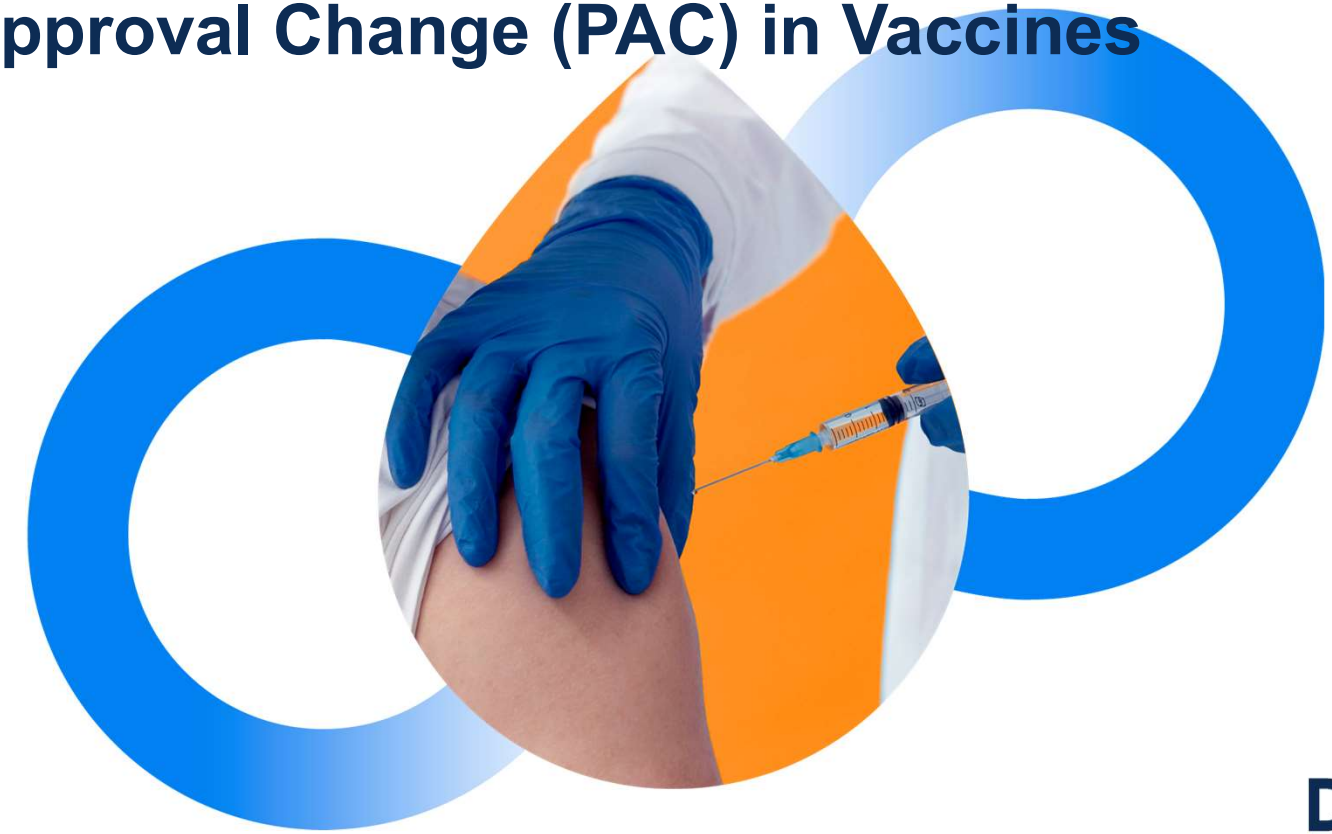
DCVMN Regulatory Affairs Working Group
Post Approval Change (PAC) in Vaccines



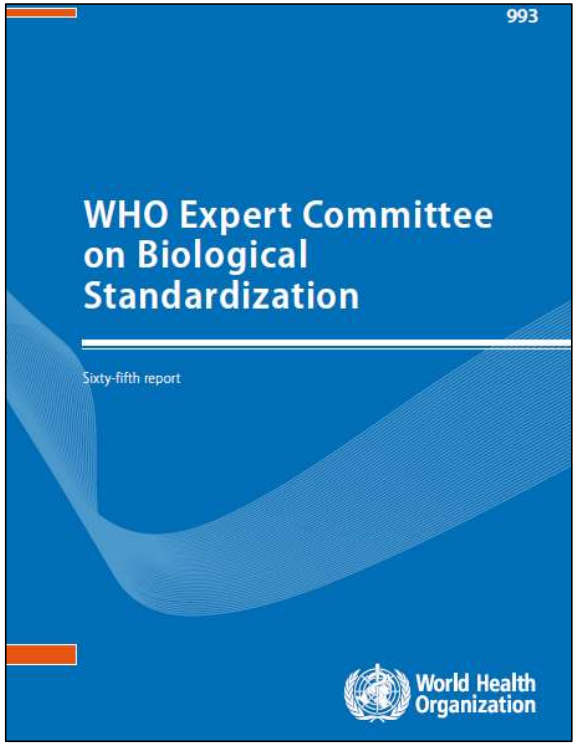
DCVMN
Developing Countries Vaccine Manufacturers Network

General

Topics covered by this presentation:

- WHO Technical Report Series (TRS) 993- Annex 4 “Guidelines on procedures and data requirements for changes to approved vaccines” (January 2015) as a worldwide reference guideline
- Main challenges experienced by manufacturers with PAC in developing countries
  - Paper published in *Vaccine* (August 2020)- Alignment in post-approval changes (PAC) guidelines in emerging countries may increase timely access to vaccines: An illustrative assessment by manufacturers
- Regional situations related to PAC
  - Assessment of developing countries in America (Latam)
  - Proposal to improve situation in America (Latam)

WHO Technical Report Series (TRS) 993- Annex 4 “Guidelines on procedures and data requirements for changes to approved vaccines”



2015

https://www.who.int/publications/m/item/procedures-and-data-requirements-changes-to-approved-vaccines-annex-4-trs-no-993

WHO Technical Report Series (TRS) 993- Annex 4 “Guidelines on procedures and data requirements for changes to approved vaccines”

Annex 4

Guidelines on procedures and data requirements for changes to approved vaccines

WHO Technical Report Series (TRS) 993- Annex 4 “Guidelines on procedures and data requirements for changes to approved vaccines”

- Reporting categories for quality changes
  - **Major quality changes:**
    - Significant potential impact on the quality, safety and efficacy of the vaccine.
    - The MAH (Marketing Authorization Holder) should summit a PAS (Prior Approval Supplement).
    - The MAH should submit a PAS and receive a notification of approval from the NRA before implementing the change.
    - Maximun review period: 6 months
  - **Moderate quality changes:**
    - Moderate potential impact on the quality, safety and efficacy of the vaccine.
    - The MAH should submit a PAS and receive a notification of approval from the NRA before implementing the change.
    - Maximun review period: 3 months

WHO Technical Report Series (TRS) 993- Annex 4 “Guidelines on procedures and data requirements for changes to approved vaccines”

- Reporting categories for quality changes
  - **Minor quality changes:**
    - Minimal potential impact on the quality, safety and efficacy of the vaccine.
    - The changes included in this category may be implemented by the MAH without prior review by the NRA but they must be available for review.
    - Maximun review period: N/A

WHO Technical Report Series (TRS) 993- Annex 4 "Guidelines on procedures and data requirements for changes to approved vaccines"

- An example of PAC for antigens

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
13. Change in equipment used in the antigen manufacturing process, such as:			
a. introduction of new equipment with different operating principles and different product contact material	None	1–6	Moderate
b. introduction of new equipment with the same operating principles but different product contact material	None	1, 3–6	Moderate
c. introduction of new equipment with different operating principles but the same product contact material	None	1–3, 5, 6	Moderate
d. replacement of equipment with equivalent equipment (including filter)	None	1, 5–7	Minor

Conditions

None

Supporting data

1. Information on the in-process control testing.
2. Process validation study reports.
3. Description of the batches and summary of results as quantitative data, in a comparative tabular format, for one (1) commercial-scale batch of the antigen produced with the approved and proposed product contact equipment/ material. Batch data on the next two full-production batches should be made available on request and reported by the MA holder if outside specification (with proposed action).
4. Information on leachables and extractables.
5. Information on the new equipment and comparison of similarities and differences regarding operating principles and specifications between the new and the replaced equipment.
6. Information demonstrating requalification of the equipment or requalification of the change.
7. Rationale for regarding the equipment as similar/comparable, as applicable.

WHO Technical Report Series (TRS) 993- Annex 4 "Guidelines on procedures and data requirements for changes to approved vaccines"

- An example of PAC for final product

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
33. Change involving a final product manufacturer/ manufacturing facility, such as:			
a. replacement or addition of a manufacturing facility for the final product (including formulation/ filling and primary packaging)	None	1–7	Major
	1–5	1–3, 5–8	Moderate
b. replacement or addition of a secondary packaging facility, a labelling/storage facility or a distribution facility	2, 3	1–3	Minor
c. deletion of a final product manufacturing facility	None	None	Minor

Conditions

1. The proposed facility is an approved formulation/filling facility (for the same company/MA holder).
2. There is no change in the composition, manufacturing process and final product specification.
3. There is no change in the container/closure system and storage conditions.
4. The same validated manufacturing process is used.
5. The newly introduced product is in the same family of product(s) or therapeutic classification as the products already approved at the site, and also uses the same filling process/equipment.

Supporting data

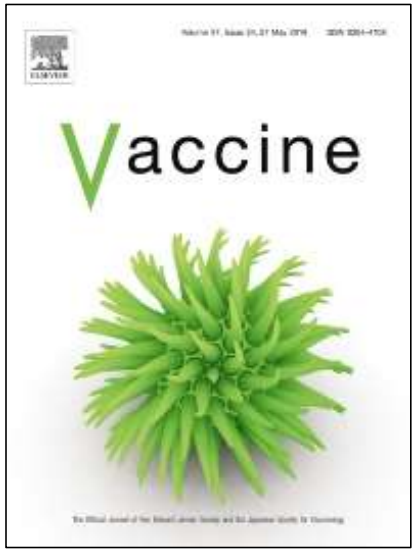
1. Name, address and responsibility of the proposed production facility involved in manufacturing and testing.
2. Evidence that the facility is GMP compliant.
3. Confirmation that the manufacturing process description of the final product has not changed as a result of the submission (other than the change in facility), or revised description of the manufacturing process.
4. Comparative description of the manufacturing process if different from the approved process, and information on the controls performed at critical steps of the manufacturing process and on the intermediate of the proposed final product.

WHO Technical Report Series (TRS) 993- Annex 4 "Guidelines on procedures and data requirements for changes to approved vaccines"

- There is a clear:
  - Classification of the different types of PACs (reporting category).
  - Conditions to be fulfilled.
  - Supporting data to be provided to NRAs.
  - Review period by NRAs

Paper published in *Vaccine* (August 2020)- Alignment in post-approval changes (PAC) guidelines in emerging countries may increase timely access to vaccines: An illustrative assessment by manufacturers

Authors: Nora Dellepiane, Sonia Pagliusi, Prashant Akut, Sebastian Comellas, Norbert De Clercq, Shubhangi Ghadge, Thierry Gastineau, Mic McGoldrick, Ida Nurnaeni and Lorenz Scheppler



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Alignment in post-approval changes (PAC) guidelines in emerging countries may increase timely access to vaccines: An illustrative assessment by manufacturers

Nora Dellepiane [a], Sonia Pagliusi [b,*], Prashant Akut [c], Sebastian Comellas [d], Norbert De Clercq [e], Shubhangi Ghadge [f], Thierry Gastineau [g], Mic McGoldrick [h], Ida Nurnaeni [i], Lorenz Scheppler [j], Regulatory Experts Working Group

[a] QRB Consultants Sàrl, 33, Chemin de la Petite Fontaine, 1270 Trélex, Switzerland
[b] DCVMN International, Route de Crassier 7A, 1262 Nyon, Switzerland
[c] Former Serum Institute of India Ltd, India
[d] Sinergium Biotech, Argentina
[e] GSK Vaccines, Belgium
[f] Serum Institute of India Ltd, India
[g] Sanofi Pasteur, France
[h] Merck Sharp & Dohme, Corp, United States
[i] PT Biofarma, Indonesia
[j] Janssen Vaccines, Switzerland

https://www.sciencedirect.com/science/article/pii/S259013622030022X

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Comparison of the PAC regulations and guidelines from 33 developing countries

- Findings
  - Significant variability of requirements and lack of predictability of timelines for regulatory review and approval by National Regulatory Authorities (NRAs).
  - Multiple data packages have to be prepared for submission to different authorities, generating a complex regulatory environment.
  - The timelines for approval by individual NRAs are variable, which results in manufacturers keeping various stocks of vaccines produced in accordance with the various approved specifications and procedures, in the different countries. This can seriously affect timely availability of vaccine in those countries.
  - WHO TRS 993- Annex 4 provides a consensual framework for alignment but it is still underused.

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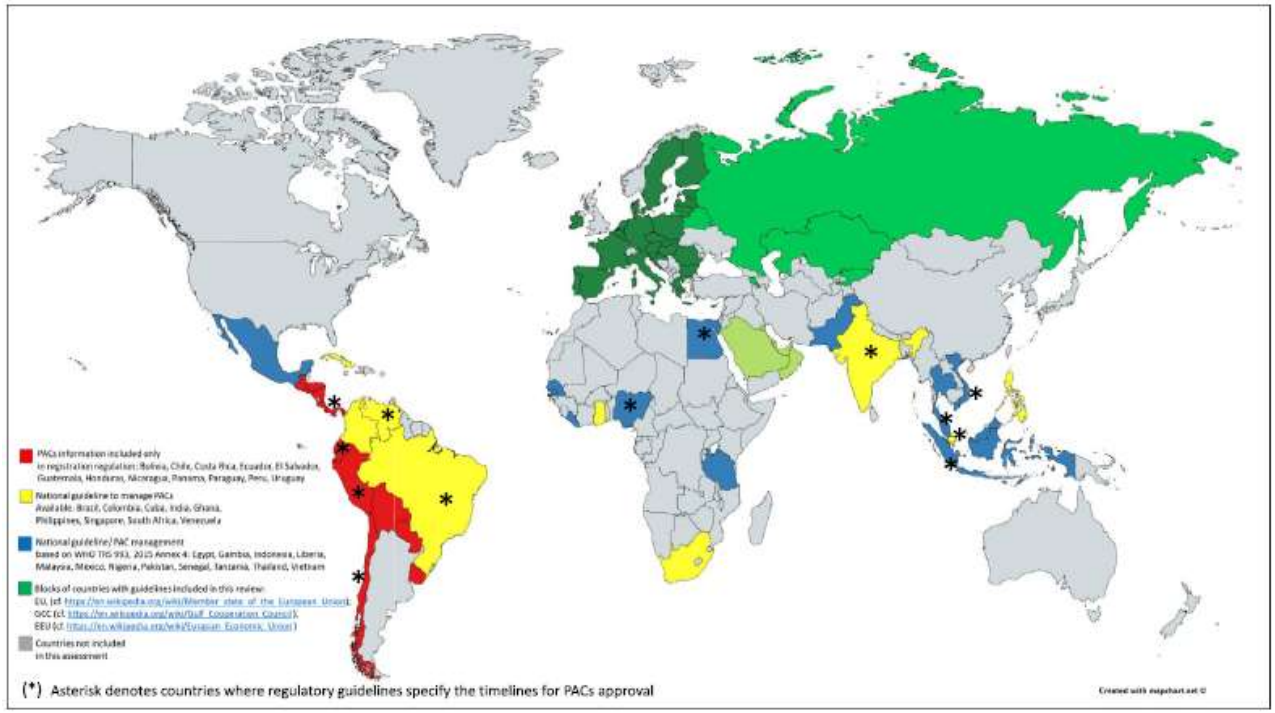

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- Conclusions

To secure the timely supply of vaccines to the populations globally, the efficient management of PACs asks for prompt action with respect to:

- alignment/harmonization of requirements (WHO TRS 993- Annex 4).
- reliance on established reliable mechanisms.
- official establishment of timelines for review and approval of changes and compliance with such commitment.
- transparent communication of the procedures in place, and
- combinations of the above proposed options or others that may be proposed, to reduce the number of PACs to be reported to NRAs.

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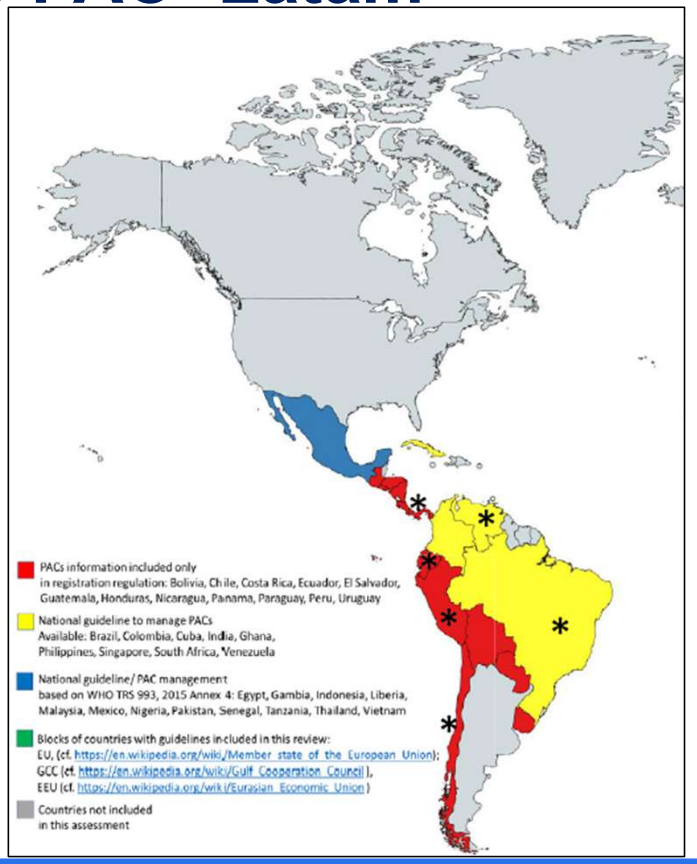
- Conclusions (continuation)

To secure the timely supply of vaccines to the populations globally, the efficient management of PACs asks for prompt action with respect to:

- reliance on both the review and approval of PACs by the NRA in the country of manufacturing or on the review performed by other NRAs recognized by WHO as stringent.

Regional situations related to PAC- Latam

Assessment of developing countries in America



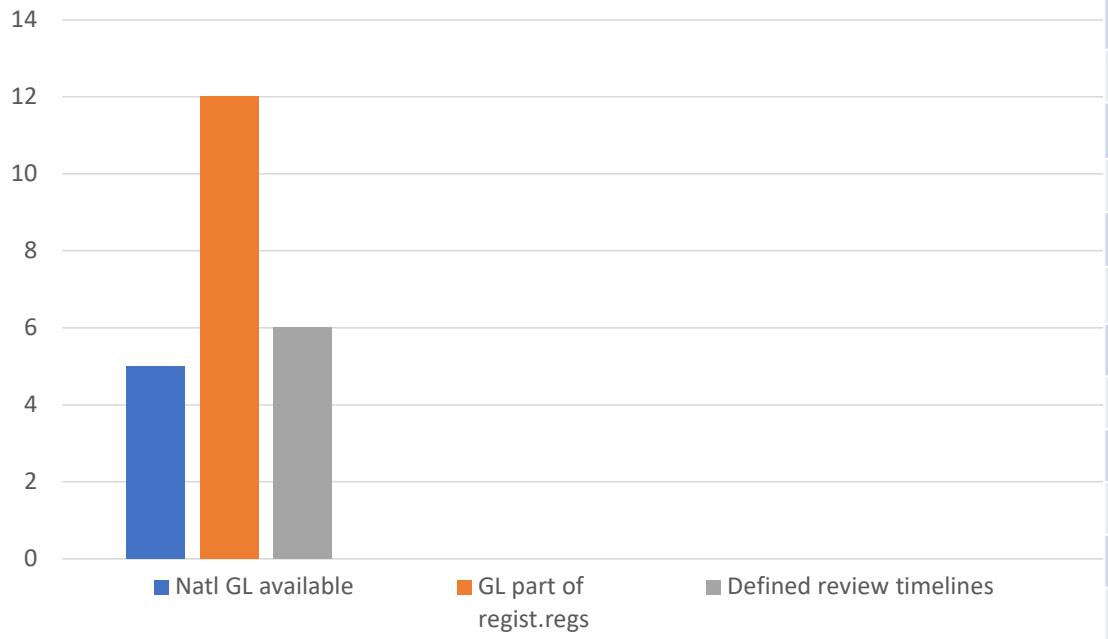
Assessment of developing countries in America

Latam- Summary of the situation:

- Only for countries manufacture vaccines:
  - Argentina
  - Brazil (by far is the most important manufacturer in the region)
  - Cuba
  - Mexico
- NRAs with more expertise in evaluating vaccine PACs:
  - NRAs level IV for PAHO: ANMAT (Argentina), ANVISA (Brazil), ISP (Chile), INVIMA (Colombia), CECMED (Cuba) and COFEPRIS (Mexico)
  - Reference NRAs in vaccine for PAHO: ANMAT (Argentina), ANVISA (Brazil), CECMED (Cuba) and COFEPRIS (Mexico)
  - The rest of the NRAs have variability in their expertise to evaluate vaccines PACs.

Assessment of developing countries in America

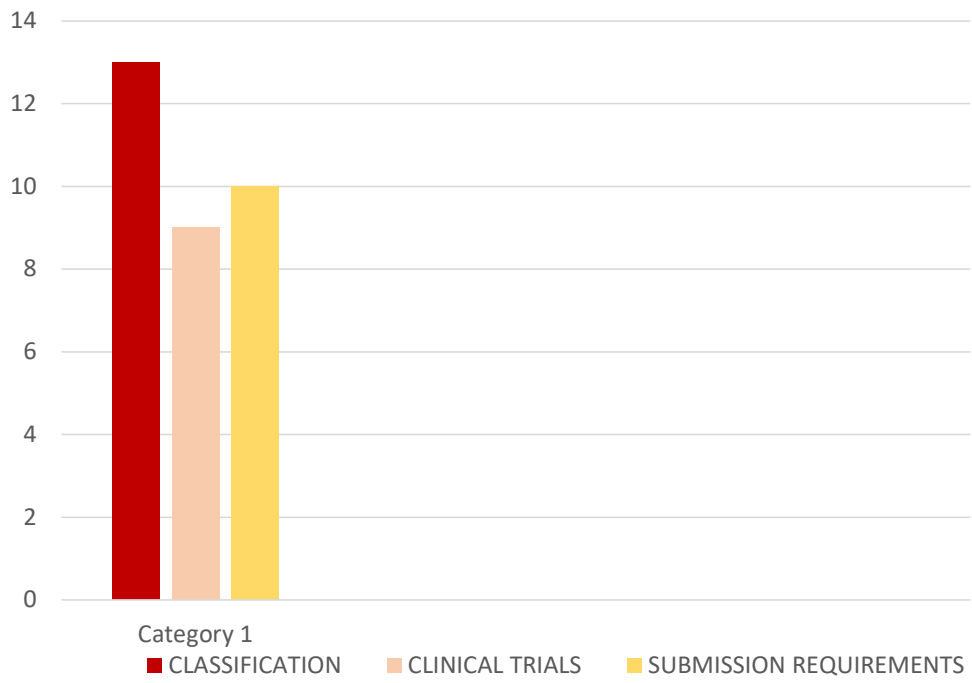
Availability of guidelines (GL) for PACs in 17 LATAM countries



Natl GL (5)	Regist Regs (12)	Def. Timelines (6)
Brazil	Bolivia	Brazil
Colombia	Chile	Chile
Cuba	Costa Rica	Ecuador
Mexico	Ecuador	Panama
Venezuela	El Salvador	Peru
	Guatemala	Venezuela
	Honduras	
	Nicaragua	
	Panama	
	Peru	
	Paraguay	
	Uruguay	

Assessment of developing countries in America

Procedures for post-approval changes (PACs) in 17 LATAM countries



Classification (13)	Clinical Trials (9)	Submission requirements (10)
Brazil	Brazil	Brazil
Chile	Chile	Chile
Colombia	Colombia	Colombia
Costa Rica	Costa Rica	Costa Rica
Cuba	Cuba	Cuba
Ecuador	Ecuador	Ecuador
El Salvador	Mexico	Mexico
Guatemala	Panama	Panama
Honduras	Venezuela	Peru
Mexico		Venezuela
Nicaragua		
Peru		
Venezuela		

Assessment of developing countries in America

Latam- Summary of the situation:

- Overview of PAC regulation:
  - Only Mexico has adopted TRS 993 Annex 4.
  - Argentina will adopt EMA regulation to manage PAC soon.
  - There are countries with a national guideline to manage PACs (in yellow in the map).
  - There are countries with PAC information included only in regulation of registration of medicines or vaccines (in red in the map).
  - (*) asterisk denotes countries where regulatory guidelines specify the timelines for PACs approval.

Assessment of developing countries in America

Latam- Summary of the situation:

- Complex context in Latam:
  - Very low adoption TRS 993 Annex 4.
  - Lack of harmonization of PAC regulation among countries.
  - Low adoption of Reliance concept to avoid redundant evaluation for NRAs.
  - Variability in the level of expertise of the NRAs to evaluate vaccine PACs.

Thank You

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Developing Countries Vaccine Manufacturers Network