Challenges for registration of vaccines in receiving countries

by Dr. Nora Dellepiane

Workshop: Global Registration and Vaccine Shortage
Taipei, Taiwan 6 to 10 March 2017
Outline of the presentation

• WHO recommended regulatory functions
• Pathways to registration of vaccines
• Constraints for registration
• Potentially useful interventions
• Potential inputs from manufacturers
WHO approach to NRA strengthening efforts: Recommended functions according to vaccine source

<table>
<thead>
<tr>
<th>Vaccine Source</th>
<th>MAA &amp; licensing</th>
<th>PMS</th>
<th>Lot release</th>
<th>Lab access</th>
<th>Regulatory Inspections</th>
<th>Authorization &amp; monitoring CT</th>
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<tbody>
<tr>
<td>UN agency supply</td>
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<td>Direct purchase</td>
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<td>Producing country</td>
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Exporting country NRA+ WHO-PQ

Exporting Country NRA

All countries where CTs are performed
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Ability to oversee clinical trials

- Producing countries:
  - Ability to review CT protocols
  - Ability to monitor CT
  - Ability to review CT data

- Countries targeted for CT:
  - Ability to review CT protocols
  - Ability to monitor CT
  - Ability to review CT data or may opt to develop none or some of this capacity and outsource the expertise whenever a trial is planned in their country
Pathway A to registration of vaccines for supply in global market

Step I: Application for evaluation (CO) → Evaluation → Approval & granting of: MA or NOC

Step II: Application for evaluation WHO/PQ → Evaluation & Granting of PQ

Step III: Application for Evaluation in 100+ countries → Waiver of registration → Recognition Of PQ in some countries → Expedited review Procedure (OLD) → Collaborative Procedure (NEW) → Approval: MA or NOC

Quality & Regulation Biologics
Pathway B to registration of vaccines for supply in global market

STEP

I

Application for evaluation (CO)

Evaluation & Granting of MA

Approval: MA or NOC

IIa

Application for evaluation WHO/PQ

Evaluation & Granting of PQ

III

Application for Evaluation in 100+ countries for UN supply

Waiver of registration

Recognition Of PQ in some countries

Expeditied review Procedure (OLD)

Independent evaluation

Approval: MA or NOC

Ia

IIb

III

MANUFACTURER

Quality & Regulation

Biologics
Pathway C to registration of vaccines for supply in global market

**STEP**

**I**
- Application for Evaluation Through EMA Art. 58

**II**
- Application for evaluation WHO/PQ
- Evaluation & Granting of PQ (1 mth)

**III**
- Without subsequent PQ
- With subsequent PQ
- Waiver of registration
- Recognition Of PQ in some countries
- Independent evaluation
- Expedited review Procedure (OLD)
- Collaborative Procedure (NEW)
- Approval: MA or NOC

WHO recommended experts NRAs of user countries

PQ staff

MANUFACTURER

Q&RB

Quality & Regulation Biologics
Constraints observed in some countries for registration: dossier

- Application form prior to submission, variety of formats
- Different dossier formats
- Differences in number and types of legal documents required
- Differences in format and contents of CTD (as discussed earlier)
- Different level of detail in dossier content requirements
- Different requirements regarding translations, legalization of documents, etc

LACK OF ALIGNMENT IN FORMAT AND CONTENTS OF DOSSIERS EVEN IF ONLY FOCUSING ON COMMON TECHNICAL DOCUMENT USED IN DIFFERENT REGIONS/ COUNTRIES OF THE WORLD
Constraints observed in some countries for registration

- Testing imposed as part of registration process
- Prior approval in a «reference country» in order for submission to be accepted
- Stability data for three consecutive lots, extensive real time stability data required
- Compliance with National Pharmacopoeias, which sometimes differ from international pharmacopoeias
- License of facilities prior to product registration
- Mandatory clinical trials at local level
- One site per license
- Repetitive GMP inspections
The time between first regulatory authority submission for a given drug or vaccine to its registration in the last (by disease burden) of 20 Sub-Saharan Africa countries was typically between 4 and 7 years.

There are many factors responsible for this lengthy timeline:
- Redundancy across steps since there was no leveraging of the technical reviews already performed by competent bodies,
- Inefficiencies in the regulatory processes themselves,
- and failure of manufacturers to meet the international standards required by WHO-PQ.

Data source: Speeding Access to Vaccines and Medicines in Low- and Middle-Income Countries Ahonkhai, V. et al. PLOS ONE | DOI:10.1371/November 16, 2016
Summary of constraints

• Inadequate and/or rigid legislation that does not allow for flexibilities as required based on scientifically sound reasons (waiver of local clinical trials).

• Lack of provisions for reliance on work performed by other regulators or WHO including in cases where the products are needed for special circumstances (orphan products, compassionate use, donations, emergency use, etc)
Summary of constraints (2)

- Technical or scientific limitations, where the necessary resources and expertise for an adequate evaluation may not exist or be insufficient,

- Imposition of irrelevant or excessive requirements in some cases.
Summary of constraints (3)

- Cumbersome, inadequate or not fully defined procedures leading to inconsistent and lengthy registration processes
- Lack of transparency with respect to processes and procedures in place including route of the dossier, expert committees involved, timeframes for different steps, etc
Availability of guidance documents. WHO is best suited for this. **GRP guidelines under development.** More implementation oriented guidelines are needed.

Training provided to facilitate implementation of the guidance, WHO and other partners

Further efforts towards alignment and harmonization of requirements, mostly through networks, economic blocks agreements, inputs from manufacturers and manufacturers associations, etc

Collaboration between regulators (reliance and recognition including mutual recognition) through networking initiatives

Technical/scientific expertise provided through joint review activities, twining between NRAs and other means
What could be potential inputs from manufacturers?
Potential inputs from manufacturers

✓ Publication in a peer reviewed and open access journal the DCVMN concept paper highlighting the constraints faced for timely registration of vaccines in receiving countries

✓ DCVMN and IFPMA jointly approaching WHO to provide:
  • Comparative analysis of format and contents of CTD requirements by different authorities across the world (showing the lack of alignment even in the supposedly harmonized technical document)
  • Review of gaps and overlaps in the most used guidelines published online providing advice on recommended processes and procedures for registration of medicines
  • A proposed common list of essential documents that could be used as a starting point for reaching some level of alignment in module 1 of the CTD and administrative requirements from authorities not using CTD format of dossier

and to request WHO to follow up on each of the topics

✓ Approach regulatory networks (AVAREF and DCVRN) and partners to discuss the above mentioned inputs and advocate for follow up

✓ Other?

Draft Concept Paper commissioned by DCVMN on “Registration of vaccines: Current challenges and opportunities”.


Thank you
Merci
Спасибо
شاكراً
Gracias
Grazie
Danke Schön
Obrigado