Regulatory pathways e workshop

RWG and work on vaccines registration

DCVMN

27 April 2020

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Developing Countries Vaccine Manufacturers Network

Outline of presentation

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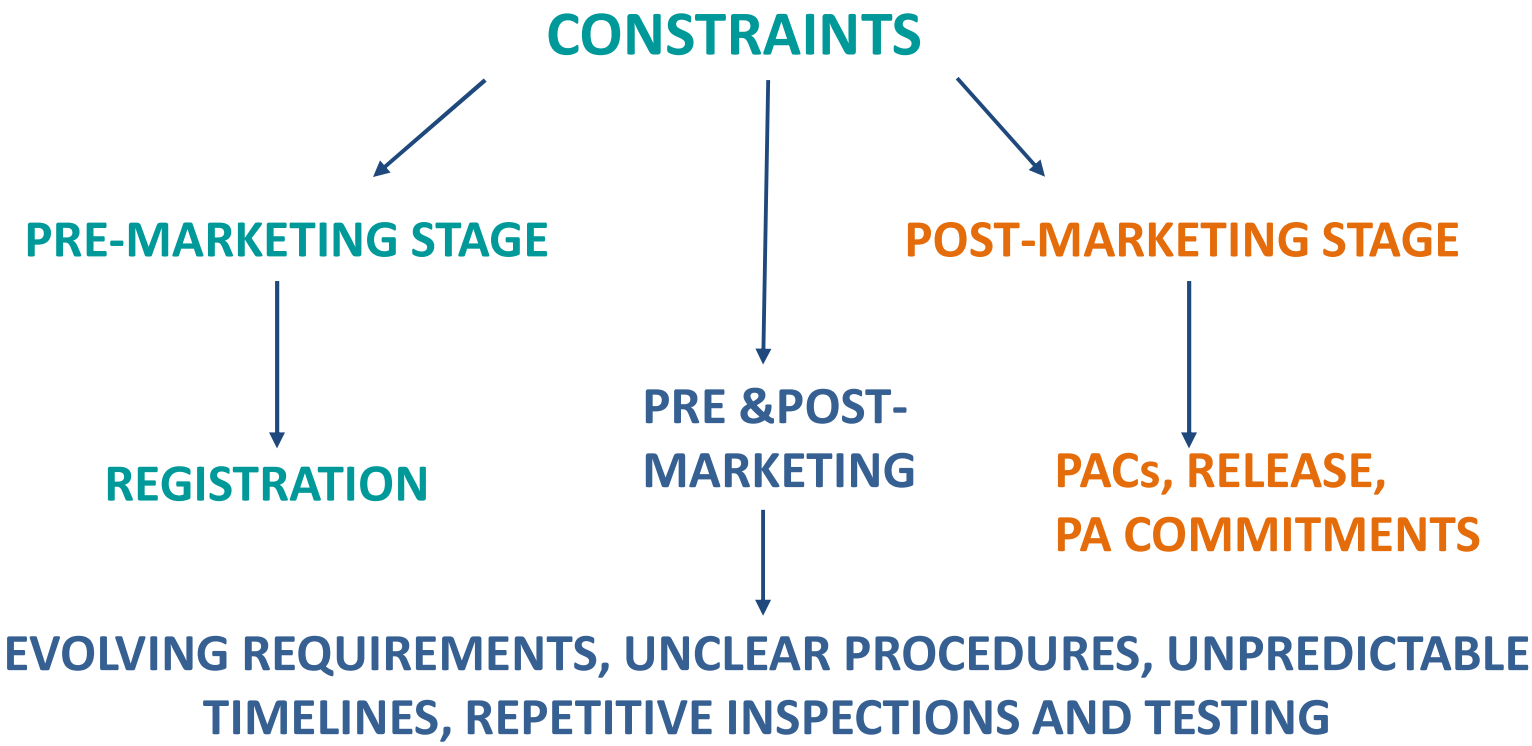
- Explain the challenges regarding vaccine regulation
- Explain DCVMN response in face of challenges
- Activities of the Regulatory Experts Working Group
- Focus on challenges for vaccine registration
- Proposals for improvement
- Relevance of the work performed
- Role of DCVMN member companies and of all immunization stakeholders in implementation of changes

The problem

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



DCVMN Initiatives

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.

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Regulatory Experts Working Group (RWG)

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FOCUS:

1) Identify challenges and opportunities for improvement of the vaccine registration procedures
2) Identify challenges an 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

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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**

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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

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Comparative review of CTD modules from different countries or regions

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

NOTE: For simplicity, the items referring to the application forms were left out of the exercise and addressed separately

Comparative review of CTD modules 2-5 from different countries (2)

CTDs from different countries were considered "different" from the ICH CTD if one of the following situations applied

Requirements country X	Requirements ICH CTD
Item/Topic not required	Item/Topic required
Item/Topic required (Other information)	Item/Topic not required
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

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Calculations of % of similarity and difference

MODULE I

- ✓ % of similarity = $\frac{\text{N° items with similar content or numbering}}{\text{N° items compared}}$ x 100
- ✓ % of difference= 100- % of similarity

MODULE 2-5

- ✓ % of similarity =

= $\frac{\text{N° items with similar content or numbering to ICH (CTD)}}{\text{N° items compared}}$ x 100

- ✓ % of difference= 100- % of similarity

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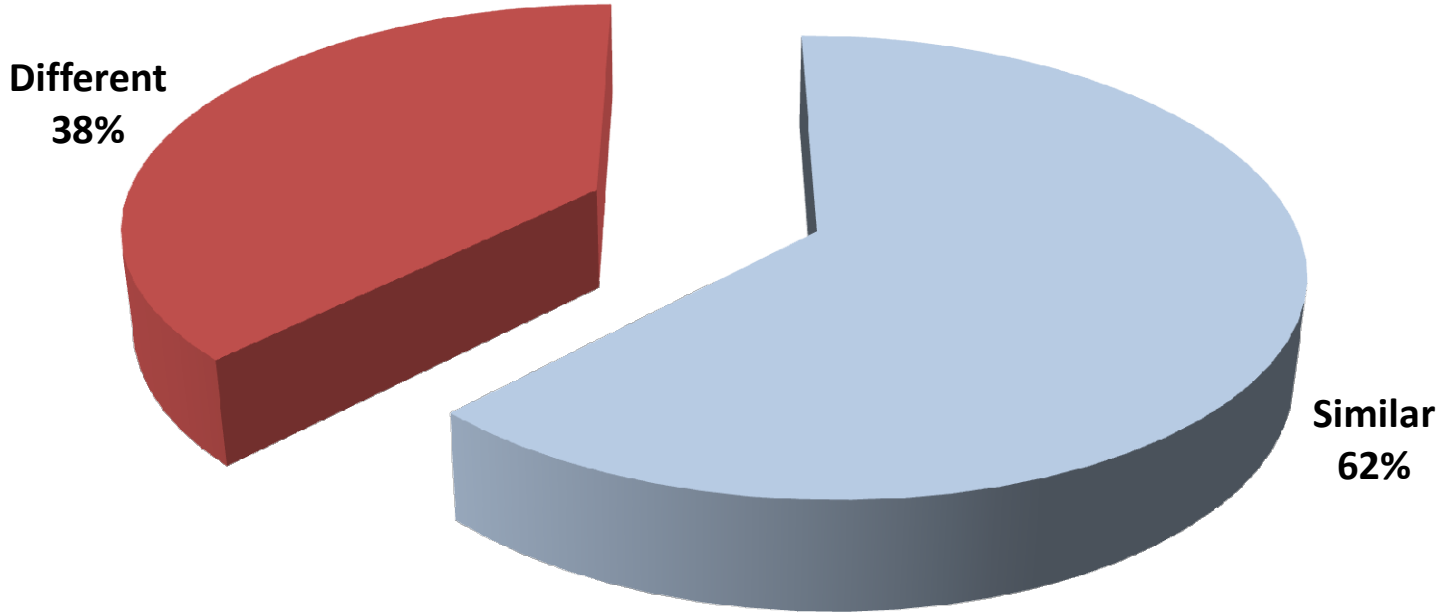
MODULE 1 CONTENT COMPARISON BETWEEN CTDs FROM AUSTRALIA, CHINA, EUROPE, GCC, INDIA, JORDAN, PAHO, TANZANIA, THAILAND, US AND WHO

NON HARMONIZED MODULE



Comparability	Similar	Different	Total
Number of items	189	114	303

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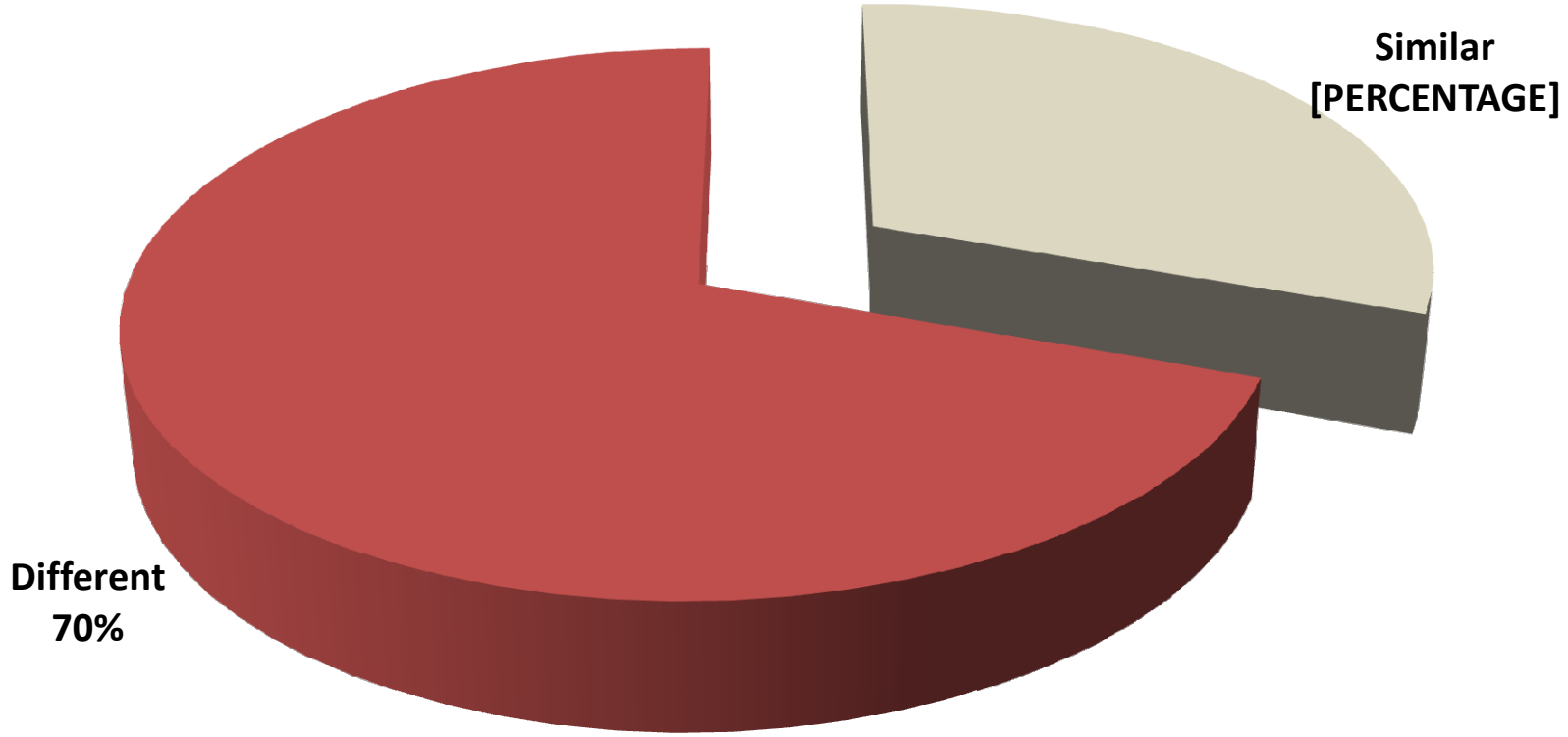
MODULE 1 NUMBERING COMPARISON BETWEEN CTDs FROM AUSTRALIA, CHINA, EUROPE, GCC, INDIA, JORDAN, PAHO, TANZANIA, THAILAND, US AND WHO

NON HARMONIZED MODULE



Comparability	Same	Different	Total
Number of items	92	211	303

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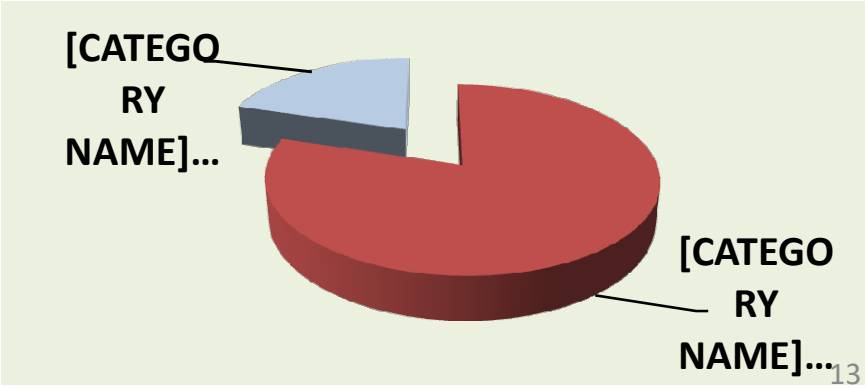
MODULES 2-5 CONTENT COMPARISON: INDIA, JORDAN, PAHO AND THAILAND AGAINST ICH (FDA)

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

ASEAN CTD IS not included in the pie since it is highly similar to the ICH CTD in contents



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MODULES 2-5 NUMBERING COMPARISON: ASEAN, INDIA, JORDAN, PAHO AND THAILAND AGAINST ICH (FDA)

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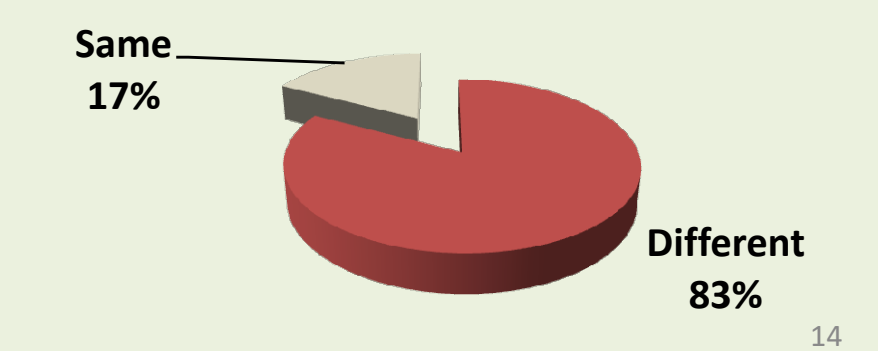
	Number of items PAHO Vs ICH (FDA)	Number of items INDIA Vs ICH (FDA)	Number of items JORDAN Vs ICH (FDA)	Number of items ASEAN Vs ICH (FDA)	Number of items THAILAND Vs ICH (FDA)	Total
Different	286	346	313	366	269	1580
Same	96	69	63	0	102	330
Total	382	415	376	366	371	1910
% similarity	25	17	17	0	27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

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)



Relevance of the difference

- 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
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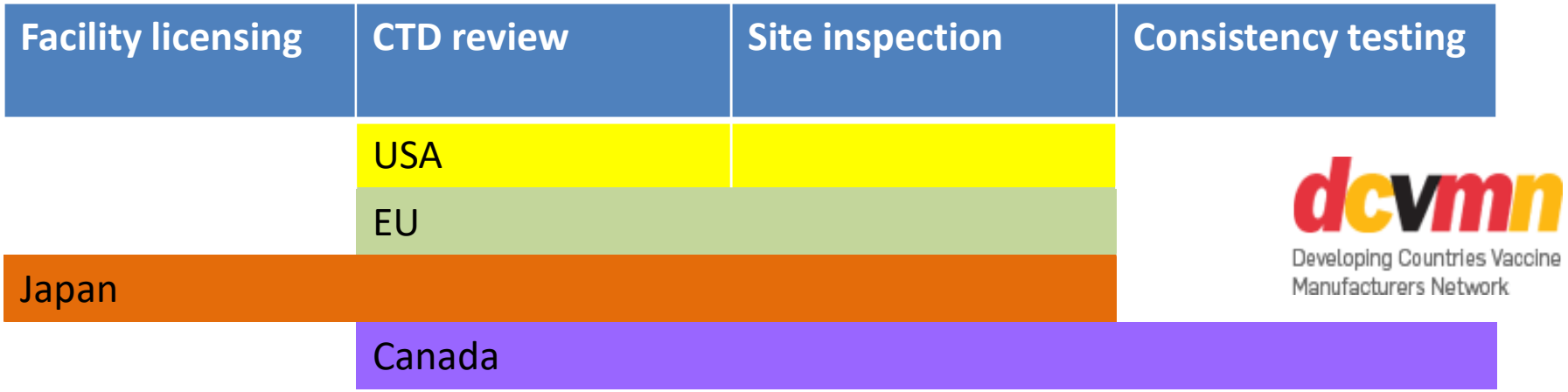
Requirements within ICH founding Countries

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



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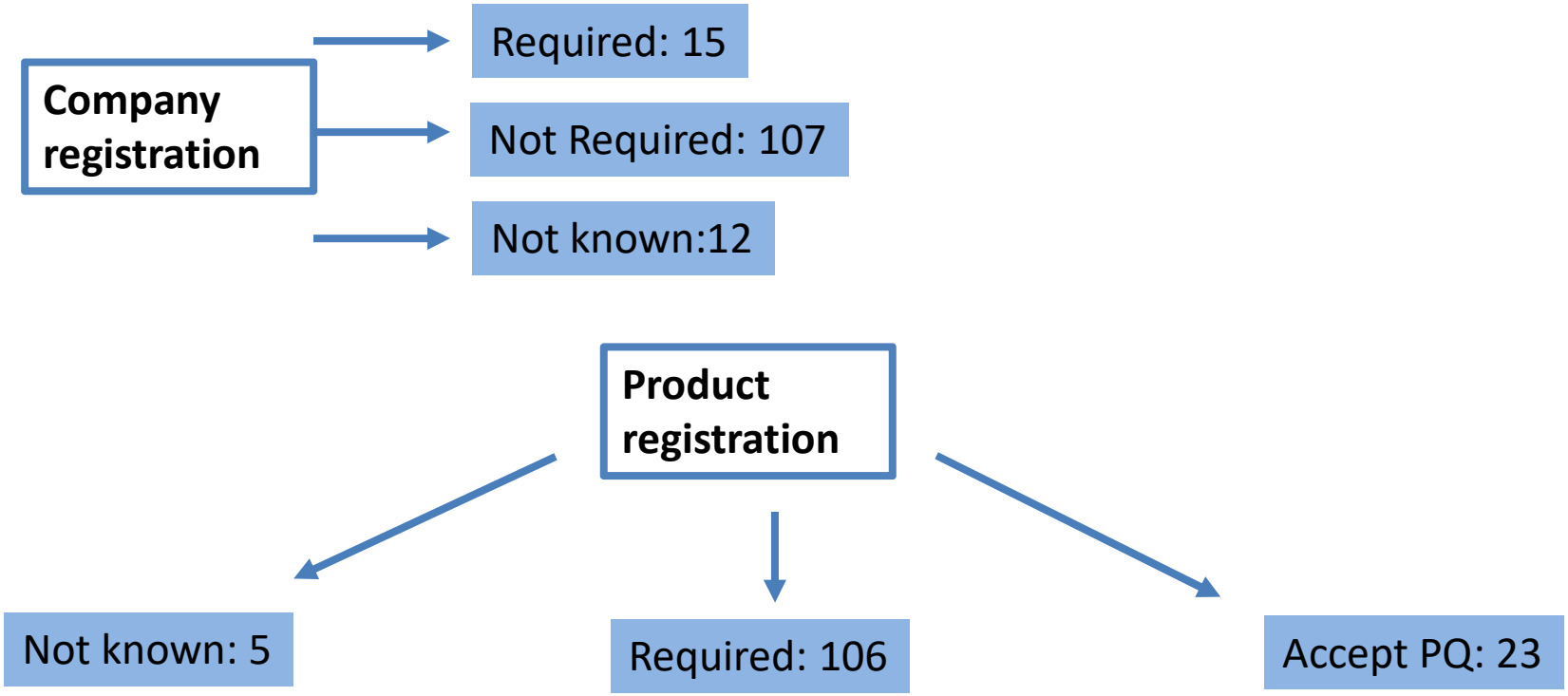
Analysis of Vaccine registration procedures in 134 countries



Countries assessed (supplied through UN agencies) N= 134

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Analysis of vaccine registration procedures in 134 countries (2)

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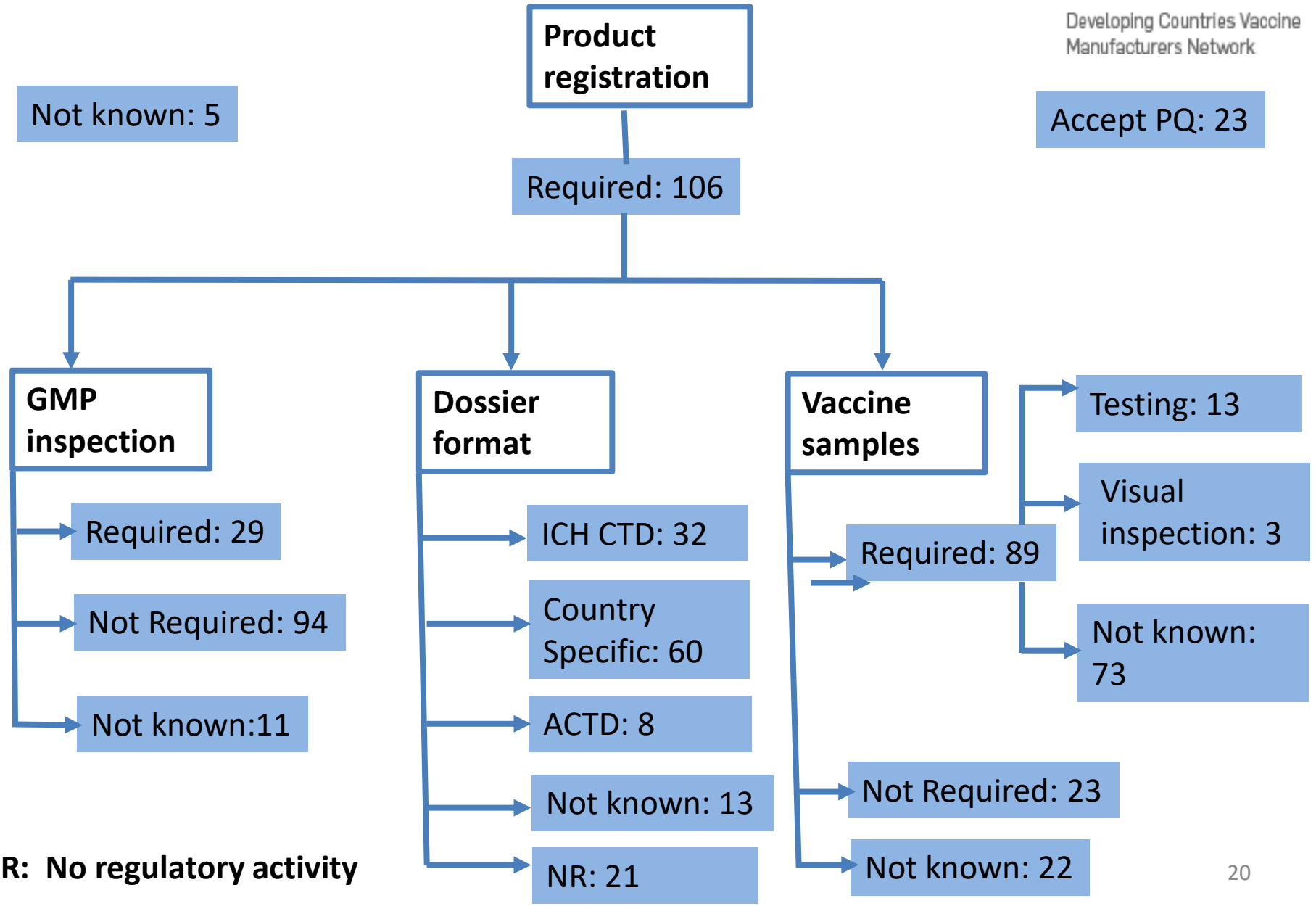

NR: No regulatory activity

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
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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.

Unpredictable timelines

- ✓ 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

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RWG outputs

A- Pre-marketing regulatory activities

DCVMN activities related to vaccine registration

Identified registration challenges in non-producing countries

→ Dellepiane, N, Pagliusi, S, Regulatory Experts Working Group. Challenges for the registration of vaccines in emerging countries: Differences in dossier requirements, application and evaluation processes. N. Dellepiane, S. Pagliusi and Registration Experts Working Group. Vaccine 2018; 36(24): 3389-3396

↓

Made proposals for improvement: alignment of requirements and procedures

→ Dellepiane, N, Pagliusi, S, Regulatory Experts Working Group. Opportunities for improving access to vaccines in emerging countries through efficient and aligned registration procedures: An industry perspective. Vaccine 2019; 37: 2982-2989.

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

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Proposals for improvement

Main Proposals for dossier alignment

- Standard model for M1with 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

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Proposals for improvement (2)

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

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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

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References

- Dellepiane, N, Pagliusi, S, Regulatory Experts Working Group. Challenges for the registration of vaccines in emerging countries: Differences in dossier requirements, application and evaluation processes. N. Dellepiane, S. Pagliusi and Registration Experts Working Group. Vaccine 2018; 36(24): 3389-3396
- Dellepiane, N, Pagliusi, S, Regulatory Experts Working Group. Opportunities for improving access to vaccines in emerging countries through efficient and aligned registration procedures: An industry perspective. Vaccine 2019; 37: 2982-2989.
- World Health Organization. Procedure for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies. WHO Technical Report Series 978, Annex 6; 2013.
- EMA procedural advice for medicinal products intended exclusively for markets outside the European Union under Article 58 of Regulation (EC) No 726/2004 in the context of co-operation with the World Health Organisation (WHO) https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/european-medicines-agency-procedural-advice-medicinal-products-intended-exclusively-markets-outside/2004-context-cooperation-world-health_en.pdf

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- ICH Harmonised Guidelines. Organisation of the Common Technical Document for the Registration of Pharmaceuticals for human use. M4. Current step 4. June 15, 2016.
- ICH CTD http://www.ich.org/products/ctd.html.
- EU Module 1 eCTD Specification. Version 3.0 1. May 2016
- The eCTD specification. Module 1 and regional information V3.2.2. Available at https://ich.org/page/ich-electronic-common-technical-document-ectd-V3.2.2 specification-and-related-files Accessed 20 April 2020
- Ahonkhai, V. Martins, S. et al. Speeding Access to Vaccines and Medicines in Low- and Middle-Income Countries: A Case for Change and a Framework for Optimized Product Market Authorization. PLOS ONE 11(11):1-12; 2016.

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THANK YOU

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