IFPMA

Global regulatory approaches to post-approval changes in biotherapeutic products

A comparative analysis against WHO guidelines

DECEMBER 2024

Contents

1. Introduction

IFPMA commissioned Clarivate to conduct a comprehensive analysis of global regulatory frameworks for post-approval changes (PACs) for biotherapeutic products.

This study consisted in searching, compiling and comparing publicly available national regulatory guidelines and regulations for PACs across twenty-one countries/regions from Latin America (LATAM), Asia-Pacific (APAC) and Middle East and Africa (MEA) regions.

Reference documents were selected for each country and procedures and data requirements were compared against the WHO Guidelines on changes on biotherapeutic products, Annex 3, TRS No 1011[1].

The study was conducted in two phases. In the first phase, PACs guidelines and regulations were compiled and assessed. The second phase involved comparing country-specific PACs guidelines for biotherapeutic products against the WHO Reference Guidelines. The aim of this study was to evaluate the level of global convergence in PACs frameworks and to inform future advocacy and harmonization initiatives.

2. Methodology

For this analysis, 21 countries/regions across 3 global areas were selected. The selected countries/regions represent different geographic regions, varying levels of regulatory maturity and different ICH-membership statuses (ICH regulatory members, observers or non-ICH countries), ensuring a manageable scope while capturing a wide range of regulatory perspectives. The countries included in this study were:

- **LATAM**: Argentina, Brazil, Colombia, Mexico and Peru
- **APAC**: China, India, South Korea, Chinese Taipei, Malaysia, Singapore, Thailand and Vietnam
- **MEA**: Egypt, Jordan, Saudi Arabia, Turkey, Nigeria, Rwanda, South Africa and Ghana

To comprehensively assess the status of PACs regulatory frameworks, the study involved retrieving publicly available reference documents (regulations, guidelines, Q&As) for each one of the selected countries in Q3 and Q4 2024. These documents were initially compiled and validated through consultations with members of the IFPMA regulatory network, leveraging input from local and regional industry affiliates to ensure accuracy. The findings were further verified and updated ahead of publication in November 2024.

Once the reference documents were selected, they were analyzed to address the following questions:

1. Is there any regulation(s) / guideline(s) on PACs?
2. Is there any specific guideline on variations for biotherapeutics?
3. Is it applicable to other modalities?
4. Is there any risk-based categorization of changes?
5. Are there timelines for approval?
6. Is grouping of changes possible?
7. Is there a submission format [CTD]?
8. Is scientific advice possible?
9. Is reliance for PACs possible?
10. Is there a grace period for implementation of CMC PACs?

The responses to these questions are presented in heatmaps to depict a global overview, showing the percentage of countries that provided affirmative answers to each question.

In a second phase, the study examined five specific chemistry, manufacturing, and controls (CMC) changes for both drug substances (DS) and drug products (DP). The goal was to compare how these changes are addressed under the WHO Reference Guidelines[1] versus each country's specific PAC regulations and guidelines for biotherapeutic products, evaluating their level of convergence to WHO. The following changes were considered for DS and DP:

1. Facility changes
    1. Change to a DS manufacturing facility.
    38. Change involving a DP manufacturer/ manufacturing facility.

2. Process changes
    7. Change to the DS purification process.
    39. Change in the DP manufacturing process.

3. Compliance to Pharmacopeia
    20. Change in the specifications for the DS to comply with an updated pharmacopoeia standard/monograph.
    53. Change in the specifications for the DP to comply with an updated pharmacopoeia standard/ monograph.

4. Specification and/or analytical methods changes
    22. Change in the specification/analytical procedure used to release the DS.
    55. Change in the specification/analytical procedure used to release the DP.

5. Shelf-life extension
    32. Change in the shelf-life of the DS or for a stored intermediate of the DS.
    67. Change in the shelf-life of the DP.

For the comparison, the following three parameters were evaluated:

a) Change categorization (e.g. major/moderate/minor), considering the specific conditions to be applied,

b) Requirements (e.g. supportive deliverables for PACs submission information), and

c) Timeframes (submission to approval timelines)

These findings were further checked and confirmed by the IFPMA network (local and/or regional affiliates) to ensure consistency in the assessment of the level of convergence or divergence compared to the WHO Reference Guidelines[1]. When the national timeframes were shorter than the ones recommended in the WHO Reference Guidelines[1], this parameter was considered as “aligned”.

The level of convergence was determined based on the three selected parameters as follows:

- **Low convergence level**: One or none of the three parameters aligned with the WHO Reference Guidelines[1].
- **Moderate convergence level**: Two parameters aligned with the WHO Reference Guidelines[1].
- **High convergence level**: All three parameters aligned with the WHO Reference Guidelines[1].

The responses were organized into tables, providing a clear visual overview of the different convergence levels and enabling easy comparison across countries and regions.
Some limitations of this study should be highlighted:

- **Draft guidelines**: A small subset of the guidelines analysed are still in draft form and not yet fully implemented, which may influence their applicability in practice.
- **Focused scope of countries**: The study concentrated on a selected number of countries to ensure depth of analysis, though this limits generalizability of the results.
- **Structured categorization of convergence levels**: The classification of convergence levels is based on a systematic interpretation of the reference documents, which may introduce a degree of subjectivity into the analysis.

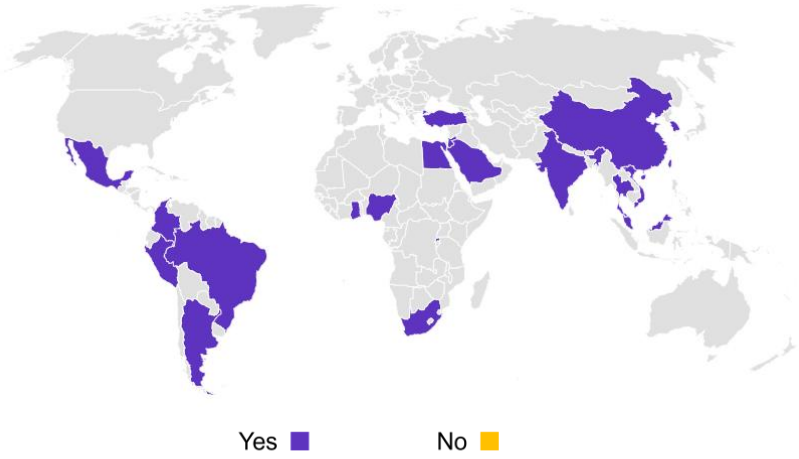
3. General questions on PACs regulatory frameworks

The first part of the study provides an overview of PACs regulatory frameworks in the selected countries/regions. With this aim, ten general questions were addressed. Descriptive results as well as heatmaps are presented hereinafter.

Countries/regions with affirmative answers are highlighted in dark purple, while those with negative answers are marked in yellow.

1. **Is there any regulation(s)/Guideline(s) on variations?**

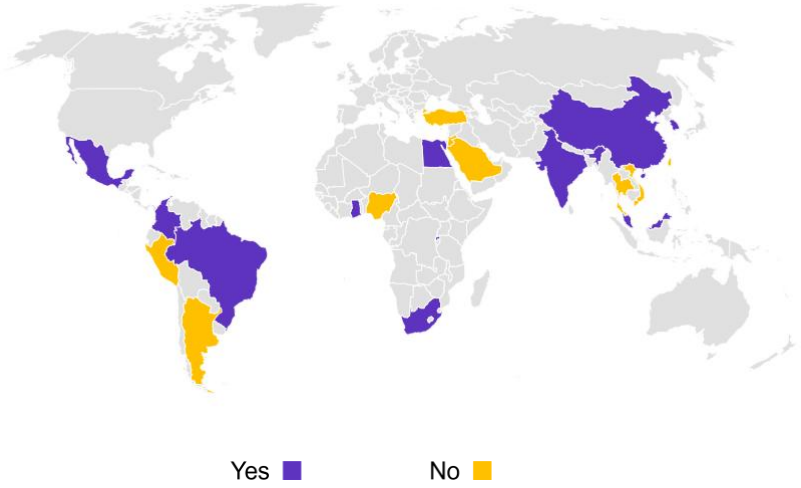
   All countries included in the scope of the study have regulations on variations.



2. **Is there any specific guideline on variations for biotherapeutics?**

57% of countries (12) have specific guidelines on variations for biotherapeutics, namely Brazil, Colombia, Mexico, China, India, South Korea, Malaysia, Singapore, Egypt, Rwanda, South Africa, and Ghana.

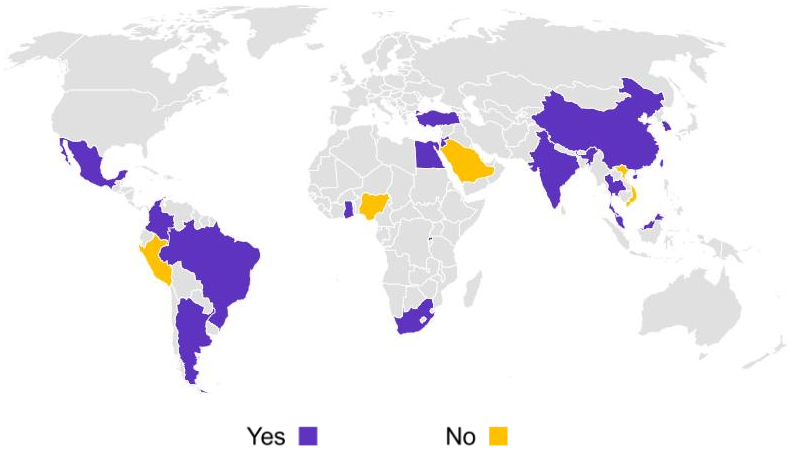
81% of countries (17) refer to the WHO Reference Guidelines[1], namely Argentina, Brazil, Colombia, Mexico, Peru, China, India, South Korea, Malaysia, Singapore, Thailand, Egypt, Jordan, Nigeria, Rwanda, South Africa and Ghana.



3. **Is it applicable to other modalities?**

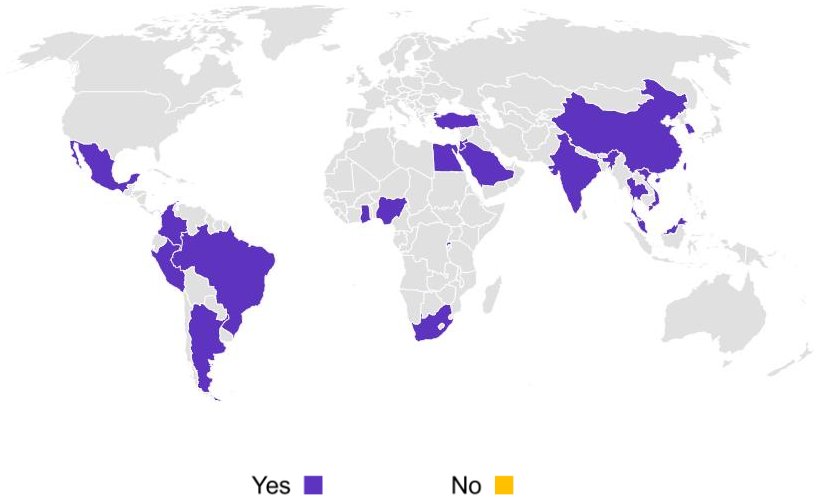
81% of countries (17) include other modalities, namely Argentina, Brazil, Colombia, Mexico, China, India, South Korea, Chinese Taipei, Malaysia, Singapore, Thailand, Egypt, Jordan, Turkey, Rwanda, South Africa and Ghana.

76% of countries (16) include vaccines. Other modalities included in the guidelines are plasma fractioned products (blood products) (9), Advanced Therapy Medicinal Product (ATMPs) (2), and Cell and Gene Therapy (CGTs) (5).



4. **Is there any risk-based categorization of changes?**

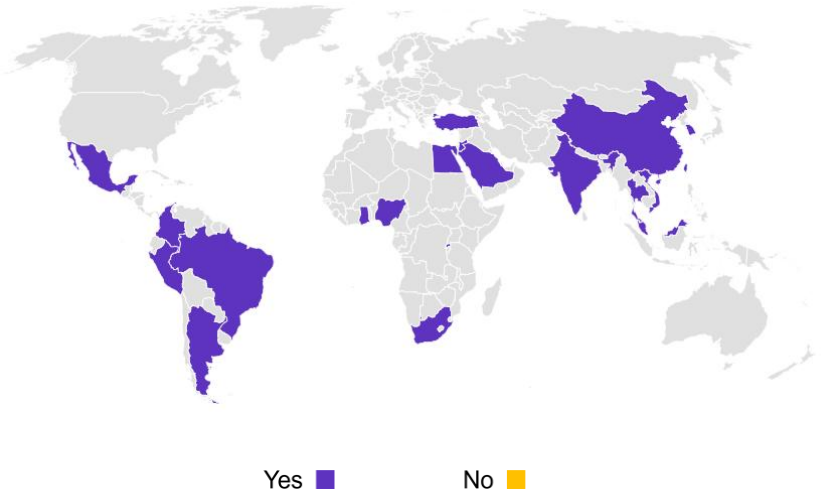
All countries (21) have risk-based categorization of changes. Changes are classified as major and minor, with moderate classification also considered in 9 countries.



5. **Are there timelines for approval?**

All countries (21) have timelines for approval.

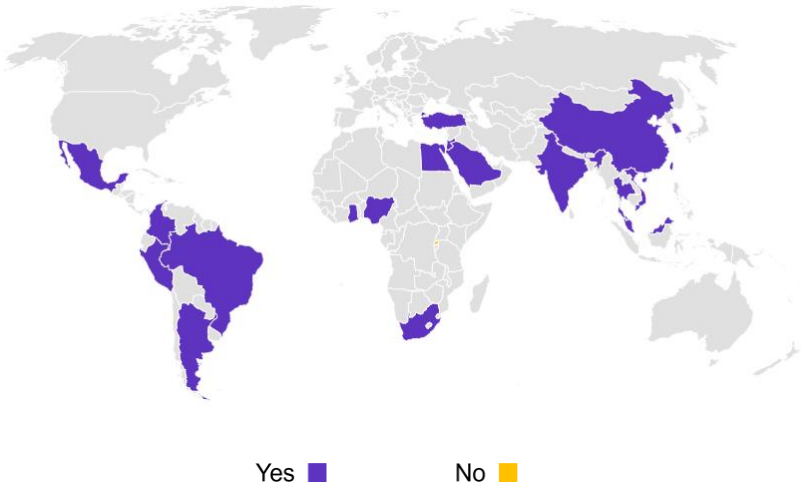
- 0-60 days are the timelines allocated for minor variations across regions, including automatic approval.
- 30-270 days are the timelines allocated for major variations across regions.



6. Is grouping of changes possible?

95% of countries (20) allow grouping of changes, with Rwanda being the exception.

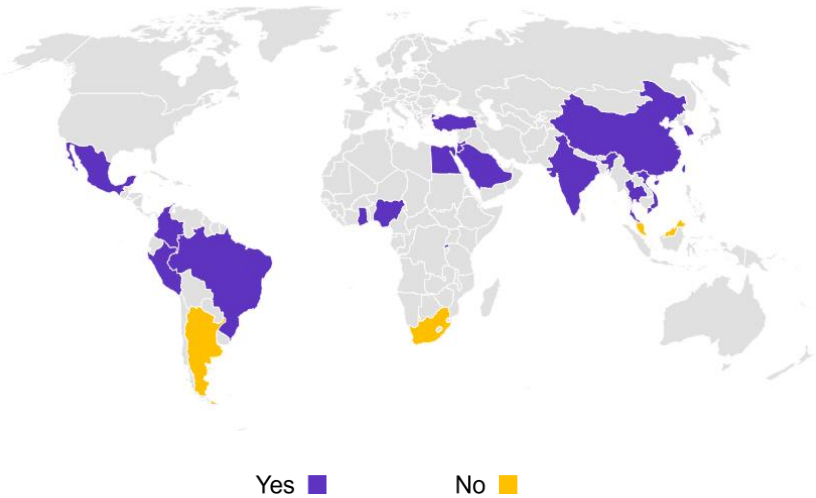
Grouping is considered if the same variations are applied to multiple products or if multiple variations are applied to the same product. This applies to both minor and major variations.



7. Is there a submission format [CTD])?

86% of countries (18) require/accept CTD submission format. eCTD is also accepted in 5 countries, namely India, South Korea, Chinese Taipei, Thailand and Jordan.

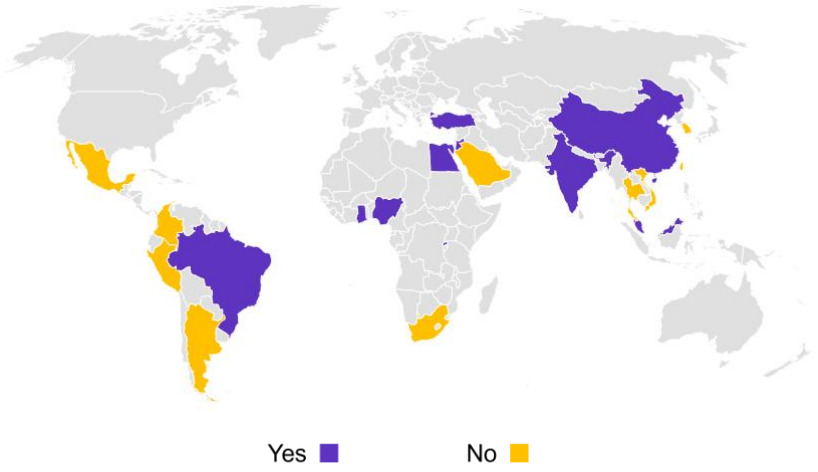
14% of countries (3) have other CTD formats, namely Argentina (local format), Malaysia (ASEAN CTD) and South Africa (ZA CTD and eCTD).



8. Is scientific advice possible?

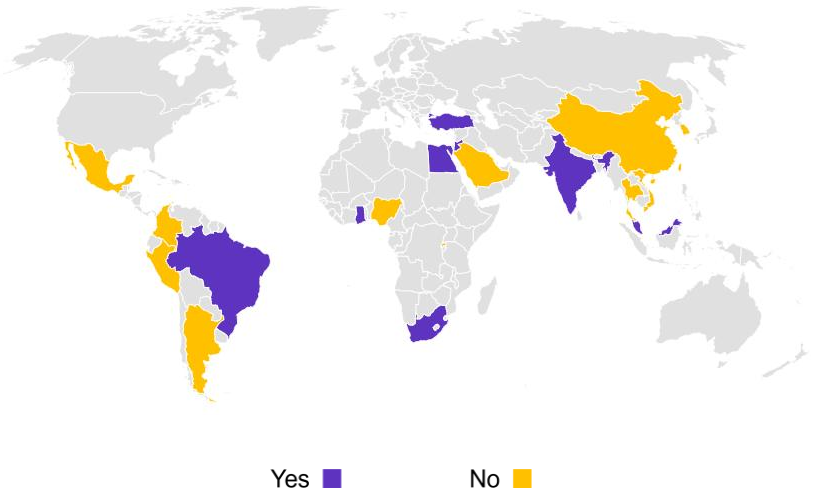
52% of countries (11) offer scientific advice, namely Brazil, China, India, Malaysia, Singapore, Egypt, Jordan, Turkey, Nigeria, Rwanda and Ghana.

This support may be provided in a pre-submission meeting, via email, or by submitting a form, depending on the country.



9. Is reliance for PACs possible?

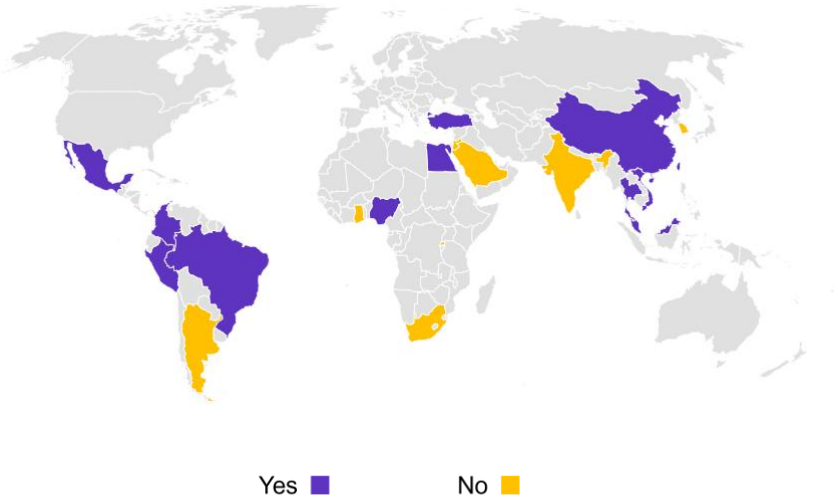
43% of countries (9) have reliance possibilities for PACs, namely Brazil, India, Malaysia, Singapore, Egypt, Jordan (although not formal but accelerated when assessed by SRA i.e. Stringent Regulatory Authority), Turkey, South Africa and Ghana. The verification or abridged routes consider assessment of the PAC by reference Competent Authorities and International Organizations, such as EMA (EU), TGA (AU), HC (CA), FDA (US), MHRA (UK), PMDA (JP), Swissmedic (CH), EDQM and WHO, depending upon the relying NRA.



10. <u>Is there a grace period for CMC PACs?</u>

62% of countries (13) include grace periods for implementation of CMC PACs, namely Brazil, Colombia, Mexico, Peru, China, Chinese Taipei, Malaysia, Singapore, Thailand, Vietnam, Egypt, Turkey and Nigeria.

Grace periods range from 6 to 12 months, although some countries do not specify grace periods or allow specific requests for implementation of some changes.



4. Specific CMC PACs for biotherapeutic products

This study assessed the convergence level of the WHO Reference Guidelines[1] versus country-specific regulations or guidelines for five specific chemistry, manufacturing, and controls (CMC) changes for drug substances and drug products for biotherapeutics:

- Manufacturing facility changes
- Manufacturing process changes
- Pharmacopoeia standard/monograph changes
- Specification and/or Analytical methods changes
- Shelf-life extension/changes

4.1 LATAM

It has been observed that countries with a significant manufacturing presence for biotherapeutic products, such as Mexico and Brazil, tend to have more detailed guidelines regarding variations in the manufacturing process for biotherapeutic products. Conversely, countries with less representation in the manufacturing of biotherapeutic products, do not yet have a variation guideline for biologics thus provide less detailed information on these types of changes.

In terms of the convergence level of LATAM countries with the WHO Reference Guidelines[1], 58% (29 CMC scenarios) show low convergence, 36% (18 CMC scenarios) show medium convergence and 6% (3 CMC scenarios) show high convergence. A summary table is provided below.

Two countries (Brazil and Mexico) show medium to high convergence in terms of change description with WHO Reference Guidelines[1]. The main differences are in the level of specific local

requirements or the risk categorization and related timelines being more stringent when using standard regulatory pathway (though Mexico has shorter approval timelines than those suggested by WHO).

Other countries show low convergence with WHO Reference Guidelines[1], which can be explained by differences in description and stricter categories of changes, in the supportive data required and result in extended timelines, especially when the moderate category is not applicable.

Notably, both Argentina and Peru are considering revisions to their guidelines around post-registration changes (*ANMAT-MED-MPR 001-00*[1] and *Regulation on major variations of pharmaceutical products with an approved marketing authorization*[2], published in the Ministerial Resolution (MR) N°893-2019/MINSA).

LATAM - Country	Argentina		Brazil		Colombia		Mexico		Peru	
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										

Legend:
DS= drug substance; DP= drug product
Parameters analyzed: Categorization, Requirements and Timeframes.
Convergence level of country vs WHO Reference Guidelines[1]:

- Light blue: Less aligned (1 or none of the 3 parameters are aligned),
- Medium blue: Moderately aligned (2 parameters are aligned),
- Dark blue: Very aligned (all 3 parameters are aligned).

[1] ANMAT-MED-MPR 001-00

[2] Ministerial Resolution N° 893-2019/MINSA: Regulation on Major variations of pharmaceutical products with an approved marketing authorization

4.2 APAC

In the APAC region, it has been observed that only half of the countries/regions analyzed for this study have specific guidelines for biotherapeutic products. Countries/regions without specific guidelines for biotherapeutics may partially address the changes considered for this study, refer to WHO or ASEAN guidelines, and/or lack any specific guideline on these type of changes for biotherapeutic products, thus leading to significant divergences in the region.

One country, Thailand, fully cross-references the WHO Reference Guidelines[1], while two other countries (Malaysia and India) have a variation guideline for biologics with changes description closely following WHO Reference Guidelines[1] (2014 version for Malaysia[3]). In India, however, there are notable divergences, including longer timelines and specific local requirements. Meanwhile, in Malaysia, the risk-based classification is more stringent, although this does not extend the timelines for evaluating major changes. Some countries do not follow exclusively the WHO Reference Guidelines[1] and have either one or more specific local guidelines or Annexes for CMC changes affecting biotherapeutic products (e.g. China, Singapore).

Finally, some countries do not have any guidelines related to CMC changes for biotherapeutic products. Thus, some changes are either not described, partly assessed as biotherapeutics (e.g. in South Korea for manufacturing process changes), and/or assessed using a general variation guideline/regulation or a guideline for small molecules (e.g. South Korea, Chinese Taipei, Vietnam also cross-references WHO/US FDA/EMA).

[3] Guidelines on procedures and data requirements for changes to approved vaccines, Annex 4, TRS No 993

The general picture of alignment in APAC with the WHO Reference Guidelines[1] shows that 76% (61 CMC scenarios) show low convergence, 11% (9 CMC scenarios) show medium convergence and 13% (10 CMC scenarios) show high convergence. A summary table is provided below.

APAC Country	China		India		S.Korea		Taiwan		Malaysia		Singapore		Thailand		Vietnam	
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/monograph changes																
4. Specification and/or Analytical methods changes																
5. Shelf-life extension/changes																

Legend:

DS= drug substance; DP= drug product

Parameters analyzed: Categorization, Requirements and Timeframes.

Convergence level of country vs WHO Reference Guidelines[1]:

- Light blue: Less aligned (1 or none of the 3 parameters are aligned),
- Medium blue: Moderately aligned (2 parameters are aligned),
- Dark blue: Very aligned (all 3 parameters are aligned).

4.3 MEA

Similar to APAC, in the Middle East and Africa (MEA) region, there are various scenarios regarding management of PACs for biotherapeutic products: countries with their own regulation on variations for biotherapeutic products, those not following WHO Reference Guidelines[1] (Saudi Arabia, Turkey), countries following WHO recommendations (Egypt, Jordan), countries with some divergences from WHO Reference Guidelines[1] (Rwanda, Ghana and South Africa), and countries with no guidelines on PACs to biotherapeutic products (Nigeria).

Two countries (Egypt and Jordan) strictly follow the WHO Reference Guidelines[1] for changes to biotherapeutics, Egypt having recently adopted its *Guideline on the regulation of post-approval changes to a registered Biotherapeutic products*[4] and Jordan cross referring to WHO Reference Guidelines[1] within its *Instructions of Changes to Drugs Registered in 2017*[5].

Two other countries (Saudi Arabia and Turkey) do not follow WHO Reference Guidelines[1] as they have a similar model to what is seen in the EU variations guideline, encompassing specific descriptions, risk-based categorization and requirements for changes affecting biotherapeutic products.

Three countries follow the WHO Reference Guidelines[1] description of changes (South Africa, Ghana and Rwanda). However, as South Africa (*SAHPGL-PEM-BIO-05 - Biotherapeutic medicines amendment guideline*[6]) also has a model similar to the EU variations guideline, it shows some divergences in reporting categories and supportive data, thus affecting the timelines. Ghana and Rwanda have adopted a similar guideline. Although variation descriptions follow the WHO Reference Guidelines[1], the reporting risk category is defined as major for all types of changes included in the study, with timelines for the evaluation of the changes longer than suggested by the WHO in Rwanda.

Lastly, Nigeria does not yet have a guideline for variations for biotherapeutic products. Applicants are requested to contact the National Agency for Food and Drug Administration and Control (NAFDAC). However, according to the *Guideline on variations to a registered vaccine for humans*[7], "the general principles set out in this document may also apply to other biotherapeutic products", and are mostly based on the WHO Reference Guidelines[1], except that there are no published timelines for approval.

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[4] Guideline on the regulation of post-approval changes to a registered Biotherapeutic products in Egypt

[5] Jordan - Instructions of Changes to Drugs Registered in 2017

[6] South Africa - SAHPGL-PEM-BIO-05 - Biotherapeutic medicines amendment guideline

[7] Nigeria - Guideline on variations to a registered vaccine for humans

In terms of the convergence level of MEA countries with the WHO Reference Guidelines[1], 62% (50 CMC scenarios) show low convergence, 13% (10 CMC scenarios) show medium convergence and 25% (20 CMC scenarios) show high convergence.

A summary table is provided below.

MEA Country	Egypt		Jordan		KSA		Turkey		Nigeria		Rwanda		S.Africa		Ghana	
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/monograph changes																
4. Specification and/or Analytical methods changes																
5. Shelf-life extension/changes																

Legend:

DS= drug substance; DP= drug product

Parameters analyzed: Categorization, Requirements and Timeframes.

Convergence level of country vs WHO Reference Guidelines[1]:

- Light blue: Less aligned (1 or none of the 3 parameters are aligned),
- Medium blue: Moderately aligned (2 parameters are aligned),
- Dark blue: Very aligned (all 3 parameters are aligned).

5. Conclusions & recommendations

The analysis of PACs regulations across 21 countries reveals that all countries have established regulations and risk-based categorizations for variations. However, the specifics of risk categorization differ among countries, with some adopting more restrictive categorization, resulting in longer evaluation periods for biotherapeutic product variations. Notably, 57% of the countries included in this study have specific guidelines for biotherapeutic products, while others either incorporate these changes into general guidelines or lack specific guidelines altogether. In terms of modalities, 81% of the countries include other modalities such as vaccines and advanced therapies. All countries have defined timelines for approval, and the majority allow grouping of changes. The CTD submission format is widely accepted, with some countries also accepting eCTD. Scientific advice is available in 52% of the countries, and reliance mechanisms are present in 43%. Additionally, 62% of the countries provide grace periods for implementing CMC PACs.

The level of convergence of specific changes affecting biotherapeutic products is very diverse among countries and when comparing national frameworks against the WHO Reference Guidelines[1]. The following country groupings can be identified based on their alignment:

- Countries that have adopted the WHO Reference Guidelines[1] (Egypt, Thailand, Jordan),
- Countries with PACs frameworks similar to the EU‘s variations guideline which encompass specific description, risk-based categorization and requirements for changes affecting biotherapeutic products (such as Saudi Arabia, Turkey).
- Countries that have adopted their own guideline (such as China, Singapore) or, while adopting WHO Reference Guidelines[1] description of changes, have introduced significant modifications (such as different risk categorization, supportive data required and/or extended timelines).
- Countries that do not have any guidelines related to CMC changes for biotherapeutic products.

Overall, pharmacopoeia compliance is the most convergent CMC PACs scenario (minor category), whereas facility changes show the least convergence to WHO Reference Guidelines[1] (major or moderate categorization).

These survey results related to PACs regulatory framework are aligned with those from an earlier industry survey[8] on PACs and reliance.

Main recommendations:

- Global regulatory convergence using a science and risk-based regulatory framework enables 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 the need for additional local requirements
- Expanding reliance practices to include life cycle management will accelerate the approval of changes, facilitating patient access to innovative, high-quality, and safe products.

This study, developed with contributions from IFPMA and industry experts, is part of IFPMA's commitment to provide robust data and evidence-based policy recommendations that support regulatory convergence and promote best practices worldwide. IFPMA welcomes continued dialogue with National Regulatory Authorities and stakeholders to discuss our findings in greater detail. We aim to foster collaborative discussions that enhance alignment and efficiency in regulatory processes, particularly for managing post-approval changes.

[8] A Global Industry Survey on Post-Approval Change Management and Use of Reliance

6. Reference Guidelines

Argentina
ANMAT-MED-MPR 001-00
Brazil
Normative instruction IN No. 65
China
Technical Guideline for Studies on CMC Changes to Marketed Biotherapeutic Products
Technical Guidelines on Clinical Changes for Marketed Chemical Drugs and Biotherapeutic Products
Chinese Taipei
Regulations for Registration of Medicinal Products
Colombia
ASS-RSA-GU049-Guideline for application for modifications of biotherapeutic products
Egypt
Guideline on the regulation of post-approval changes to a registered Biotherapeutic products in Egypt
Ghana
Ghana - Guidelines for reporting variations to a registered biotherapeutic product
India
Post Approval Changes in Biotherapeutic Products: Quality Safety and Efficacy Documents
Jordan
Instructions of Changes to Drugs Registered in 2017
Malaysia
Malaysian Variation Guideline for Biologics (MVGB)
Mexico
Criteria for the classification of variations to the marketing authorization conditions of biotechnological and biotherapeutic products, and vaccines
Nigeria
Guideline on variations to a registered vaccine for humans
Peru
Ministerial Resolution N° 893-2019/MINSA: Regulation on Major variations of pharmaceutical products with an approved marketing authorization
Rwanda
Guidelines for variation of registered biotherapeutic products
Saudi Arabia
Guidelines for Variation Requirements
Singapore
Guideline on therapeutic product registration in Singapore

Appendix 14A - Guidance on Therapeutic Product Registration in Singapore – Part A: Checklist on Dossier Requirements for MIV-1 Variation for Biotherapeutic Therapeutic Products
Appendix 14B - Guidance on Therapeutic Product Registration in Singapore – Part B: Checklist on Dossier Requirements for MIV-2 (Notification) Variation for Biotherapeutic Therapeutic Products
Appendix 14C - Guidance on Therapeutic Product Registration in Singapore – Part C: Checklist on Dossier Requirements for MIV-2 (Do-and-Tell) Variation for Biotherapeutic Therapeutic Products

South Africa

South Africa - Biotherapeutic medicines amendment guideline

South Korea

Guideline on the Comparability of Biopharmaceuticals in Manufacturing Process Changes

Thailand

Guideline for Variation of Drug Dossier

Turkey

General guideline on variations for medicinal products for human use

Vietnam

Circular No. 08/2022/TT-BYT: Regulating the Registration of Drugs and Drug Raw Materials
ASEAN Variation guideline for pharmaceutical products

WHO

Guidelines on procedures and data requirements for changes to approved biotherapeutic products, Annex 3, TRS No 1011
Guidelines on procedures and data requirements for changes to approved vaccines, Annex 4, TRS No 993

Acknowledgements

This report has been prepared through a collaborative effort between Clarivate and IFPMA. Clarivate™ is a leading global provider of transformative intelligence. We offer enriched data, insights & analytics, workflow solutions and expert services in the areas of Academia & Government, Intellectual Property and Life Sciences & Healthcare. For more information, please visit clarivate.com.

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