Developing Countries Vaccine Manufacturers Network

Opportunities for improvements in vaccine registration procedures in emerging countries

19th AGM Meeting

Kunming, China 29 to 31st October 2018

presented by Dr Nora Dellepiane

The Challenges

1) Diversity of procedures

2) Divergence in structure and contents of dossier

3) Divergence in format and contents of application forms

4) Country specific requirements

1) Diversity of procedures

- At least 29 vaccine importing countries perform redundant GMP inspections of WHO-PQd vaccines
- At least 89 countries require submission of vaccine samples (rather than mock ups) during the registration procedure

2) Divergence in dossiers

- 32 countries require the ICH CTD mostly with local adaptations
- 8 countries require the ASEAN CTD
- At least 60 countries still require a national format for the dossier

3) Application forms are country specific

4) Additional country specific requirements introduce additional timeframe for compliance (process for legalisation of documents)

Comparison of CTD structure and contents

CTD Modules	Contents and format	ASEAN/ICH	Avg of 5-10 countries or regions
Module 1	Contents	62% similar	
	Numbering	30 % similar	
Modules 2-5	Contents	93% similar	23% similar
	Numbering	0 % similar	17% similar

OPTIONS FOR IMPROVEMENT

After having reviewed the challenges for registration the Joint DCVMN-IFPMA regulatory experts WG has made

4 Proposals for alignment of requirements and streamlining of registration procedures

1. Suggestions for improvement of registration procedures
2. Proposal for alignment of CTDs across countries and regions
3. Proposal for a standard application form
4. Other considerations for improvement of the registration procedures

1. Registration procedures

Suggestions for improvement of registration procedures in the case of WHO-PQ vaccines

- Highly regulated in country of origin (CoO)
- Reviewed by WHO for Q,S,E and for specific programmatic aspects
- Continuing regulatory oversight by CoO and WHO

↓

Based on the **PRINCIPLE OF RELIANCE**
Three options can be considered for registration by NRAs in the importing countries

↓

1. Issue registration automatically based on WHO-PQ
2. Apply the WHO Collaborative Registration Procedure (CRP)
3. Independent dossier evaluation with reliance on WHO test results and inspection outcome

1, 2 or 3 + review of labels, PI and legal documents

1. Registration procedures

Suggestions for improvement of registration procedures in the case of vaccines that are not WHO-PQ

Vaccines regulated in country of origin (CoO), in many cases by stringent NRAs:
Need to emphazise on **RELIANCE**
whereby costs and time may be reduced, resources saved and duplication of activities avoided; leading to faster access of vaccines to the target populations.

Examples of reliance include

a) Mutual recognition agreement between EMA and USA,
b) Reinforcement of collaboration between USA and Japan,
c) EMA article 58, and
d) Agreements between ANVISA, ANMAT and ANVIMA for mutual recognition of inspections

Other options to be considered include

a) Establishing bilateral or regional agreements to rely on assessment performed by the NRA in CoO, or by a reference NRA having already registered the vaccine
b) Conducting an independent review of the dossier and accepting results of tests conducted independently from the manufacturer (NCL of CoO or other) and avoiding duplication of site inspections.

Second Meeting of the WHO-NNB

The National Control Laboratory Network for Biologics (WHO-NNB)

- The objective of the Network is to increase trust between NCLs worldwide and to provide a platform for recognition/ reliance of release activities by laboratories in the network and for information sharing.
- The WHO-NNB held its 2nd Meeting in Rome from 25 to 27 September 2018. Mfgs associations participated.
- Manufacturers are invited to sign information sharing agreements and become observers to the network.
- The DCVMN-IFPMA regulatory experts working group presented a proposal for data sharing between member countries, particularly to provide information to vaccine importing countries either registering or releasing vaccine lots in their markets

Outcome of the proposal by manufacturers

- Manufacturers are requested to sign the agreements (request letter will be sent by WHO) for test data sharing within the network at earliest.
- Manufacturers are requested to support WHO in encouraging vaccine importing countries to join the network as associate members, ensuring a maximum of participation in the Network, as the Network acts as a confidential platform for information / data exchanges.
- The Network platform will upload information e.g. on the number of lots released of the vaccine in question by Network members on consent of manufacturer. Info provided to contact directly the testing lab to get additional information under confidentiality (including test results) is possible among Network members and WHO.

1. Registration procedures Conclusions

The working group suggests

- ✓ fostering adoption of the CRP and increased reliance on WHO prequalification to streamline the registration procedures in countries that primarily access vaccines through UN agencies
- ✓ fostering reliance through agreements for recognition of assessments conducted by other regulators (NRA in CoO, regional or sub-regional basis, reference NRAs having registered the product)
- ✓ Promote joining WHO-NNB Network between manufacturers and vaccine importing countries to facilitate access to test data on specific vaccines and thus avoiding unnecessary international transportation of samples.

2. Proposal for alignment of CTDs across countries and regions

Proposal for alignment of Module 1

- Development of a proposal for alignment of the numbering system for module 1. The most frequently used structure and headings are proposed for alignment. It provides options on where to fit country specific requirements that may not be required by other countries.
- The format proposed was created prior to and is distinctly different from the recent WHO guidance which updated WHOs Module 1 expectations.

Proposal for alignment of Modules 2-5

- The proposal for alignment of modules 2-5 is to follow ICH (EU) CTD (EU Notice to Applicants). This structure is also recognized by WHO for their prequalification procedure. The EMA dossier is used or recognized by many countries worldwide. If certain information is not required by a specific country, the section could be skipped for that country , in which case it is suggested that the numbering for other sections be maintained.

2. Proposal for alignment of CTDs across countries and regions

Proposal for alignment of Module 1

- Development of a proposal for alignment of the numbering system for module 1. The most frequently used structure and headings are proposed for alignment. It provides options on where to fit country specific requirements.
- The format proposed was created prior to and is distinctly different from the recent WHO guidance which updated WHOs Module 1 expectations.

Proposal for alignment of Modules 2-5

- The proposal for alignment of modules 2-5 is to follow ICH (EU) CTD (EU Notice to Applicants). This structure is also recognized by WHO for their prequalification procedure. While many countries utilize the ICH CTD structure, the EMA dossier is used or recognized by many countries worldwide.
- If certain information is not required by a specific country, the section could be skipped for that country , in which case it is suggested that the numbering for other sections be maintained.

3. Proposal for a standard application form

An application form essentially covers three main sections containing

- information about the applicant and the legal representative in the country,
- information about the product and
- information about its regulatory status.

These 3 main sections and main subheadings were kept

- Proposed in table format
- Brief description of expected information/documentation to be provided under each sub-heading is given

4. Other considerations for improvement of the registration procedures

a) Promote pre-submission meetings between the applicant and the regulators (scientific advice or similar)

- Good line of communication between regulators and sponsors has been associated with increased chance of market access. Compliance with the outcome and recommendation of the advice appears to be a predictor of a positive outcome. Particularly important for clinical development plans

b) Promote understanding of the scientific rationale to conduct additional domestic clinical trials for imported vaccines.

- Through development of a WHO guideline?
- Through training? Other?

c) Pharmacovigilance

- Focus on establishing functional pharmacovigilance systems, WHO's Triple-S project (smart safety surveillance) represents a useful approach to achieving this goal

d) Testing waiver

- Good review of documentation can replace testing at registration stage, use of WHO-NNB to provide results to importing countries?

e) GMP inspection waiver

- GMP certificate by NRA, CPP, desk audit (PICs guidance doc), outcome of inspections or reports from other NRAs

THANK YOU

This work has been produced by the Developing Countries Vaccine Manufacturers Network (DCVMN) in collaboration with the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA)

Partially funded by the Bill and Melinda Gates Foundation (BMGF)