Regulatory pathways e workshop
RWG and work on vaccines registration
DCVMN
27 April 2020
Facilitator Dr Nora Dellepiane
Outline of presentation

• Explain the challenges regarding vaccine regulation
• Explain DCVMN response in face of challenges
• Activities of the Regulatory Experts Working Group
• Focus on challenges for vaccine registration
• Proposals for improvement
• Relevance of the work performed
• Role of DCVMN member companies and of all immunization stakeholders in implementation of changes
Supply of vaccines to countries is often hampered or delayed by regulatory constraints for registration, for review of post-approval changes, for the acceptance of alternative/innovative testing methods, or due country specific requirements among other.
Initiative 3: Efforts to advance regulatory convergence approaches and to address challenges in vaccine regulation

In May 2017 DCVMN established a Regulatory Experts Working Group (RWG) aimed at

- sharing best practices in regulatory science and regulatory affairs.
- collaborating for the identification of regulatory challenges at both the pre- and post-marketing stages of vaccines life cycle, and to explore potential opportunities for increased efficiency of regulatory processes worldwide.
FOCUS:
1) Identify challenges and opportunities for improvement of the vaccine registration procedures
2) Identify challenges and opportunities for improvement of post-approval changes (PACs) management all along the vaccine lifecycle.

COMPOSITION
Regulatory Affairs and/QA staff from ten DCVMN member companies

CRITERIA FOR PARTICIPATION
Companies with prequalified vaccines that supply these vaccines internationally.
Experience in vaccine registration at global level.

MODUS OPERANDI
Close collaboration with IFPMA member companies to join forces and to elaborate proposals that are result of a consensus among a broad group of vaccine manufacturers.
Publish proposals in peer reviewed Journals and share with relevant vaccine stakeholders to foster implementation for improvement
RWG LoP

DCVMN

S. Comellas, Sinergium Biotech, **Argentina**

M. Collaço de Moraes Stávale, Bimanguinhos- Fiocruz, **Brazil**

Q. Liang, Sinopharm, **China**

Ve Hariharan, Bharat Biotech International Ltd, **India**

S. Kosaraju, Biological E, **India**

N. Chokshi, Cadila Healthcare Limited, **India**

S. Desai, Cadila Healthcare Limited, **India**

S. Ghadge, Serum Institute of India Pvt. Ltd, **India**

I. Nurnaeni, PT Biofarma, **Indonesia**

Arabio (Saudi Arabia) and LG (South Korea) membership to be confirmed

IFPMA (informal collaboration)

N. de Clercq, GSK. **Belgium**

Th. Gastineau, Sanofi Pasteur, **France**

L. Scheppler, Janssen Vaccines, Branch of Cilag GmbH International, **Switzerland**

M. McGoldrick, Merck Sharp & Dohme, Corp, **USA**

J. Dias, Pfizer, **Belgium**
Challenges for vaccines registration

- Lack of alignment in dossier format and contents
- Lack of alignment in registration procedures
- Repetitive testing and inspections
- Country specific requirements
- Unpredictable timelines
## Comparative review of CTD modules from different countries or regions

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Module 1</th>
<th>Modules 2-5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Countries included in comparison</td>
<td>Australia, China, Europe, the Gulf Cooperation Council (GCC) India, Jordan, PAHO, Tanzania, Thailand, the US and the WHO</td>
<td>PAHO, India, Jordan FDA and Thai FDA</td>
</tr>
<tr>
<td>Compared against</td>
<td>each other</td>
<td>ICH CTD as implemented by US FDA.</td>
</tr>
<tr>
<td>Nature of comparison</td>
<td>For contents and numbering</td>
<td>For contents and numbering</td>
</tr>
<tr>
<td>Data organization</td>
<td>Alignment on basis of contents independently of numbering</td>
<td>Alignment on basis of contents independently of numbering</td>
</tr>
<tr>
<td>Comparison of contents</td>
<td>Contents requiring the same information were considered similar; and contents that differed between the CTDs were considered different</td>
<td>See the following slide</td>
</tr>
<tr>
<td>Comparison of numbering</td>
<td>Numbering used for each topic compared to each other</td>
<td>Numbering used for each topic compared to ICH CTD (US)</td>
</tr>
</tbody>
</table>

**NOTE:** For simplicity, the items referring to the application forms were left out of the exercise and addressed separately.
CTDs from different countries were considered “different” from the ICH CTD if one of the following situations applied:

<table>
<thead>
<tr>
<th>Requirements country X</th>
<th>Requirements ICH CTD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Item/Topic not required</td>
<td>Item/Topic required</td>
</tr>
<tr>
<td>Item/Topic required (Other information)</td>
<td>Item/Topic not required</td>
</tr>
</tbody>
</table>
| Item under same heading as for ICH  
Data requirements not specified | Same heading  
Data requirements specified |
| Item under same heading as for ICH  
Data requirements specified | Same heading  
Data requirements not specified |
| Item under same heading as for ICH  
Data requirements different | Same heading  
Data requirements different |
Calculations of % of similarity and difference

**MODULE I**

✓ % of similarity = \( \frac{\text{N° items with similar content or numbering}}{\text{N° items compared}} \) \times 100

✓ % of difference = 100 - % of similarity

**MODULE 2-5**

✓ % of similarity = \( \frac{\text{N° items with similar content or numbering to ICH (CTD)}}{\text{N° items compared}} \) \times 100

✓ % of difference = 100 - % of similarity
MODULE 1 CONTENT COMPARISON BETWEEN CTDs FROM AUSTRALIA, CHINA, EUROPE, GCC, INDIA, JORDAN, PAHO, TANZANIA, THAILAND, US AND WHO

<table>
<thead>
<tr>
<th>Comparability</th>
<th>Similar</th>
<th>Different</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of items</td>
<td>189</td>
<td>114</td>
<td>303</td>
</tr>
</tbody>
</table>

NON HARMONIZED MODULE

- Similar: 62%
- Different: 38%
MODULE 1 NUMBERING COMPARISON BETWEEN CTDs FROM AUSTRALIA, CHINA, EUROPE, GCC, INDIA, JORDAN, PAHO, TA NZANIA, THAILAND, US AND WHO

**Non Harmonized Module**

<table>
<thead>
<tr>
<th>Comparability</th>
<th>Same</th>
<th>Different</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of items</td>
<td>92</td>
<td>211</td>
<td>303</td>
</tr>
</tbody>
</table>

Different 70%

Similar [Percentage]
## MODULES 2-5 CONTENT COMPARISON: INDIA, JORDAN, PAHO AND THAILAND AGAINST ICH (FDA)

<table>
<thead>
<tr>
<th></th>
<th>Number of items</th>
<th>Number of items</th>
<th>Number of items</th>
<th>Number of items</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PAHO Vs ICH (FDA)</td>
<td>INDIA Vs ICH (FDA)</td>
<td>JORDAN Vs ICH (FDA)</td>
<td>Thailand Vs ICH (FDA)</td>
<td></td>
</tr>
<tr>
<td>Different</td>
<td>333</td>
<td>334</td>
<td>308</td>
<td>332</td>
<td>1,307</td>
</tr>
<tr>
<td>Similar</td>
<td>101</td>
<td>103</td>
<td>84</td>
<td>108</td>
<td>396</td>
</tr>
<tr>
<td>Total</td>
<td>434</td>
<td>437</td>
<td>392</td>
<td>440</td>
<td>1,703</td>
</tr>
<tr>
<td>% similarity</td>
<td>23</td>
<td>24</td>
<td>21</td>
<td>25</td>
<td>23</td>
</tr>
<tr>
<td>% difference</td>
<td>77</td>
<td>76</td>
<td>79</td>
<td>75</td>
<td>77</td>
</tr>
</tbody>
</table>

ASEAN CTD IS not included in the pie since it is highly similar to the ICH CTD in contents
**MODULES 2-5 NUMBERING COMPARISON: ASEAN, INDIA, JORDAN, PAHO AND THAILAND AGAINST ICH (FDA)**

<table>
<thead>
<tr>
<th></th>
<th>Number of items PAHO Vs ICH (FDA)</th>
<th>Number of items INDIA Vs ICH (FDA)</th>
<th>Number of items JORDAN Vs ICH (FDA)</th>
<th>Number of items ASEAN Vs ICH (FDA)</th>
<th>Number of items THAILAND Vs ICH (FDA)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Different</td>
<td>286</td>
<td>346</td>
<td>313</td>
<td>366</td>
<td>269</td>
<td>1580</td>
</tr>
<tr>
<td>Same</td>
<td>96</td>
<td>69</td>
<td>63</td>
<td>0</td>
<td>102</td>
<td>330</td>
</tr>
<tr>
<td>Total</td>
<td>382</td>
<td>415</td>
<td>376</td>
<td>366</td>
<td>371</td>
<td>1910</td>
</tr>
<tr>
<td>% similarity</td>
<td>25</td>
<td>17</td>
<td>17</td>
<td>0</td>
<td>27</td>
<td>17</td>
</tr>
<tr>
<td>% difference</td>
<td>75</td>
<td>83</td>
<td>83</td>
<td>100</td>
<td>73</td>
<td>83</td>
</tr>
</tbody>
</table>

CTDs in different countries/regions of the world differ even more in terms of numbering, particularly the ASEAN CTD has a completely different structure and numbering to the ICH CTD (100% different).
CTDs from different countries/regions differ substantially in contents (77%) except for the ASEAN and ICH CTDs which are quite similar (93%)

The difference is greater in the numbering system with an average difference of 83 %, and a 100% difference between the ASEAN and the ICH CTD due to their completely different structure

One may argue that differences in numbering are trivial, while differences in content are important
Relevance of the difference (2)

- Differences in numbering are a big problem since the information/data, even if identical, has to be organized to fit the numbering required by each target country,
  - represents huge workload to regulatory affairs staff for no added value, and
  - leading to delays in vaccine availability
- Efforts towards alignment by manufacturers, vaccine stakeholders and regulators should enable
  - faster dossier preparation by manufacturers,
  - faster and easier review work by NRAs,
  - Increased work and information sharing opportunities among NRAs (same language)
  - Most importantly, quicker access to medicines in countries, which is the end goal
Challenges for vaccines registration

• Lack of alignment in dossier format and contents
• Lack of alignment in registration procedures
• Repetitive testing and inspections
• Country specific requirements
• Unpredictable timelines
The process followed by countries for MA evaluation also differs. US and EU base the assessment on the review of the CTD and inspection if needed, Japan requires a previous license of the facilities, Canada requires licensing of the establishment, an on-site evaluation (for Biologics only) and testing of batches.
Analysis of Vaccine registration procedures in 134 countries

Company registration
- Required: 15
- Not Required: 107
- Not known: 12

Product registration
- Not known: 5
- Required: 106
- Accept PQ: 23

Countries assessed (supplied through UN agencies) N= 134
Analysis of vaccine registration procedures in 134 countries (2)

Product registration

Required: 106

Accept PQ: 23

GMP inspection

Required: 29

Not Required: 94

Not known: 11

Dossier format

ICH CTD: 32

Country Specific: 60

ACTD: 8

Not known: 13

NR: 21

Vaccine samples

Required: 89

Testing: 13

Visual inspection: 3

Not known: 73

Not Required: 23

NR: No regulatory activity

Not known: 5
Options to decrease the variability in registration procedures

✓ Company registration can be done in parallel to MA submission, hence avoiding one unnecessary step
✓ GMP inspections are often redundant and can be avoided (other regulatory agencies have inspected the companies, reliance or information sharing concepts to be applied)
✓ Vaccine sample requirements can be replaced by photographs of containers and labelling info
✓ Testing may be avoided during the registration step and be performed as part of lot release when necessary
Challenges for vaccines registration

- Lack of alignment in dossier format and contents
- Lack of alignment in registration procedures
- Repetitive testing and inspections
- Country specific requirements
- Unpredictable timelines
Examples of country specific requirements

✓ Some countries require the Certificate of Pharmaceutical Product (CPP) issued by the regulatory authority from the producing country.

✓ In addition, some countries require prior approval in “reference countries” (Stringent NRAs) as per own list.

✓ Requirement limited to marketing authorization in the reference country or include actual commercialization in the reference country.

✓ Labelling and packaging requirements differ between countries, in contents and language. Container labels are normally required to be printed in the local language.
Many countries in Central and East Africa need an average of 24 months for registration.

Most countries in West Africa need 6 -12 months for registration but require prior approval in France or EU.

Many countries in the Middle East follow a quicker process, if the product has been pre-approved in Saudi Arabia.

A study by Ahonkhai et al. reports that the time between the first and last registration of 8 vaccines in 20 countries of Sub Saharan Africa took a medium of 78 months and the time span for the registration of a new drug showed a median of 52 months.
A- Pre-marketing regulatory activities

DCVMN activities related to vaccine registration

Identified registration challenges in non-producing countries

Made proposals for improvement: alignment of requirements and procedures


NOTE: Regulatory Experts Working Group in collaboration with representatives from IFPMA member companies. Constituted mostly by Regulatory Affairs staff.
Proposals for improvement

Main Proposals for dossier alignment

- Standard model for M1 with harmonized numbering system
- Country specific requirements to be added at the end, no alteration of numbering order
- Standard model for application form
- Adoption of EU CTD for all other modules
Main Proposals for procedural improvements

- First and foremost need for expert understanding and knowledge of regulatory pathways available and accessible to DCVMN manufacturers
- Fostering adoption of CRP for prequalified vaccines
- Use of bilateral agreements between countries and/or of regional agreements based on economic blocks’ collaborations.
- Fostering reliance and information sharing mechanisms as a preliminary step towards recognition or mutual recognition
What is needed to foster implementation of the proposals?

Implementation of proposed improvements by regulatory bodies depends on the work of all of us.

1. Full understanding by DCVMN members of the different possible mechanisms, regulatory pathways and proposals
2. When meeting regulators, share the publications and the proposed forms and invite them to consider adoption
3. Explain how simple it is, no legislation or regulation amendments are required
4. Use all possible opportunities to divulgate DCVMN proposals
5. Engage, be active and proactive
References

References

THANK YOU