum
Network approach to regulation of clinical trials in Africa

Scope

Regulation of medicines
Regulation of vaccines
Regulation of clinical trials

Support from US FDA, Health Canada, European regulators
New vaccines in clinical development presented by sponsors/vaccine developers
Recognized and supported by donors as an efficient platform

Structure allows rapid and dynamic response as per needs identified

National Regulatory Authority
Ethics Committees
Concluding Remarks

- All regulators have a duty to ensure the efficiency, effectiveness and transparency of operations.
- At the same time, not all regulators have the resources or capacity to perform all regulatory functions: decisions have to be made nationally on which areas to focus and build capacity, and in which areas rely on other regulator’s work.
- Good regulatory practices, flexible regulatory frameworks and reliance/networking a must for meeting the challenges of an increasingly complex global regulatory environment.
Thank you for your attention
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Overview of Vaccine Prequalification

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Structure of the Prequalification Team

Essential Medicines and Health Products [EMP]

Prequalification Team Coordinator

Coordinator’s office

Vaccines Assessment

Medicines Assessment

Diagnostics Assessment

Pesticides

Inspections

Technical Assistance/Labs
A service provided to UN purchasing agencies. Provides independent opinion/advice on the quality, safety and efficacy of vaccines for purchase. Ensures that candidate vaccines are suitable for the target population and meet the needs of the programme. Ensures continuing compliance with specifications and established standards of quality.
Principles

- Reliance on NRA
- Meeting WHO requirements and tender specifications
- Consistency of final product characteristics
- Clinical data
- GMP
Prequalification process

- Scientific review of quality dossier
- Scientific review of clinical data
- Testing of samples
- Consultation with responsible NRA
- Inspection to manufacturing facilities
Prequalification process: timelines (excluding applicant response times)

1. Submission of application for PQ
2. Screening (30 days + 90 days if there is critical PSPQ non compliance)
3. 270 days internal time
4. Streamlined based on SRA approval and sharing of NRA reports
5. 90 days internal time
6. Submission of variation
7. Screening
8. 90 days internal time
Past and current challenges

<table>
<thead>
<tr>
<th>Quality</th>
<th>Clinical</th>
<th>Programmatic</th>
<th>GMP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incomplete dossier</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Lack of data at commercial scale |
No history of characterization |
Master and Working cell banks |
Inappropriate devices: nasal administration |
| Lack of clinical consistency data, unclear ethical oversight |
Clinical trial comparator product not acceptable |
Lack of access to data and/or old data not meeting current GCP |
Lack of registration of CTs |
| Deviation |
Programmatic suitability criteria (PSPQ): eg, non autodisable prefilled syringes, stability profile and VVM |
| Quality systems Manufacturing process |

| Regulatory |
National Vs WHO requirements: Test methodologies and GMP Schedules and target population Monodose Vs multidose presentation (preferred) |
Past/current Challenges and solutions

- Programmatic suitability criteria
- Quality, safety and efficacy
- Regulatory
- Post-PQ monitoring

Publication of PSPQ criteria and establishment of Standing committee on PSPQ

Briefing on PQ expectations (workshops and webinar)
Guidance documents
Pre-submission meetings

Collaboration agreements with National Regulatory Authority of record for PQ

Consolidated investigation, reporting and communication in response to quality or safety concerns
Post Prequalification WHO Activities

- Variations
- Annual Report evaluation
- Reassessment
- Targeted testing program
- Monitoring/Investigation of vaccine quality and cold chain complaints
- Monitoring/investigation of Adverse Events following immunization (AEFI)
- Collaborative National Registration
- Technical Review of tenders for UNICEF
Technical assistance and capacity building

Meetings with manufacturers at early stages of vaccine development. Advice on product characteristics and clinical development.
PQ briefing workshops
Support to IFPMA and DCVMN
Support to regulatory networks: DCVRN, AVAREF
Why is Vaccines PQ important for user countries and its NRAs?

It represents a source of vaccines of "assured quality"

In addition the evaluation is focused on programmatic needs

WHO follows up on complaints and reports of AEFI's and publishes the outcome of investigations

WHO monitors the quality of prequalified vaccines on a continuing basis, through testing of samples, reassessment of the products, targeted audits, and delists vaccines if they do not meet the established specifications and/or standard

Opportunity for NRAs in user countries to save resources to focus on other priorities, since registration can be granted through a facilitated and shortened procedure
Implementation of Procedure for expedited review of imported prequalified vaccines for use in national immunization programmes (WHO/IVB/07.08)

Firstly used for registration of MenAfriVac in 26 countries of the belt
Collaborative procedure

WHO

NRA

Manufacturers

Agreement

Facilitated license
Principles of the procedure

1. Procedure is voluntary for manufacturers and NRAs and providing benefits to both parties.

2. With consensus from manufacturer, full PQ PSF and site audit report plus initial testing results will be shared with interested NRAs to facilitate national regulatory decisions making (registrations, variations, withdrawals).

3. No interference with national legislation, decision making process and regulatory fees – but PQ expertise is available to NRAs.
Principles of the procedure

4. Since there is agreement to share reports, the registration dossier should be in principle the same as the PSF approved by PQ.

5. Each participating authority commits to adopt registration decision within 90 days after having access to full PQ reports.

6. The NRA has the right to:
   – decline to adopt procedure for specific products
   – decide differently from PQ, but keep PQ informed and clarify the reasons for deviation.
Win-win situation

- NRAs
  - Availability of WHO assessment and inspection outcomes to support national decisions
  - Opportunity to learn from PQ assessors and inspectors
  - Saving internal capacities
- WHO and UN agencies
  - Prequalified vaccines are available sooner
  - Feed-back on WHO prequalification outcomes
- Manufacturers
  - Harmonized data for PQ and national registration
  - Accelerated and more predictable registration
Path forward

- Advocacy workshops and joint reviews:
  - EURO, AFRO, SEARO
  - AMRO, WPRO

- Capacity building activities: Rotational fellowships and participation of regulators in PQ assessments
Vaccines for emergency (PQ and non PQ activities)

- Yellow Fever, cholera and meningococcal vaccines:
  - Fractional dose (YFV)
  - Alternative suppliers

- Pandemic influenza preparedness

- Vaccines Emergency use and assessment process listing EUAL

- Other vaccines such as smallpox (stockpile),
ENSURING THE VACCINE SUPPLY CHAIN

The role of Immunization Devices in ensuring the safe transport, storage, distribution and administration of vaccines
COLD CHAIN CHALLENGES

• INCREASE IN VACCINE VOLUME PER FIC
  – Increased number of vaccines
  – Extension of immunization targets
  – Increased supplementary immunization activities (SIAs)
  – Growth of single dose presentations
  – Integration of vaccine with device
  – Incorporation of the diluent

• THIS CAN BE OFFSET IN FUTURE BY
  – Controlled Temperature Chain (CTC)
  – Intradermal administration (requires less dose for same immune response)
## Vaccine-related equipment (PQS) categories: progress overview

<table>
<thead>
<tr>
<th>PQS Categories</th>
<th>Description</th>
<th># Products PQ 2009</th>
<th># Products PQ 2010</th>
<th># Products PQ 2011</th>
<th># Products PQ 2012</th>
<th># Products PQ 2013</th>
<th># Products PQ 2014</th>
<th># Products PQ 2015</th>
<th># Products PQ 2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>E001</td>
<td>Cold rooms and related equipment</td>
<td>0</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>4</td>
<td>4</td>
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<tr>
<td>E002</td>
<td>Refrigerated trucks</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Still under development</td>
</tr>
<tr>
<td>E003</td>
<td>Refrigerators and freezers.</td>
<td>7</td>
<td>16</td>
<td>28</td>
<td>33</td>
<td>36</td>
<td>44</td>
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<td>63</td>
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<tr>
<td>E004</td>
<td>Cold boxes and vaccine carriers.</td>
<td>1</td>
<td>32</td>
<td>32</td>
<td>34</td>
<td>37</td>
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<td>41</td>
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<tr>
<td>E005</td>
<td>Coolant packs - water-packs</td>
<td>0</td>
<td>16</td>
<td>16</td>
<td>18</td>
<td>17</td>
<td>17</td>
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<tr>
<td>E006</td>
<td>Temperature monitoring devices.</td>
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<td>10</td>
<td>11</td>
<td>17</td>
<td>22</td>
<td>24</td>
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<td>E008</td>
<td>AD syringes</td>
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<td>36</td>
<td>39</td>
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<tr>
<td>E010</td>
<td>Waste management: Safety boxes</td>
<td>9</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>11</td>
<td>12</td>
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<tr>
<td>E013</td>
<td>Therapeutic injection devices</td>
<td>37</td>
<td>48</td>
<td>61</td>
<td>72</td>
<td>80</td>
<td>84</td>
<td>89</td>
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<td><strong>Total</strong></td>
<td></td>
<td>93</td>
<td>162</td>
<td>187</td>
<td>216</td>
<td>238</td>
<td>258</td>
<td>284</td>
<td>298</td>
</tr>
</tbody>
</table>
International Shipments of Vaccines – Guidance 1

• The ‘Guidelines for International Shipment of Vaccines’ published in 2005 is the main guidance document for packaging and shipment of vaccines

• Currently under revision with publication of the revised version scheduled for Q4 2017

• Purpose of the revision is to incorporate changes in technology and policies over the last 10 years since the first version was published
International Shipments of Vaccines – Guidance 2

- Guidelines contain a section on insulated packaging standards for OPV, Freeze dried vaccines (BCG, Measles, MR, MMR, Meningococcal A&C, yellow fever) and freeze sensitive vaccines (DTP, DTP Hep-B, IPV, TT etc)

- Also contains sections on temperature monitoring devices, storage volume standards, labelling and packaging and shipping arrival procedures
International Shipments of Vaccines – Monitoring Devices

• Electronic shipping indicators-
  – single use pre-programmed electronic time-temperature loggers which accompany vaccines from the manufacturers warehouse to the receiving country’s primary store.
  – They display the shipment’s time-temperature exposure without the need for download onto a PC

• Cold Chain Monitors (CCMs) –
  – provide a warning when excessive heat exposure occurs during transport.
  – They are used primarily to monitor the international shipment of freeze-dried vaccine consignments where dry ice is used as the cooling medium.
Expanding the scope?

Snake antivenoms

mAb

World Health Organization
Relevant PQ information

http://www.who.int/immunization_standards/vaccine_quality/pq_system/en/
http://www.who.int/immunization_standards/vaccine_quality/pq_suppliers/en/
http://www.who.int/immunization_standards/vaccine_quality/ps_pq/en/
http://www.who.int/immunization_standards/vaccine_quality/expedited_review/en/