PROPOSALS FOR ALIGNMENT FROM MANUFACTURERS

DCVMN Common Technical Document (CTD) Workshop

Brazil, 18 to 20 June 2018

Dr. Nora Dellepiane

This is ongoing work from the Developing Countries Vaccine Manufacturers Network (DCVMN) in collaboration with the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) based on data available in the participating companies.

With funding from the Bill and Melinda Gates Foundation (BMGF)

Areas with potential for alignment

There are three major areas with potential for alignment:

Registration procedure

CTD architecture or structure

Application form

PROCEDURE

STEP OF REGISTRATION PROCEDURE	PROPOSED INTERVENTION
DOSSIER ARCHITECTURE/ STRUCTURE	
Common Technical Document	Alignment of architecture/structure for module 1 and for modules 2-5
Application form (part of module 1)	Proposal of a common (model) AF
STEPS OF THE REGISTRATION PROCEDURE	
Testing of samples	Proposal for reliance on results from GLN
Facilities inspection	Proposal for reliance on already existing inspection reports
OTHER CONSIDERATIONS FOR ALIGNMENT AND IMPROVEMENT OF PROCEDURE	
Scientific Advice	Proposal for meetings between applicants and regulators
Need for local clinical trials	Careful consideration
Pharmacovigilance	Focus on strengthening system
Company licensure	At time of first product registration
Renewals	Risk based approach

Implementing the principle of reliance
a) The case of prequalified vaccines

Possible options to overcome current constraints for registration

1. Granting a marketing authorization relying fully on the WHO prequalification without any further review of the product
2. If registration is based on additional review, allowing supply of the vaccine in the country based on the WHO prequalification until the official registration procedure is completed, within a predefined reasonable timeframe; thus avoiding any delays in supply
3. Implementing the collaborative procedure, including sharing of dossier review reports, test results and the WHO inspection reports, as the basis for decision-making about granting the Marketing Authorization (MA).

Implementing the principle of reliance
b) The case of non-prequalified vaccines

Possible options to overcome current constraints for registration

1. Relying on a reference NRA that has already registered the vaccine for use in their country
2. Establishing a bilateral agreement with the NRA of the producing country for information sharing about the specific vaccine in question (e.g. dossier evaluation reports, test results and inspection reports as available)
3. Establishing regional agreements to rely on the evaluation performed by other countries that have registered the same vaccine previously
4. Conducting an independent review of the dossier and accepting test results available with the manufacturer that have been conducted independently (e.g. NCL of country of origin, Global Laboratory Network or other)

Alignment of module 1

General criteria for alignment

1. If certain information is not required by a country, the section should be skipped. However, it is suggested that the numbering for other sections be maintained
2. Documents that are related to the suggested content of the section, should go in that section
3. If document requirements by a country are not covered in any of the defined sections, Section 1.13 and any additional sections are available for country specific requirements
4. A common, harmonized Application Form is also being proposed
5. A table proposing harmonized numbering and description of documentation to be included has been developed

Alignment of modules 2-5

General criteria for alignment

1. Harmonizing the architecture, numbering system against the EU/ ICH CTD
2. Harmonizing the contents under each item and heading according to the EU Notice to Applicants.
3. If certain information is not required by a country , the section should be skipped . However , it is suggested that the numbering for other sections be maintained.
4. If a country requires information not included in the EU/ICH CTD, this could be integrated in the respective sections of the CTD.

Options to integrate information not normally included in CTD

Additional Information requirements by countries	Location in EU ICH CTD
Thermostability	3.2.P.8.3
Excursion stability- shipping	3.2.P.8.3 /3.2.S.7.3
In-use/reconsistution stability	3.2.P.8.3
Cold chain validation Shipping qualification	3.2.P.3.5
Bulk leachability	3.2.S.6
Full validation protocol	3.2.P.3.5
Stability at end of shelf-life for multidose vaccines	3.2. P.8.3
In-country clinical trial	5.3.5
Clinical literature	5.4

APPLICATION FORM

An application form essentially covers three main sections containing

1. information about the applicant and the legal representative in the country,
2. information about the product and,
3. information about its regulatory status.

APPLICATION FORM (1)

HEADING	DESCRIPTION OF REQUIRED INFORMATION
1. Information about the applicant and the legal representative in the country	
1.1 Name of pharmaceutical company	This presents the name of the pharmaceutical entity which is concerned with the finished product registration.
1.2 Name and Address of manufacturer of drug substance(s)	This presents the name and address of the manufacturer(s) of the drug substance(s) used in the manufacturing of the finished product.
1.3 Name and Address of manufacturer of the finished product	This presents the name and address of the manufacturer(s) of the finished product.
1.4 Name and Address of applicant/legal representative/ marketing authorization holder	This presents the name and address of the Marketing Authorization Holder (MAH) of the finished product. This may be a pharmaceutical company, a legal representative of any local consultation firm, any authorized and designated person thereof OR any person authorized to place the product on the market.
1.5 Name and address of other manufacturer(s) involved in the manufacturing process	This presents the name and address of all the manufacturer(s) which are involved in a part of the manufacturing process of finished product.
1.6 Contact person for Quality and Pharmacovigilance	This presents the name and address of the authorized representative(s) on behalf of the applicant/MAH. Contact person for quality is responsible for the overall quality of the finished product intended for marketing and contact person for Pharmacovigilance is responsible for the overall health and safety of the intended patient population and also responsible for any returns and recalls related finished products due to safety concerns.
1.7 Person/company authorized for communication between the MAH and NRA & Official(s) responsible for batch testing and batch release of finished product	This presents the name and address of the authorized representative(s) on behalf of the applicant/MAH. Any communication regarding the intended products/applications should be forwarded from NRAs only to the person/company authorized for communication between the MAH and NRA. For all the product batches destined to be marketed in the proposed NRAs wherein the requirement of batch release exists should have a provision of a designated person/company responsible for the releasing of the batches of finished product.

APPLICATION FORM (2)

1. Information about the product	
2.1 Name of the medicinal product including non-proprietary name or common name of vaccine	This presents the non-proprietary/generic/invented name of the finished product or common name of the vaccine for which the registration application is applied.
2.2 Pharmaceutical form	This presents the dosage form in which finished product is intended to be marketed for use.
2.3 Physical description of pharmaceutical form	This presents complete physical appearance throughout shelf life of the finished product being applied for the registration.
2.4 Commercial presentation(s)	This presents the amount/quantity of unit dose of finished product per pack intended to be marketed.
HEADING	DESCRIPTION OF REQUIRED INFORMATION
2.5 Indication(s)	This presents the therapeutic indication(s) for which the finished product is intended to be approved for.
2.6 List of excipients, product shelf-life, storage condition, packaging configuration(s)	This presents the list of excipients used in the manufacturing of finished product, proposed product shelf-life and/or in-use shelf-life of product; storage condition during shelf-life and primary packaging of the finished product intended for the marketing.
2.7 Dosage and Administration	This presents the posology of the finished product and method of administration.
2.8 Qualitative and Quantitative Composition	This presents full details of drug substance(s) and excipients. Quantity of drug substance(s) and excipients should be expressed per dosage unit/per unit volume/per unit of weight, as per internationally recognized standard terms.
2.9 Name of drug substance(s)	This presents name of drug substance(s) present in finished product.

APPLICATION FORM (3)

3.0 Regulatory status	
3.1 Date and number of registration in origin country	This presents the date of first authorization in country of origin and registration number assigned to that approval as per the prevalent regulations of NRA(s).
3.2 List of countries in which finished product is registered	This presents the list of countries where the intended finished product is registered.
3.3 List of countries where the product is marketed	This presents the list of countries where the intended finished product is marketed.
3.4 Did you apply for scientific advice before submission	Any scientific advice sought before submission from the respective NRA(s) should be outlined here.
3.5 Type of application	This presents the type of application to be registered as per the regulatory guideline(s) of the respective NRA(s).
3.6 Annexed documents	This presents any additional information provided as separate documents.

Other considertions for alignment: Scientific advice

Benefits	Challenges
• Adherence to the outcome and suggestions might reduce timelines and lengthy discussions during the application review	• Requires a formal process to be implemented and adhered to
• Faster access for patients	• Requires dedicated resources and capabilities
• Clarity and visibility on mutual expectations for all stakeholders	• Establishing reasonable timelines in order not to delay the overall application processes and access for patients

Other considerations for alignment Local clinical trials (2)

- Clinical trial data are the basis for any market authorization application but sponsors are often confronted with requests for additional clinical trial data with no clear rationale or representing a duplication of clinical trials already conducted elsewhere.
- Reliance on existing data from clinical trials and post marketing surveillance are likely to cover a great part if not all of the need to consider duplicative trails.
- In addition, the group highlighted there are potentially considerable ethical issues when repeating clinical trials with no clear scientific or medical need for patients.

Other considerations for alignment (3) Pharmacovigilance

Although, access to medicines and vaccines has improved in many countries in the past two decades, there has not been a proportionate improvement in pharmacovigilance infrastructure and activities to monitor adverse events and address safety issues.

- The group's recommendation is to focus resources on establishing a good working pharmacovigilance, which can only be done at local level. For this , it is recommended to consider the WHO "Triple S" (Smart Safety Surveillance) approach.
- Key principles of this include

  - (A) the development of a single system for both vaccines and medicine where possible ;
  - (B) leveraging existing systems and platforms (CIOMS (https://cioms.ch/#), ICH) ;
  - (C) use reliance where possible;
  - (D) build an infrastructure step by step to enable sustainability.

Other considerations for alignment (4) Company licensure

Some countries require company registration and in addition, manufacturing site registration in advance to any filing for products registration.

- While there could be a rationale for doing this in the case of a new company with limited experience, including not having marketed products, this represents a constraint to vaccine access.
- This constraint could be overcome by performing the company registration and site registration at the time of a first product registration submission.

Other considerations for alignment (5) Registration renewals

Renewals are necessary in the interest of public health and public trust and to ensure continued compliance with GMP during the product life cycle. However, as the experience with a particular product and its manufacturer evolves and as it is documented, a risk based approach should be considered to rationalize and abbreviate these renewals.

- For products with a good body of evidence, (semi-) automatic renewals could be envisaged based on a risk based approach.
- A decreasing frequency could make sense for products with long successful track records on the market even if mainly in other countries.

Acknowledgements

Working Group Members

THANK YOU
OBRIGADO
GRACIAS