Post-approval Changes/Variations

Thursday 14 November 2024

1330 – 1500 hrs Jakarta Time

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Session Objectives

- The objective of the session is to provide an overview of the post-approval change management for medical products approved under the collaborative registration procedure from the perspective of WHO, NRAs and industry, as well as to provide recommendations on efficient PAC management using reliance.

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Session Overview

Moderator: Marie Valentin, Team Lead, Facilitated Product Introduction, WHO

Speakers:

- Sunday Kisoma, Technical Officer, Facilitated Product Introduction, WHO
- Nyasha Maregere, Consultant, Facilitated Product Introduction, WHO
- Richard Kasonogo, Senior Dossier Assessor, Tanzania Medicines and Medical Devices Authority (TMDA)
- Evelyn Paintsil, Regulatory Officer, Food and Drugs Authority (FDA), Ghana
- Janis Bernat, Director of Scientific & Regulatory Affairs, International Federation of Pharmaceutical Manufacturers and Associations (IFPMA)

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Session outline

The session will cover:

- Current processes for PAC management for medical products by WHO for PQ CRP and SRA CRP products including the scope of PAC in this context
- Current PAC management for PQ and SRA CRP by NRAs including available guidelines, documentation required, timelines and assessment approaches
- Opportunities for improved PAC management
- Industry experiences with PAC management using reliance approaches/mechanisms such as CRP
- Recommendations/proposals for PAC management for the different CRP pathways – WHO, NRAs and industry

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Session Layout

- Introduction to the session, objectives and speakers - Moderator (5min)
- Post Approval Changes Management for PQ CRP – WHO (10 min)
- Post Approval Changes Management for SRA CRP – WHO (10 min)
- Post Approval Changes Management for CRP – TMDA (10 min)
- Post Approval Changes Management for CRP – FDA, Ghana (10 min)
- Post Approval Changes Management – Industry perspectives (20 min)
- Questions and answers - All (30 minutes)

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Post Approval Changes – WHO PQ CRP

Sunday Kisoma
Technical Officer,
WHO/MHP/RPQ/REG/FPI

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Management of Post approval changes in CRP

WHO/PQT and participating NRAs receive applications for the same pharmaceutical or vaccine product.

In CRP context, the same product is characterized by:

- the same product dossier;
- the same manufacturing chain, processes, control of materials and finished product, and in the case of vaccines also by the same batch release scheme;
- the same active ingredient and finished product specifications;
- the same essential elements of product information

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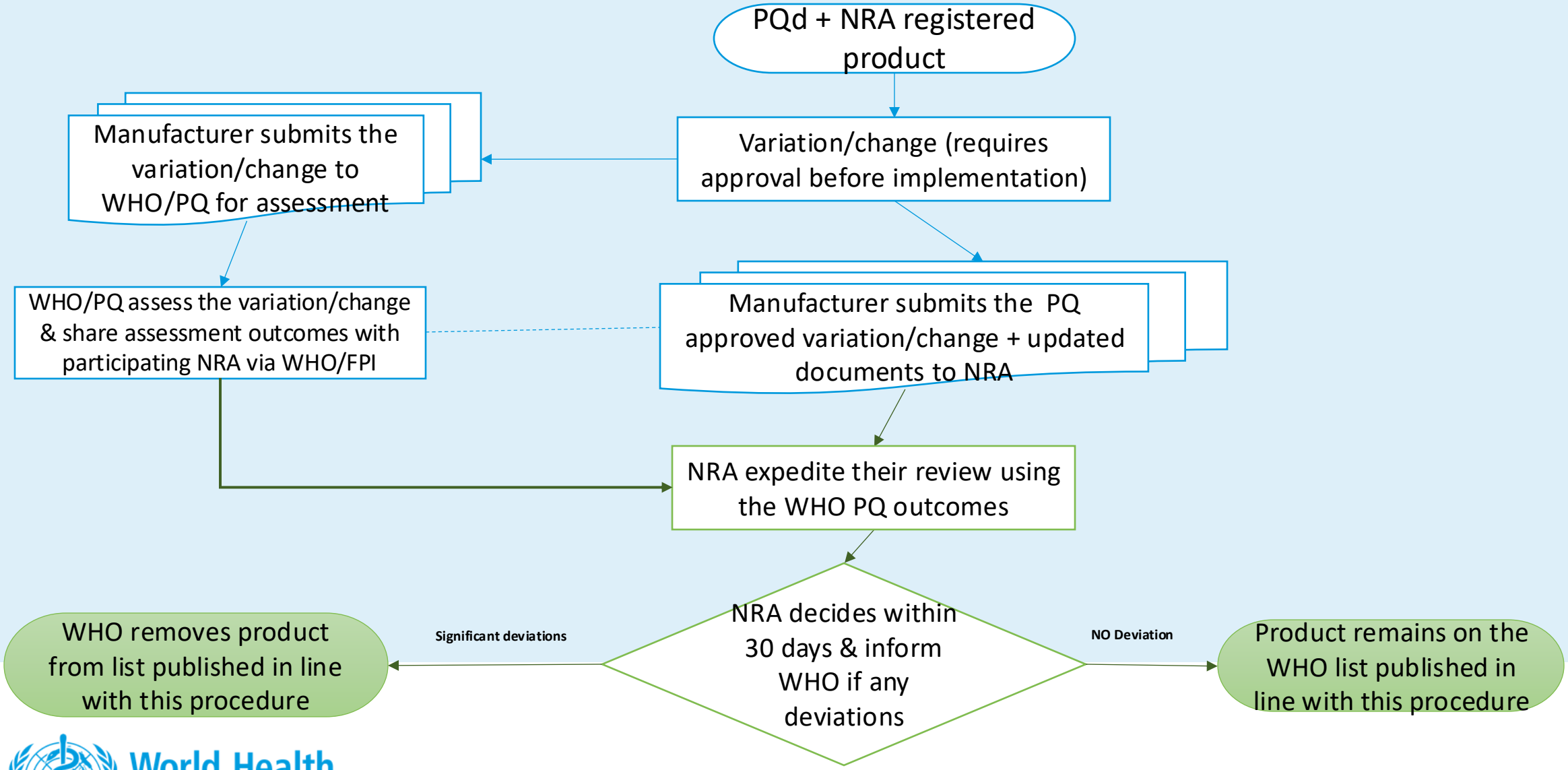
Management of Post approval changes in CRP



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Principles

- **Submission and handling of variations in the context of CRP**
- **The main principle for handling variations in the context of CRP or reliance-approaches**
- **Classification of variations**
- **Managing the variations**
- **Processing variations by the national regulatory authorities and communication to WHO**

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Pain points

- Harmonization : variations requirements, classification, documentation requirements
- Consesus on depth and extent of review among regulators?
- Report everything vs available resources?
- Many variation files for same product, at different status
- Recommendations from Harmonization initiatives, joint assessments and work sharing
- Longer approval timelines
- NRA responsiveness
- In country submissions, numbers and records

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To consider

Adapt WHO and/or International PAC Guidelines

Pre – approval applications : Major Post PQ changes

Pre – approval application : Vmin, involving e. g formulation, label, FPP manufacturing process, scale up

Notifications: Vmin (rest) and Notifications (IN, AN)

Notifications : admin changes

Lessons from PAC Pilots

Consultation and CRP GL

Enforce/updated legal requirements?

Harmonization

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Discussion

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Thank you

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Post Approval Changes/Variations Procedure – SRA CRP

Nyasha Maregere
Consultant, Facilitated Product Introduction Team
WHO - HQ

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Post Approval Changes/ Variations

- A change to any aspect of a medicine, including but not limited to, the change of use of a starting material, a change to formulation, method and site of manufacture, specifications for the finished product and ingredients, container and container labelling and product information.
- Includes CMC changes, labelling updates based on additional safety and efficacy data
- Urgent safety updates are not within the scope of this discussion – NRAs should be notified in line with existing commitments/requirements

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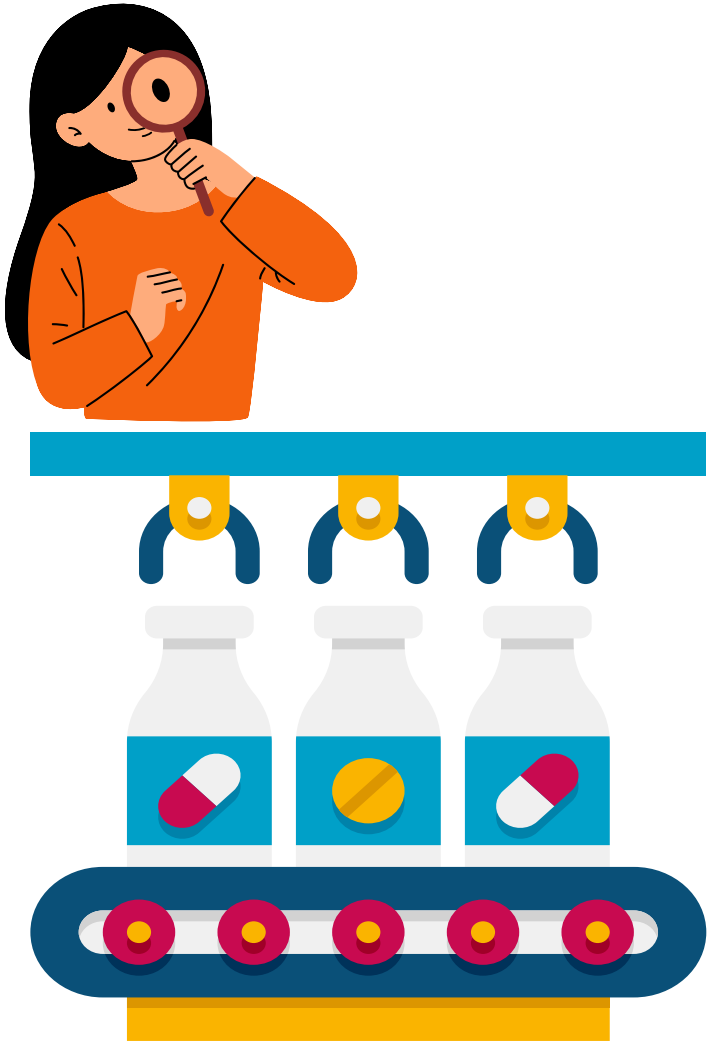
PAC management – why this discussion

- PACs affect medicines supply when prior approval before implementation is a requirement
  - Regulatory processes should have predictable timelines to allow appropriate planning and avoid disruption of supply
- NRAs receive many variations in their national processes with limited resources
- For innovative products, additional quality and clinical/safety data is still being received
- Long timelines for approval of variations documented for various processes worldwide – need for effective management



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SRA CRP Guideline: PAC management

SRA Approved product

Product submitted to NRA for approval under CRP

For this Procedure, the same medicine is characterized by:

- the same qualitative and quantitative formulation;
- the same manufacturing site(s)[6] for API and FPP including specific block(s)/unit(s), chain, processes, control of materials and final product, and in the case of vaccines also by the same batch release scheme;
- the same specifications for excipient, API and FPP;
- the same essential elements of product information.[7]

- Product sameness is the underlying principle of CRP
- Significant deviations e.g. different manufacturing sites ≠ same product
- Significant deviations can be reason for non-applicability of Procedure

[6] "Sameness" of the manufacturing sites for APIs and FPPs means that the specific site must be approved by the reference SRA for the specific product under consideration and included as part of the marketing authorization in the reference SRA country. Any additional sites, regardless of their GMP status, are not acceptable under this procedure. Any changes or variations to include additional sites should be approved by the reference SRA before inclusion in the submission to the participating NRAs.

[7] The essential elements of product information include the indications, contraindications, posology (dosing), special warnings and precautions for use, adverse reactions, storage conditions, primary packaging and shelf life. For pharmaceutical products, differences in brand name, the name of the applicant, language, format and degree of detail of the product information, labelling of primary, secondary and tertiary packaging, among others, are not considered essential for the purposes of this Procedure. The language of the product information may be different as long as the information content is the same as that approved by the reference SRA.

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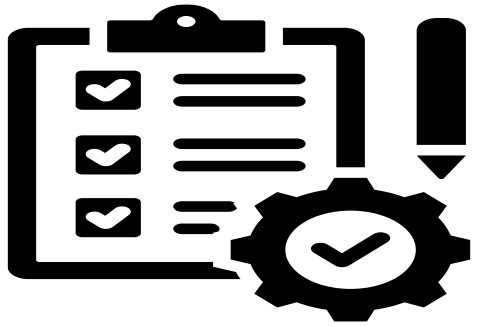
SRA CRP Guideline: PAC management (2)

Variations of local relevance

- Submitted in line with local requirements



Variations under assessment by SRAs at time of submission to NRA

- Should be listed in Appendix 4/QIS SRA
- 3 options proposed for NRAs:
  - Grant MA with conditional approval of variations
  - Defer MA decision until SRA approval – no longer ideal
  - Register product based on current SRA-approved conditions & submission of variations after

B9. List of variations pending in the reference SRA up to the date of verification

Variation number	Variation	Type of variation according to reference SRA regulations

Variations approved by reference SRA after national approval is granted

- To be submitted to NRA within 30 calendar days of approval by reference SRA unless justified
- Submitted with updated, validated QIS-SRA and evidence of approval/acceptance by SRA
- NRA Regulatory decision within **30 days**

Experiences under SRA CRP – WHO

- Limited data on variations submitted to NRAs through SRA CRP
- One case:
  - A minor variation approved by SRA while product was still pending in some relying countries and approved in others
  - NRAs that had granted approval/registration were notified of variation and access to updated, validated QIS shared – reliance implemented
  - Manufacturer engaged NRAs still assessing application for registration on preferred approach:
    - manufacturer to update dossier pre-approval and the NRA to register according to latest information **or**
    - NRA to only accept submission of variation after initial approval
  - Different approaches preferred by NRAs
  - Observations:
    - Requires additional resources for coordination of information sharing activities
    - Need for balance between facilitating reliance without additional steps

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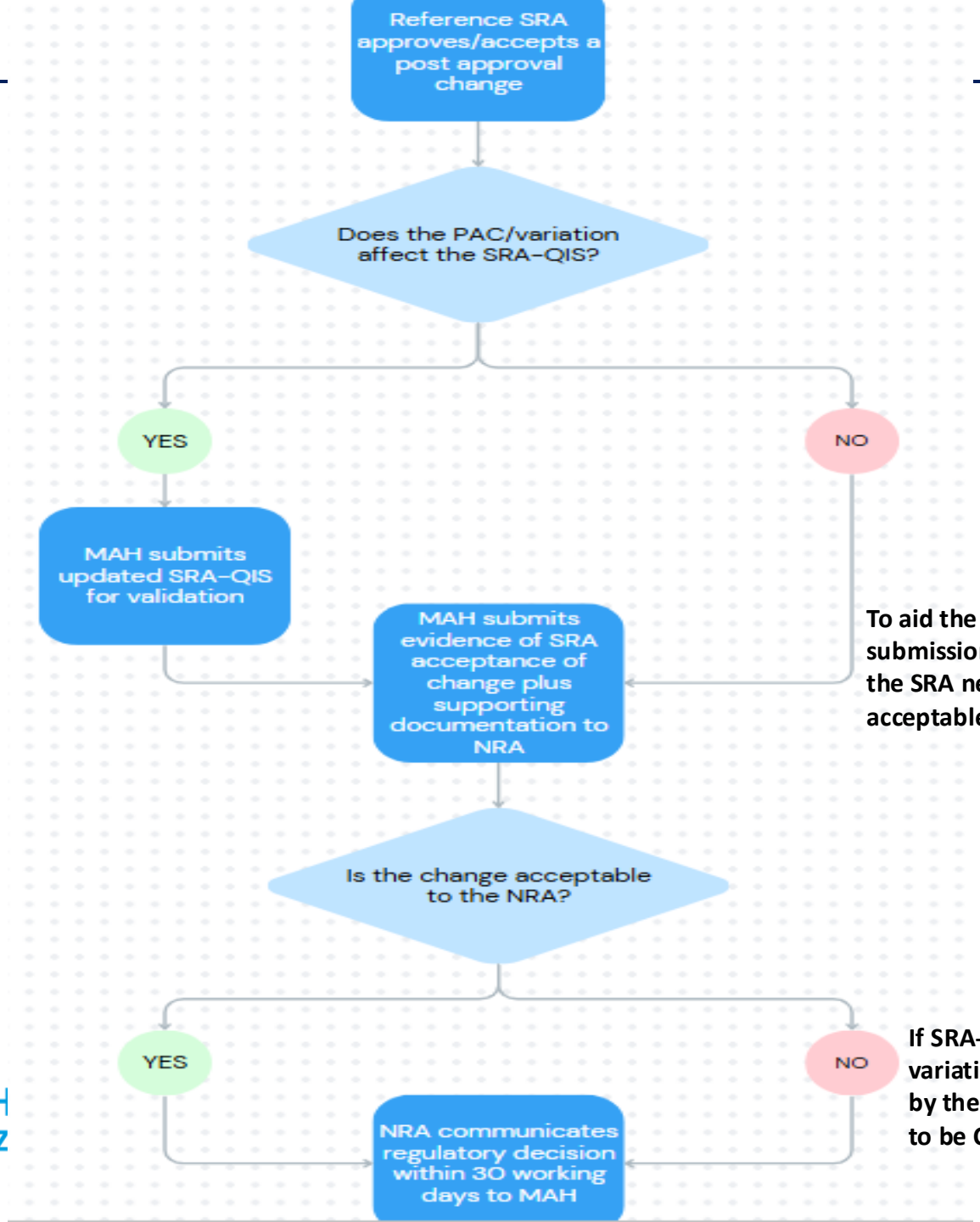
PAC Proposal



To aid the process, the submission package to the SRA needs to be acceptable to NRA

If SRA-approved variation is rejected by the NRA, it ceases to be CRP product

- WHO to notify NRAs of an updated, validated QIS as soon as it is available on the WHO-NRA information sharing platform
- WHO will request a list of all SRA approved variations (e.g. quality, labelling) from manufacturers every 6 months/12 months (?)
- List will be uploaded on NRA-WHO information sharing platform
- NRAs can utilise this list based on their requirements for variations approval
- Manufacturers to submit variations in line with any applicable local requirements
- Urgent safety updates are **not** within the scope of this proposal

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Recommendations

- Implementation of reliance throughout lifecycle of products
  - Identify CRP products and ensure all regulatory functions are aware of the Procedure and the timelines
- Risk-based approach - identify the best fit for your NRA:
  - Level of assessment
  - Required documentation
- Incorporate CRP PAC management and timelines in NRA procedures
- Use of existing resources in implementation of reliance e.g. Model acknowledgement/approval letter in **WHO Good practices of NRAs in implementing CRP for medical products** guideline (Appendix 6)
- Harmonization and increased visibility of variation requirements – classification, required documentation
- Continued experience-sharing with all stakeholders

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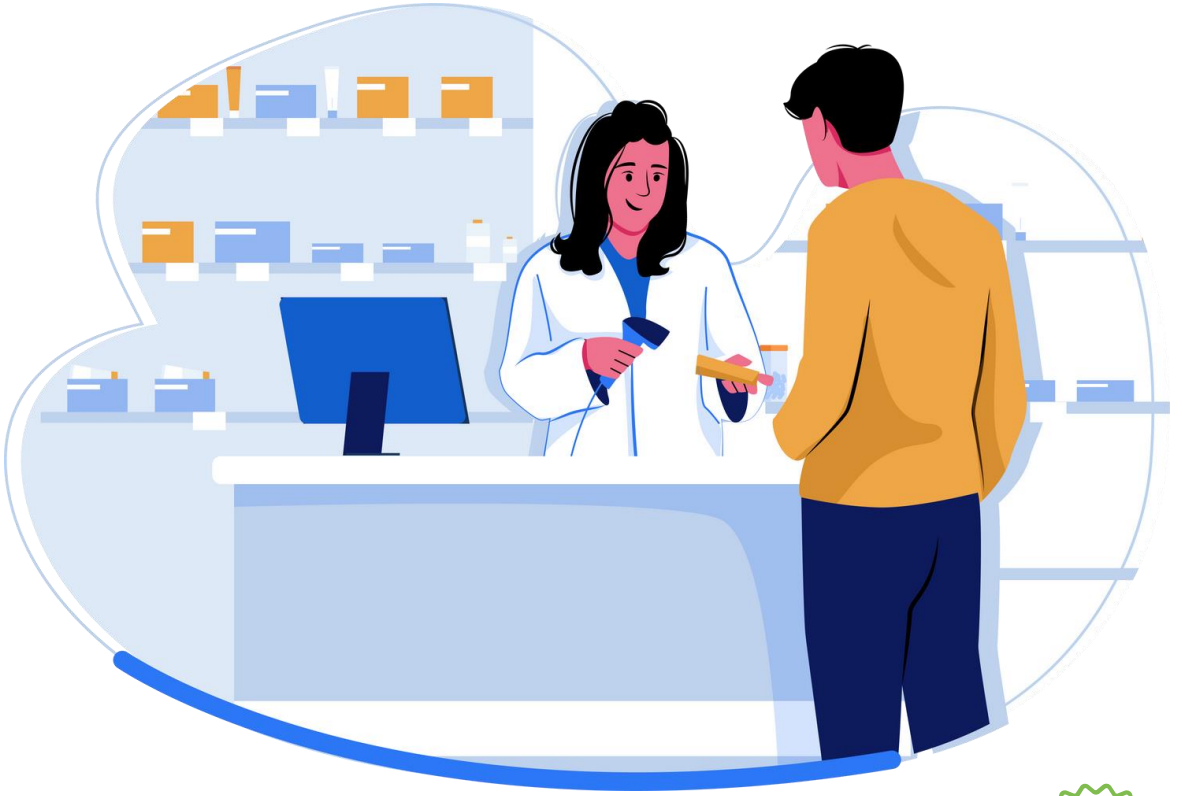
Next steps

- Continued discussions on effective PAC management
- Refinement of PAC procedures under CRP – based on stakeholder feedback



Continued patient access to quality-assured medical products

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Thank you

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POST APPROVAL CHANGES (PAC) –EXPERIENCE FROM TMDA

Presenter's name: RICHARD KASONOGO
Title: SENIOR DRUG REGISTRATION OFFICER
Affiliation/Institution: TMDA

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Outline

- Types of Alterations/Variation in Pharmaceuticals
- Variation Applications for WHO/SRA approved products
- Why do we use reliance on PAC.
- Challenges
- Way forward

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Types of Post Approval Changes

- Immediate notification (IN): Do not require prior acceptance, but must be notified to Authority immediately after implementation. These variations are considered approved if there is no objection from TMDA within 2 months of application submissions.
- Annual notification (AN): ANs should be submitted to TMDA within 12 months of implementation of the changes. AN will be considered as one minor variation and will be charged as one minor variation.

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Types of Post Approval Changes

- **Minor changes: H**ave minor effects on the overall safety, efficacy and quality of the FPP. examples: extension of shelf life, change in batch size, change in MAH (N) Replacement or addition of a packaging site of the FPP.
- **Major changes**: Have major effects on the overall safety, efficacy and quality of the FPP. For these changes, prior acceptance by TMDA is required. **Example:** Change in immediate packaging of FPP, change in composition of FPP involving addition and removal of certain excipients.

- NB: The minor and major changes can only be implemented on receipt of a letter of acceptance from the Authority.

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Type of Variation Applications to considered for product approved through CRP –SRA & WHO –SRA Products

- These variations follow under **Immediate Notifications (IN**): The applicant has to provide proof of variation approval from SRA/WHO to TMDA (section 2.0 of the variations guidelines).
- The Authority needs to be notified immediately and implementation may start immediately at the time of submission. It may be considered accepted if 2 months have passed without any communication from the Authority.
- Submitted IN will be considered as one minor variation and will be charged as such as per TMDA's Fees and Regulations which are in force at the time of submission.

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Why a reliance route?

- Reduce procedural timelines to maintain supply and avoid delays in access to the product on variation applications.
- Apply the principles of reliance as a tool to improve the efficiency of regulatory oversight, representing a simplification of the management of PAC.
  - Development/ contribution to the harmonization of regulatory/ quality requirements and processes
  - Help alleviate the many challenges including an increased regulatory workload, resource limitations.
- Use of reliance principles/ mechanisms for lifecycle submissions is encouraged, advocated and supported by various national and supranational agencies.

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These tiger moths are from the same family

What variations can you see?

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Challenges

- Market Authorization Holder do not submit approved variations by WHO/SRA to TMDA as evident through WHO monthly communication.
  - NRA might be thinking that, they are dealing with defferent products compared to the one prequalified by WHO/approved by SRA.
  - It might lead to decrease in trust between NRA and manufacturers.

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Way forward

- Requires a commitment of both regulators, manufacturers and collaborating partners (WHO);
- For smooth communication of SRA/WHO-approved variations, there is a need to streamline the approval notification those come from the SRA/WHO to Manufacturer.

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Thank you

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Management of Post Approval Changes for Medical Products for PQ CRP and SRA CRP Products in Ghana

Evelyn A Paintsil
Regulatory Officer/Focal person for CRP
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Outline

- Legal Mandate
- Types of Variations
- Regulatory tools for PAC/Variations
- Current Processes for the management of PAC for PQ CRP and SRA CRP products
- Current Measures for Process Improvement
- Recommendations

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Legal Mandate

- In Ghana the legal mandate for PAC changes is found in the **Public Health Act 2012, Act 851, Section 119(3)**
- **A person responsible for the registration of a drug , herbal medicinal product, cosmetic, medical device or household chemical substance who fails to inform the Authority of a change in the information submitted for its registration commits an offence.**

- **Guidelines on Variations**
- Classify changes that may occur related to all the major sections of a dossier, to understand the considerations necessary to assess the risk of each change, and to determine the documentation required to support the change.

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Types of Variations & Processing Times

Notification :
Immediate – **1 month**
Annual-**12months**

Minor Variations – **3 months**

Major Variations – **6 months**

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Regulatory Tools for Post Approval Changes

- Variation Guideline

  -helps applicants to classify proposed changes

  -to understand the considerations necessary to assess the risk of each change

  -to determine the documentation required to support the change

- Variation Application Form

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Regulatory Requirements

- A completed variation application form
- Supporting documents (summary of proposed changes, scientific justification, etc)
- Updated Quality Information Summary (if applicable)
- Prescribed variation fee
- Copies of SmPC, PIL and labels (if applicable)

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Processing Post Approval Changes

Regular Applications

- Full review of supporting documents in line with the current variation guideline
  - full dossier assessment
  - laboratory analysis
  - GMP inspection
- Request for additional information where applicable
- Request for a prescribed fee
- Request for an updated QIS if not provided

PQ CRP and SRA CRP Products

- Identification of a product as a PQ CRP or SRA CRP product
- Request applicant to submit proof of approval of changes by WHOPQ
- Abridged review (verification) to confirm sameness of submitted variation to the PQ accepted changes
- Pay a prescribed fee where applicable
- Request for an updated QIS if not provided

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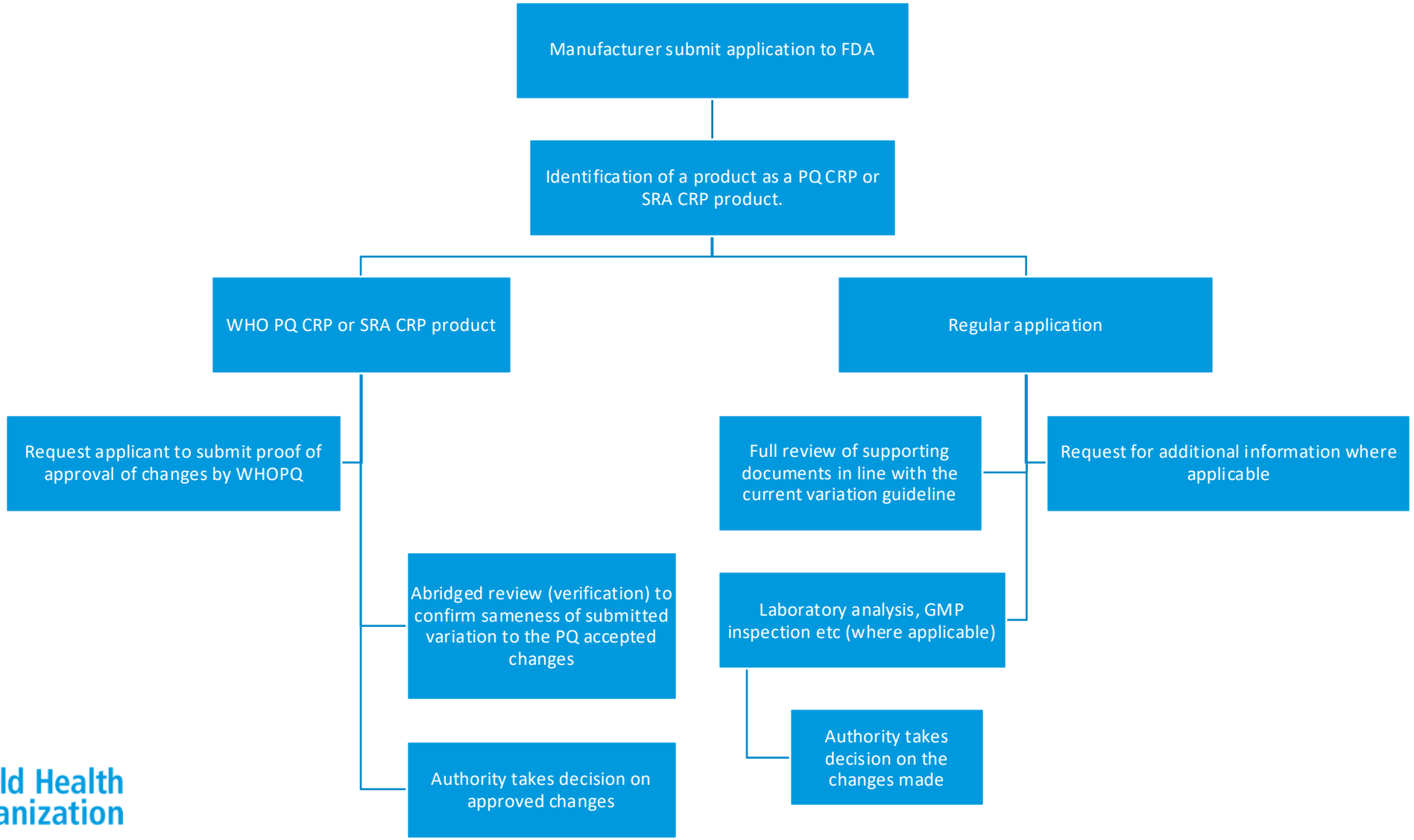
Variation process workflow



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Current Measures for Process Improvement

- Revision of variation guideline to include a procedure for managing PAC for PQ CRP and SRA CRP products.
- Provision of a checkbox on the variation application form for CRP products.
- Provision of a dedicated variation assessment form for CRP products.

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Recommendations

- Immediate notification to allow NRAs to align more quickly with WHO's decision, expediting the national approval process for PACs.

- Efficient application tracking and communication systems

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Thank you

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Importance of Convergence and Reliance in the Post-Approval Change Space

Industry Activities & Recommendations

Janis Bernat
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IFPMA – International Federation of Pharmaceutical Manufacturers & Associations

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Content overview

1. PACs Frameworks Comparison Project
2. Industry engagement in CMC PACs Pilots
3. PACs in the context of CRP

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PACs Frameworks Comparison Project

Scope

- Project conducted by Clarivate with the input from the IFPMA membership
- Review of available regulatory frameworks on Post-Approval Changes (PACs) in 21 countries
- Compare the level of convergence of specific PACs for biological products in countries vs WHO guideline on procedures and data requirements for changes to approved biotherapeutic products, Annex 3, TRS No 1011

Countries

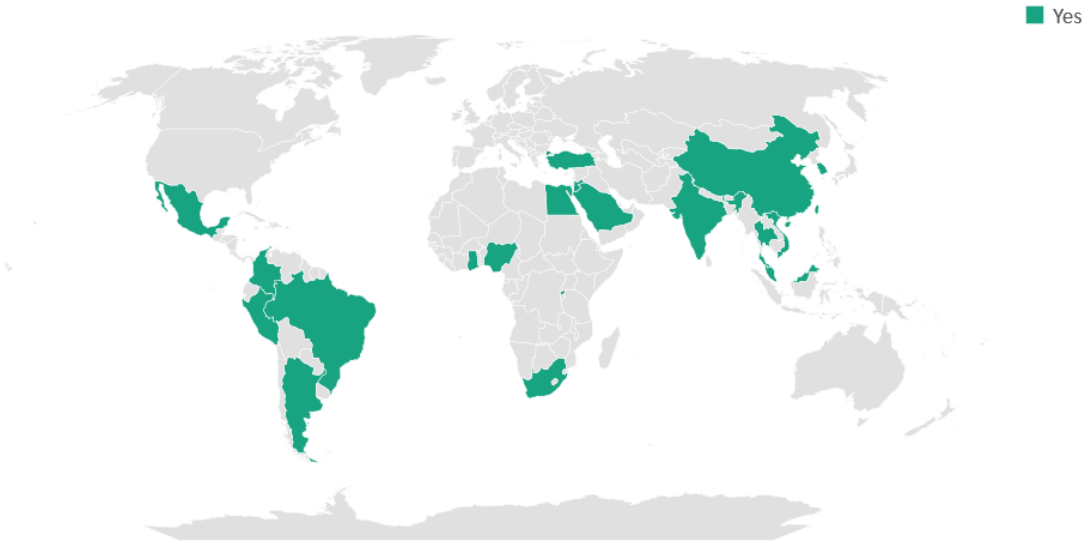
Region	ICH RA Members	ICH Observers	Non-ICH Members
APAC (8)	China, South Korea, Singapore, Chinese Taipei	India, Malaysia	Thailand, Vietnam
LATAM (5)	Brazil, Mexico	Argentina, Colombia	Peru
MEA (8)	Egypt, Saudi Arabia, Turkey	Jordan, Nigeria, South Africa	Ghana, Rwanda

Source and Provider : Clarivate Inc.

PACs Frameworks Comparison Project - General Questions

Q1. Regulation(s) on variations

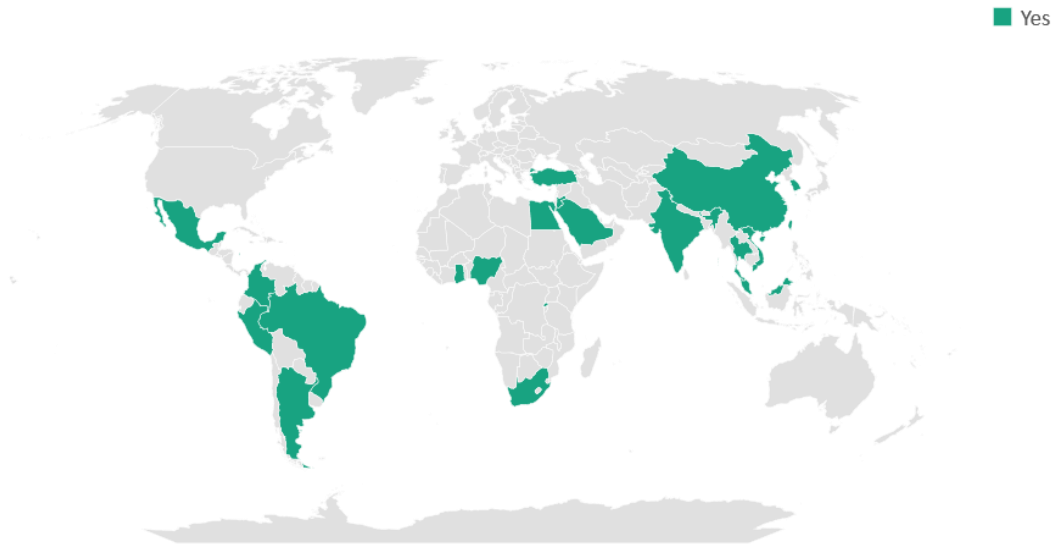
1. Is there any regulation(s) on variations (yes/no)?



100%	of countries have regulations on variations.

Q4. Risk-based categorization

4. Is there any risk-based categorization of changes (yes/no)?



100%	of countries (21) have risk-based categorization of changes. Changes are classified in major and minor. Though moderate classification is contemplated in only 9 countries.

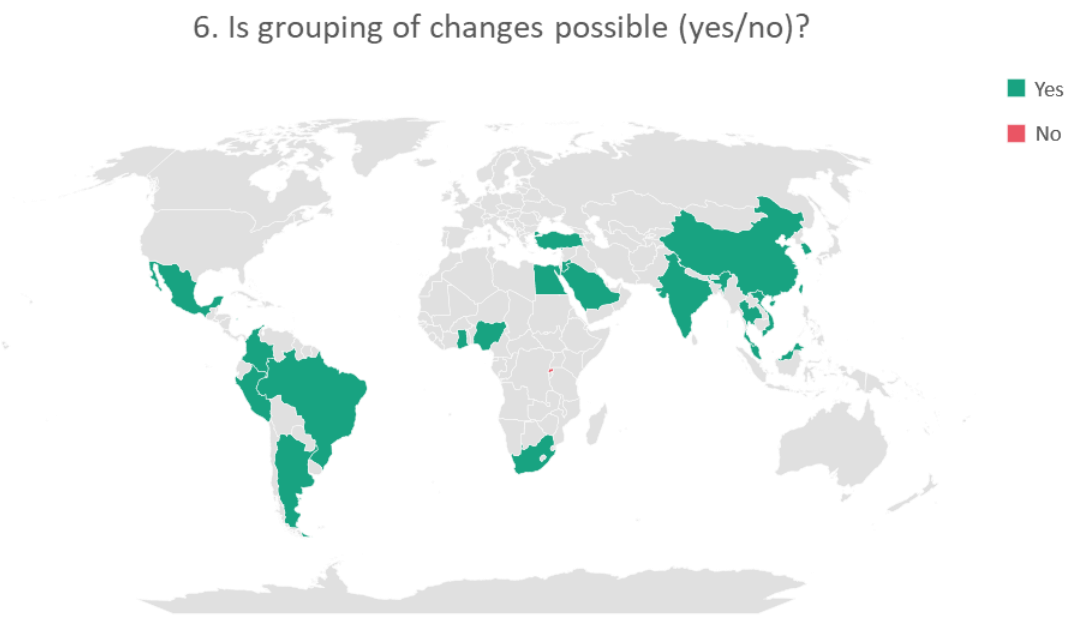
Source and Provider: Clarivate Inc.

PACs Frameworks Comparison Project - General Questions

Q5. Timelines

100%	of countries (21) have timelines for approval.
0-60	days is the timeline for minor variations across regions, including automatic approval.
30-270	days is the timeline for major variations across regions.

Q6. Grouping changes

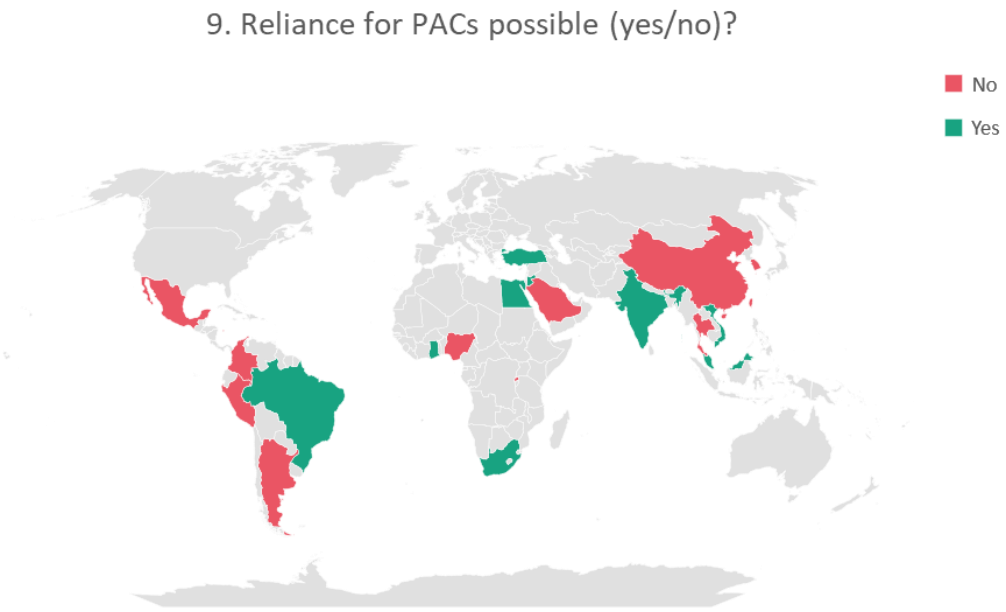


95%	of countries (20) allow grouping of changes. *Grouping is considered if the same variations are applied to multiple products or if multiple variations are applied to the same product. Grouping applies to both minor and major variations.*

Source and Provider: Clarivate Inc.

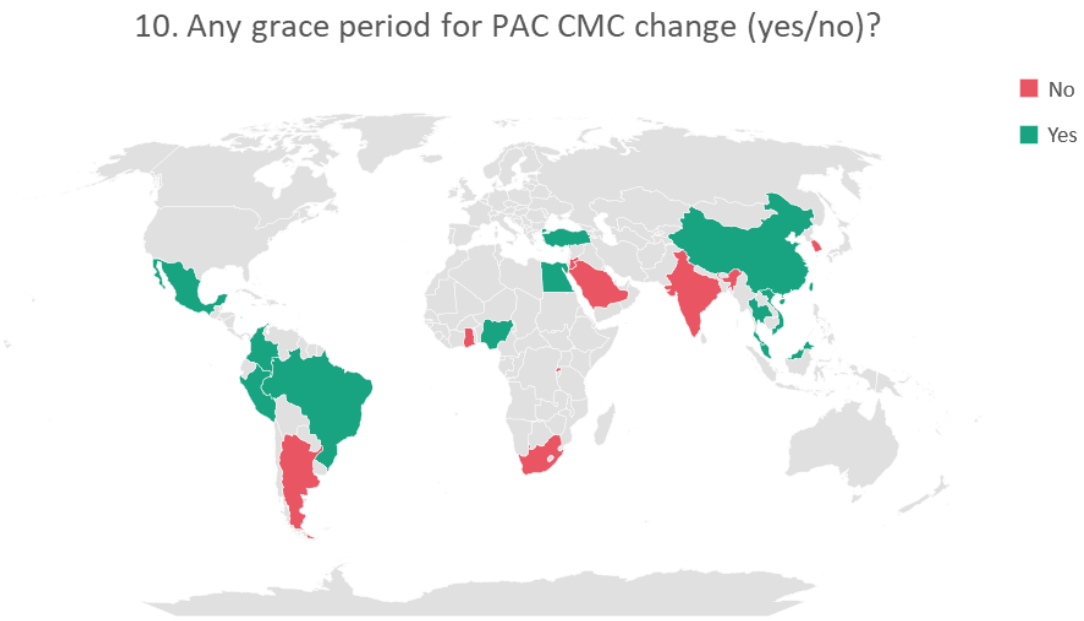
PACs Frameworks Comparison Project - General Questions

Q9. Reliance



48%	of countries (10) have reliance for PACs through verification or abridged pathways.

Q10. Grace period for implementation



62%	of countries (13) include grace periods
6-12	months are the grace periods contemplated in the countries or to be requested to the Authorities.

Source and Provider: Clarivate Inc.

PACs Frameworks Comparison Project – Convergence Levels

LATAM - Country	A		B		C		D		E	
CMC changes	DS	DP	DS	DP	DS	DP	DS	DP	DS	DP
1. Manufacturing Facility changes										
2. Manufacturing Process changes										
3. Pharmacopoeia standard/ monograph changes										
4. Specification and/or Analytical methods changes										
5. Shelf-life extension/ changes										

Level of convergence 58% 36% 6%

APAC Country	F		G		H		I		J		K		L		M	
CMC changes	DS	DP	DS	DS	DS	DP	DS	DP	DS	DP	DS	DP	DS	DP	DS	DP
1. Manufacturing Facility changes																
2. Manufacturing Process changes																
3. Pharmacopoeia standard/mono-graph changes																
4. Specification and/or Analytical methods changes																
5. Shelf-life extension/ changes																

Level of convergence 76% 11% 13%

MEA Country	N		O		P		Q		R		S		T		U	
CMC changes	DS	DP	DS	DP	DS	DP	DS	DP	DS	DP	DS	DP	DS	DP	DS	DP
1. Manufacturing Facility changes																
2. Manufacturing Process changes																
3. Pharmacopoeia standard/mono-graph changes																
4. Specification and/or Analytical methods changes																
5. Shelf-life extension/ changes																

Level of convergence 62% 13% 25%

Legend:
Parameters analyzed: Categorization, Requirements and Timeframes.
DS: drug substance, DP: drug product.

Low convergence
(1 or none of the 3 parameters are aligned)

Medium convergence
(2 parameters are aligned)

High convergence
(all 3 parameters are aligned)

Source and Provider: Clarivate Inc.

PACs Frameworks Comparison Project - Takeaways

General framework on PACs

- **All countries** (21) have **risk categorization**, **timelines** and **95%** (20) allow **grouping**.
- **86%** of countries (18) **require/ accept CTD** submission format, of which 5 accept also eCTD.
- **52%** of countries (11) offer **scientific advice**
- **48%** of countries (10) have **reliance** for PACs
- **62%** of countries (13) include **grace periods** for implementation

Specific to PACs for Biologics

- **Only 57%** of countries (12) have **specific guidance for PACs for biologics**
- 81% of countries (17) include other modalities (Vaccines, blood products, ATMPs)
- The level of convergence between countries and vs WHO guideline for changes to biotherapeutics is very diverse
- Pharmacopoeia compliance changes are the most convergent (minor change) in 6 markets whereas facility changes are the least convergent in 17 markets for both DS and DP

Source and Provider: Clarivate Inc.

PACs Frameworks Comparison Project – Discussion & Next Steps

These survey results related to PACs regulatory framework are aligned with those from A Global Industry Survey on Post-Approval Change Management and Use of Reliance (2024). It highlights:

- **Global regulatory convergence** using a science and risk-based regulatory framework enables a more efficient management of PACs, especially when specifically adapted to biologics (and other modalities)
- Establishing national or regional variation guidelines in line with **international standards (e.g WHO, ICH Q12) in terms of categorization, requirements and timelines** allows predictability and consistency in the handling of changes without need for additional local requirements
- It will also facilitate the **expansion of reliance to life cycle management**, accelerating approval of changes and facilitating patients access to innovative products of the highest quality and safety

Next steps:

- Second round of review to update results and share them on the IFPMA website - publication by the end of the year
- **IFPMA is interested in sharing the detailed survey results with WHO, NRAs and all interested parties (at country or regional level) to review data and discuss possible further collaboration**

CMC PAC Reliance – Industry Pilots

Sanofi: Transfer of Vaccine Filling & Packaging activities from Canada to France. Supply critical variation. Timeline impact: From 4 years to 6 months. 1 standard dossier, 21 countries participating.

Roche: Major drug substance process change for mAb. Supply critical variation Timeline impact: From 2,5 years to 6,5 months - 1 standard dossier, 48 countries participating.

Current status:

- 2 completed pilots demonstrating Reliance is feasible - Standard dossier and timelines accepted by participating NRAs
- More NRAs getting involved leveraging reliance
- IT Tool connecting agencies further supports the process

More pilots are underway leveraging EMA as reference agency

- Amgen, AstraZeneca, GSK, Pfizer, Roche, Sanofi

What's next

⇒ **From PILOT to STANDARD PRACTICE** - industry is working on best practices to facilitate implementation of Reliance pathways globally

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CMC PAC Reliance – Industry Best Practice

Objective:

Produce Industry Best Practice guidance document for CMC PAC Reliance to support companies and NRAs to adopt reliance**.**

- → Gather learnings across Industry from completed and ongoing CMC PAC industry reliance pilots to ensure Industry alignment and foster a harmonized approach for CMC PAC reliance practices;
- → Facilitate Industry / NRA engagement;
- → Build on & incorporate NRAs feedback e.g. standardized NRA Q&A document;
- → Support future CMC PAC reliance pilots in the first instance, but as more Industry-wide experience is gained, incorporate and continue to develop best practices;
- → **Collaboration and transparency is key to drive this forward – both within / between Industry & NRAs.**

Status: Document includes key reliance topics and specific recommendations regarding reliance parameters, recognizing both Industry and NRAs are still developing. Several new CMC PAC reliance pilots are initiated / planned, with staggered completion through 2025.

Management of PACs – Considerations in the context of the WHO SRA CRP

1. **Increase the use of CRP for PACs**: There are provisions for PACs both on the PQ CRP and SRA CRP. To better leverage the benefits of the WHO CRP, such provisions should be used and CRP applied throughout the entire product lifecycle (i.e. products that have received initial approval through CRP should also continue having PACs managed through the procedure).

2. **Additional guidance on how to assess PACs through CRP:** Guidance on required documents; how they are used; who is providing which documents (e.g. reference NRA vs applicant).

3. **Regulatory convergence to facilitate unilateral reliance & use of CRP**: National PACs guidelines should strive to converge with WHO guidelines, particularly in terms of change classification, data requirements, timelines and use of reliance, complemented by ICH Q12. Recommendations for maximum review periods of PACs approved by a SRA for both medicines and vaccines.

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Thank you

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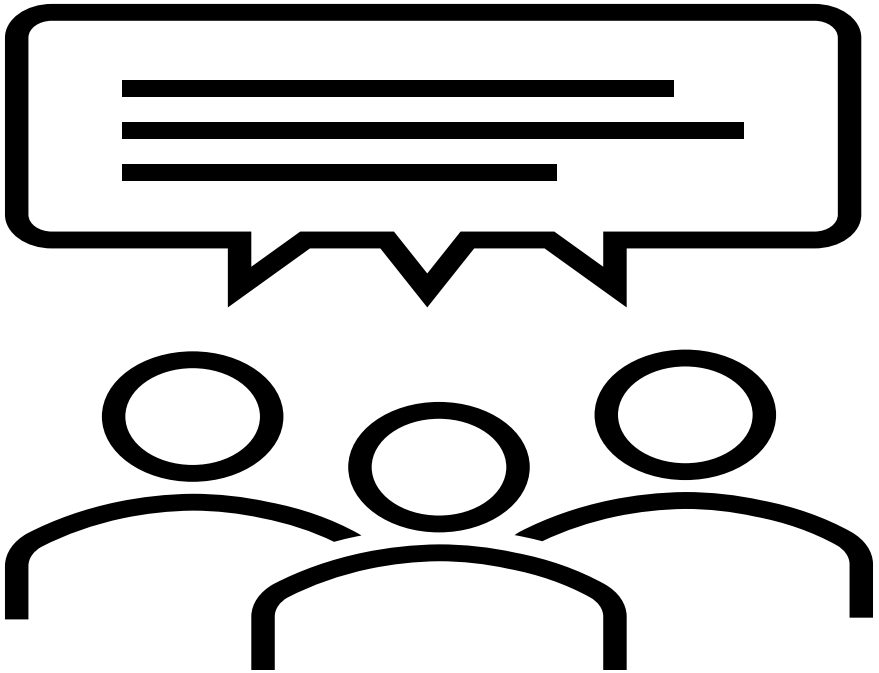
Q & A



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Thank you

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