IFPMA

Global regulatory approaches to post-approval changes in biotherapeutic products

A comparative analysis against WHO guidelines

OCTOBER 2025

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 22 countries from Latin America (LATAM), Asia-Pacific (APAC), Middle East and Africa (MEA), and Europe.

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

The study was conducted in two phases. In the first phase, PACs guidelines and regulations were compiled and assessed to address general questions related to PACs regulatory frameworks. The second phase involved comparing country-specific PACs guidelines for biotherapeutic products against the current *WHO Reference Guideline*[1]. The aim of this study was to evaluate the level of global convergence in PACs frameworks and to inform future advocacy and harmonization initiatives.

[1] Guidelines on procedures and data requirements for changes to approved biotherapeutic products, Annex 3, TRS No 1011

2. Methodology

For this analysis, 22 countries/regions across 4 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 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
- **Europe**: European Union

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 from 2024 up to June 2025. 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.

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 the overall scenario, 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 Guideline*[1] versus each country's specific PAC regulations and guidelines for biotherapeutic products, providing a comprehensive view of their alignment. 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)

c) Timeframes (submission to approval timelines) extracted from the source documents identified at the beginning from each country.

These findings were further checked and confirmed by the IFPMA network (local and/or regional affiliates) as well as EFPIA to ensure consistency in the assessment of the level of convergence

or divergence compared to the *WHO Reference Guideline*[1]. When the national timeframes were shorter than the ones recommended in the *WHO Reference Guideline*[1], this parameter was considered as "aligned."

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

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

The responses were organized into tables, providing a clear visual overview of the different alignment levels and enabling easy comparison across countries and regions.

Some limitations of this study should be highlighted:

- **Draft guidelines**: Of note only published guidelines were considered, either in draft or effective. For guidelines in draft form and not yet fully implemented, this 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.

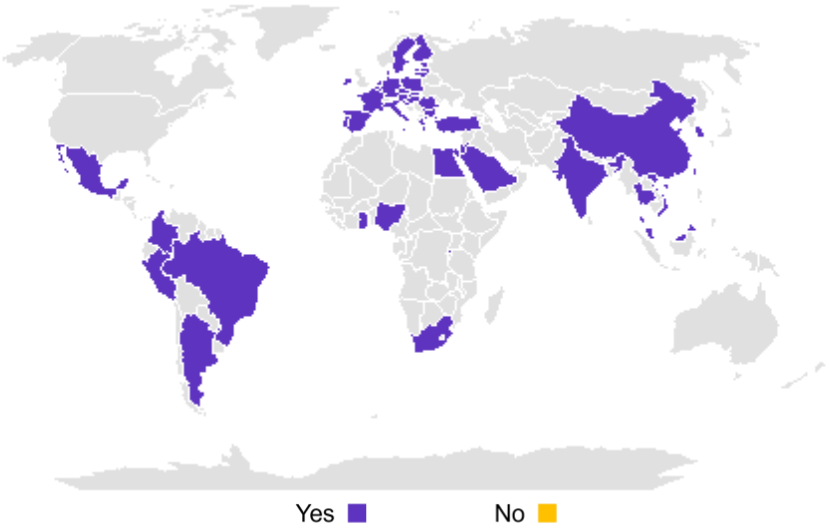
3. General questions on PACs regulatory frameworks

The first part of the study provides an overview of PACs regulatory frameworks in the selected countries/regions. With this aim, 10 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?**

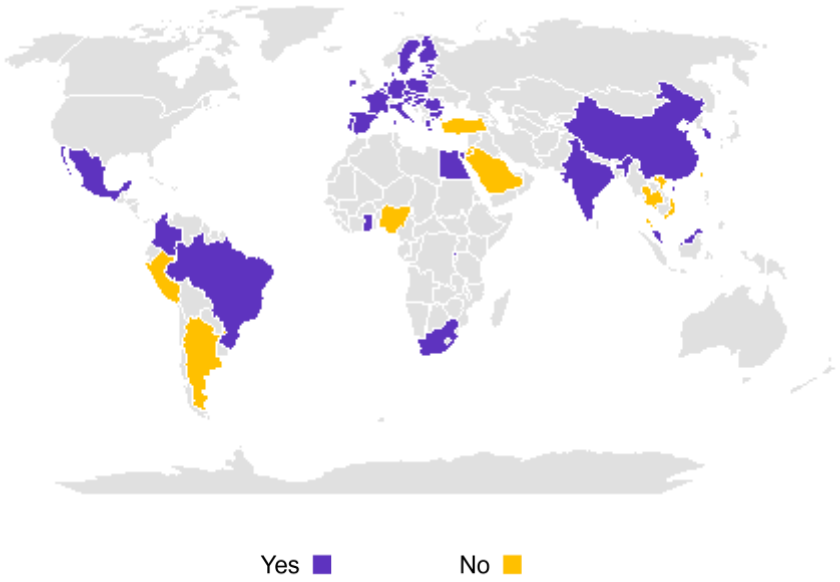
   All markets included in the scope of the study have regulations on variations.



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

   59% of markets (13) have specific guidelines on variations for biotherapeutics, namely Brazil, Colombia, Mexico, China, India, South Korea, Malaysia, Singapore, Egypt, Rwanda, South Africa, Ghana, and European Union.

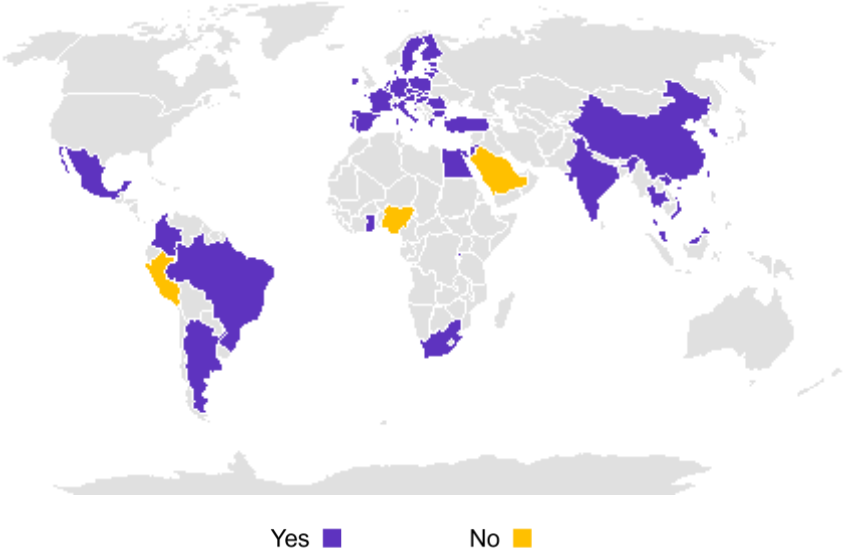
   82% of markets (18) refer to the *WHO Reference Guideline*[1], namely Argentina, Brazil, Colombia, Mexico, Peru, China, India, South Korea, Malaysia, Singapore, Thailand, Vietnam, Egypt, Jordan, Nigeria, Rwanda, South Africa, and Ghana. Saudi Arabia refers to European Medicines Agency (EMA) guidelines.



3. **<u>Is it applicable to other modalities?</u>**

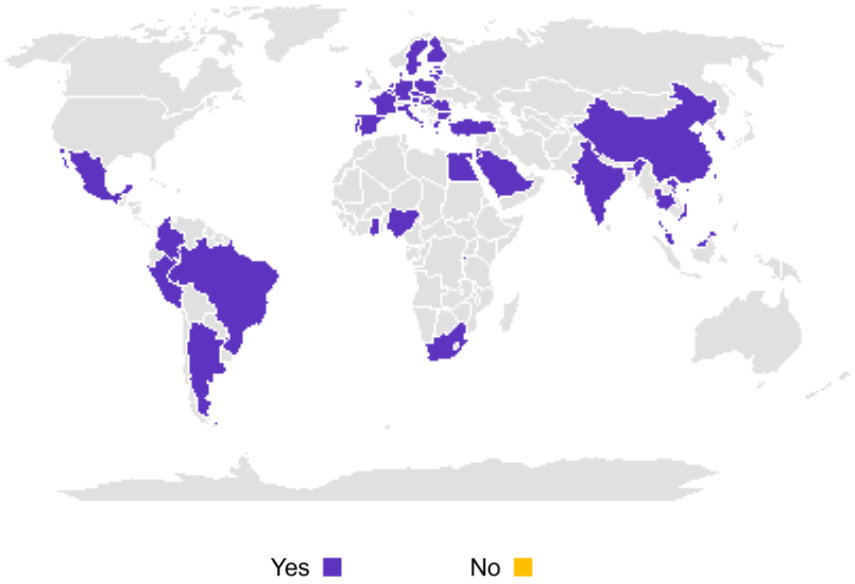
86% of markets (19) include other modalities, namely Argentina, Brazil, Colombia, Mexico, China, India, South Korea, Chinese Taipei, Malaysia, Singapore, Thailand, Vietnam, Egypt, Jordan, Turkey, Rwanda, South Africa, Ghana, and European Union.

82% of markets (18) include vaccines. Other modalities included in the guidelines are plasma fractioned products (blood products) (10), Advanced Therapy Medicinal Product (ATMPs) (3), and Cell and Gene Therapy (CGTs) (6).



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

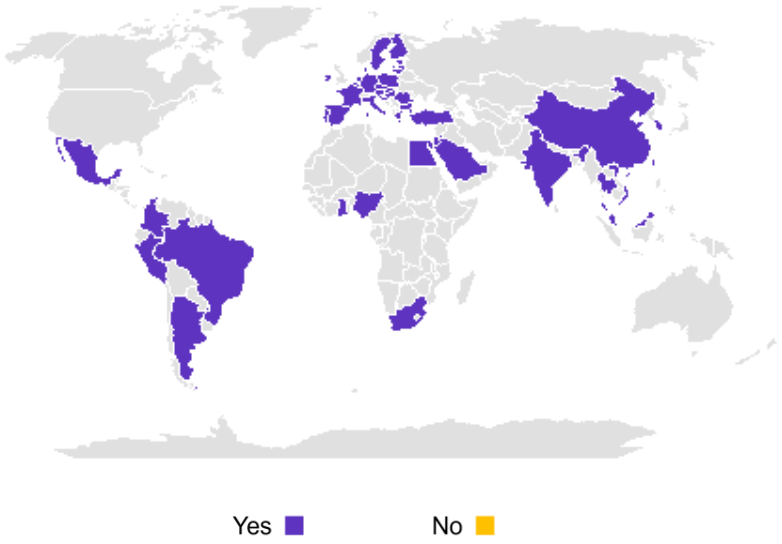
All markets (22) have risk-based categorization of changes. Changes are classified as major and minor, with moderate classification only considered in 15 markets, with different terminology, definition, and process (notification or prior approval).



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

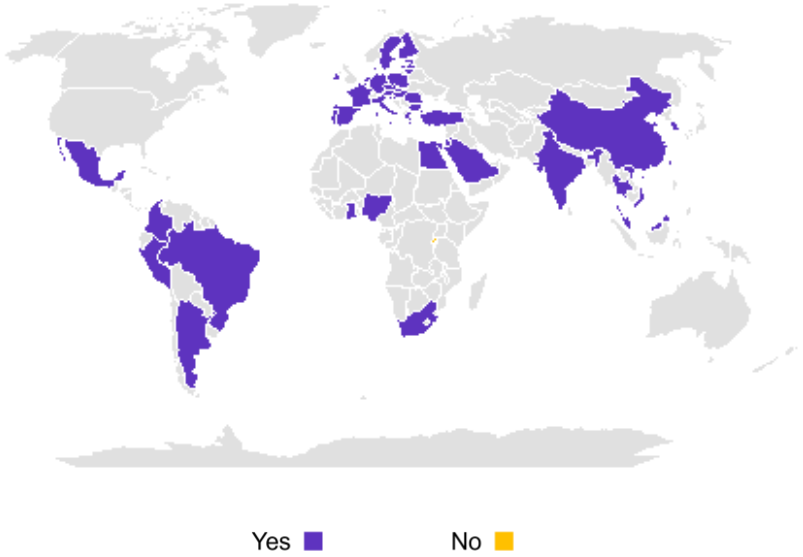
All markets (22) have timelines for approval.

- 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 markets (21) 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.

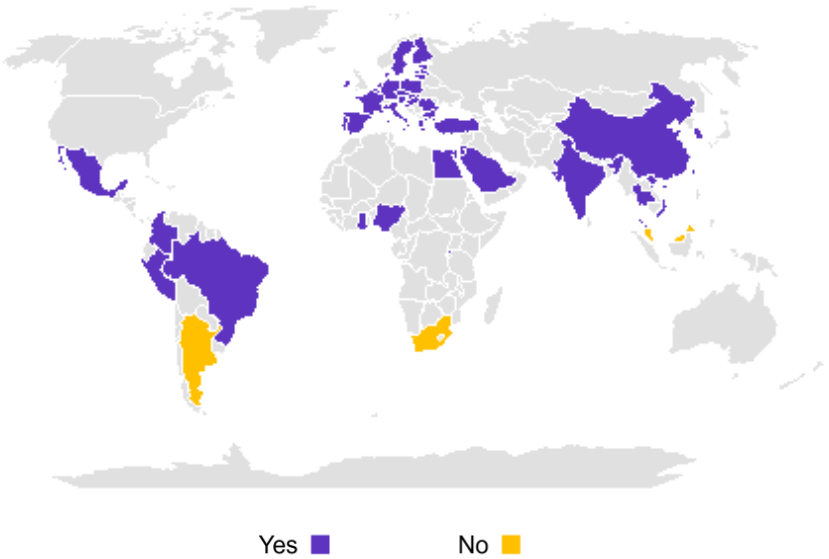


7. **Is there a submission format [CTD])?**

91% of markets (20) require/accept CTD submission format. eCTD is also accepted in nine markets, namely China, India (although no eCTD guidance), South Korea, Chinese Taipei, Thailand, Jordan, Saudi Arabia, South Africa, and European Union.

9% of markets (2) have other submission formats, namely Argentina (local format) and Malaysia (ASEAN CTD).

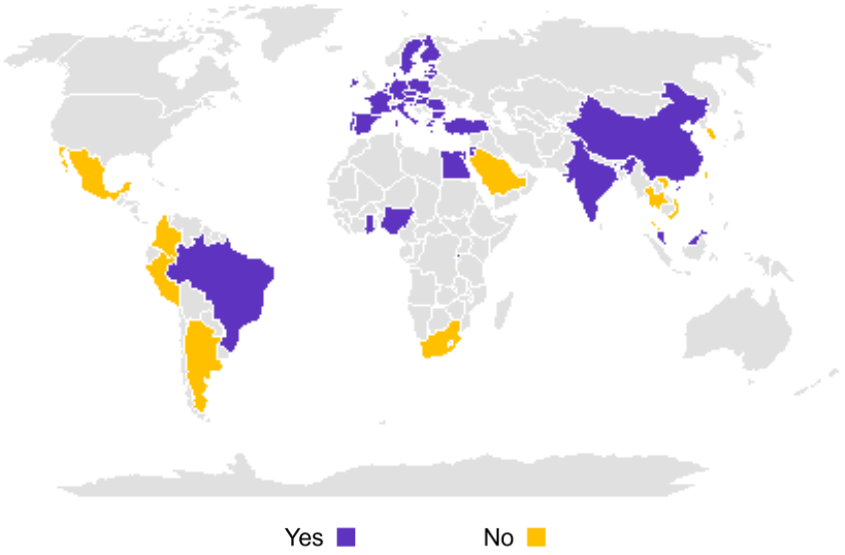
Some countries (e.g. Egypt and Singapore) consider implementing eCTD as of 2026.



8. **Is scientific advice possible?**

55% of markets (12) offer scientific advice, namely Brazil, China, India, Malaysia, Singapore, Egypt, Jordan, Turkey, Nigeria, Rwanda, Ghana, and European Union.

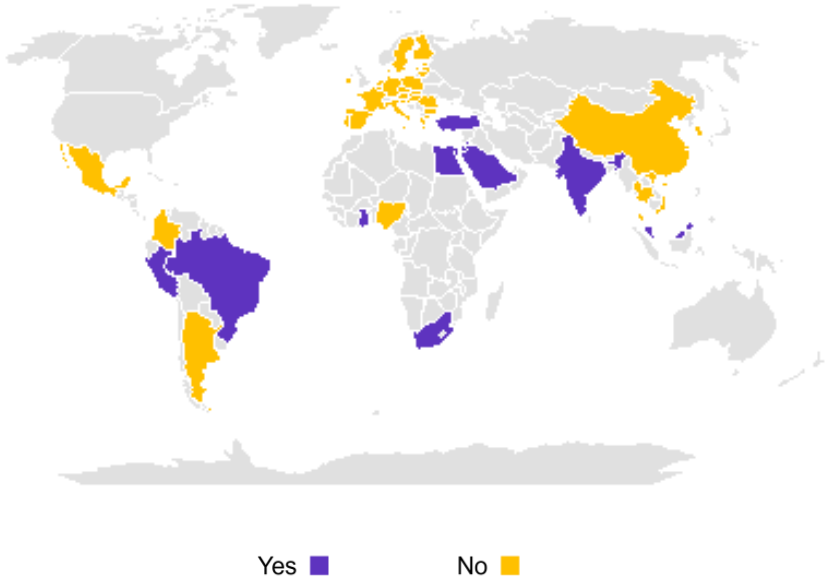
This support may be provided in a pre-submission meeting, via email, or by submitting a form, depending on the country.



9. **Is reliance for PACs possible?**

50% of markets (11) have reliance possibilities for PACs, namely Peru, Brazil, India (for biologics under specific conditions), Malaysia, Singapore, Egypt, Saudi Arabia (draft guideline on abridged pathway published in May 2025), Jordan (although not formal but accelerated when assessed by SRA i.e. Stringent Regulatory Authority), Turkey, South Africa, and Ghana.

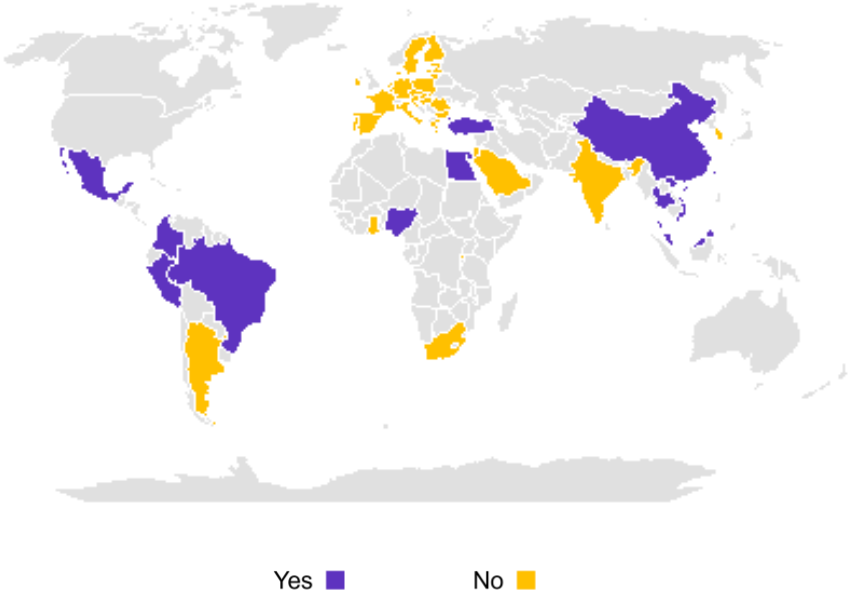
The verification or abridged routes consider assessment of the PAC by Reference Competent Authorities and International Organizations, such as EMA (EU), TGA (AU), HC (CA), FDA (US), MHRA (UK), PMDA (JP), Swissmedic (CH), EDQM, and WHO, depending upon the relying national regulatory authority (NRA).



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

59% of markets (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 Guideline*[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 Guideline*[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 Guideline*[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 Guideline*[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* [2] and *Regulation on major variations of pharmaceutical products with an approved marketing authorization*[3], 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 Guideline*[1]:

- **Low convergence** (1 or none of the 3 parameters are aligned),
- **Medium convergence** (2 parameters are aligned),
- **High convergence** (all 3 parameters are aligned).

[2] ANMAT-MED-MPR 001-00

[3] 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 biologics may partially address the changes considered for this study, refer to WHO or ASEAN guidelines, and/or lack any specific guideline on these types of changes for biotherapeutic products, thus leading to significant divergences in the region.

One country, Thailand, fully cross-references the *WHO Reference Guideline*[1], while two other countries (Malaysia and India) have a variation guideline for biologics with changes description closely following *WHO Reference Guideline*[1] (2014 version for Malaysia[4]). 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 Guideline*[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).

The general picture of alignment in APAC with the *WHO Reference Guideline*[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																

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

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

- **Low convergence** (1 or none of the 3 parameters are aligned),
- **Medium convergence** (2 parameters are aligned),
- **High convergence** (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 Guideline*[1] (Saudi Arabia, Turkey), countries following WHO recommendations (Egypt, Jordan), countries with some divergences from *WHO Reference Guideline*[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 Guideline*[1] for changes to biotherapeutics, Egypt having recently adopted its *Guideline on the regulation of post-approval changes to a registered Biotherapeutic products*[5] and Jordan cross-referencing to *WHO Reference Guideline*[1] within its *Instructions of Changes to Drugs Registered in 2017*[6].

Two other countries (Saudi Arabia and Turkey) do not follow *WHO Reference Guideline*[1] as they have a similar model to what is seen in the *EU Variation Guidelines 2013*[10], encompassing specific descriptions, risk-based categorization, and requirements for changes affecting biotherapeutic products.

Three countries follow the *WHO Reference Guideline*[1] description of changes (South Africa, Ghana, and Rwanda). However, as South Africa (*SAHPGL-PEM-BIO-05 - Biotherapeutic medicines amendment guideline*[7]) also has a model similar to the EU variations guideline, it shows also 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 Guideline*[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*[8], "The general

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

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

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

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

principles set out in this document may also apply to other biotherapeutic products," and are mostly based on the *WHO Reference Guideline*[1], except that there are no published timelines for approval.

In terms of the convergence level of MEA countries with the *WHO Reference Guideline*[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 Guideline*[1]:

- **Low convergence** (1 or none of the 3 parameters are aligned),
- **Medium convergence** (2 parameters are aligned),
- **High convergence** (all 3 parameters are aligned).

4.4 Europe

The European Commission has recently released the *Draft EU Variation Guideline 2025*[9], which will replace the current *EU Variations Guidelines*[10] and reflect the 2024 amendment of the *Commission Regulation (EC) No 1234/2008*[10] through *Commission Delegated Regulation (EU) 2024/1701*[11]. The final version of the new Variation Guidelines is expected to enter into force on 15 January 2026.

As with the previous framework, the new *Draft EU Variation Guidelines 2025*[9] encompass post-authorization changes for all types of registered products, including biological products. Variations are classified into three risk-based categories—Type IA, Type IB, and Type II—corresponding to minor, moderate, and major changes, respectively, which are also reflected in the *WHO Reference Guideline*[1]. However, WHO mentions that the marketing authorization holder should submit a PAS (post-approval supplement) for moderate changes and receive a notification of approval from the NRA before implementing the change.

The timelines for regulatory approval of these changes remain broadly consistent with those outlined by WHO. The EU framework also permits multiple changes for the same product filed in a single submission provided that the changes are related and/or supported by the same information and goes beyond with work-sharing (where the same variation, or group of variation(s) affect several medicinal products from the same MAH) and super-grouping, which enables the submission of identical changes across multiple marketing authorizations in a single notification, provided specific conditions are met. Similarly, WHO encourages the use of comparability protocols (also referred to as “post-approval change management protocol – PACMP") while EC provides further clarity by introducing different risk-based categories for supporting the introduction of PACMP and related results; the EMA also allows possible use of “broader protocols” as per ICHQ12.

The EMA conducts independent assessments of PACs and applies recognition within the EU/EEA, but there are no reliance procedures on countries outside the EU/EEA. However, EMA actively participates in international collaborative initiatives supporting reliance for PACs through pilots and specific pathways, such as *ICMRA PQKM Collaborative Pilot*[12], *EMA/WHO/industry pilots*[13], *WHO Collaborative Registration Procedure using Stringent Regulatory Authorities (WHO SRA-CRP)*[14].

To further understand the alignment between the *Draft EU Variation Guidelines 2025*[9] and *WHO Reference Guideline*[1] in the classification of PACs for biological products, the following table presents a comparative summary of the ten CMC scenarios that are subject of this analysis, including both

[9] Draft EU Variation Guidelines 2025

[10] Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products

[11] Commission Delegated Regulation (EU) 2024/1701 of 11 March 2024 amending Regulation (EC) No 1234/2008 as regards the examination of variations to the terms of marketing authorisations for medicinal products for human use

[12] Extension of the ICMRA PQKM Collaborative Pilots

[13] Reliance for post-authorisation changes: pilots for the pharmaceutical industry

[14] WHO collaborative registration procedure using stringent regulatory authorities’ medicine evaluation: reliance in action?

drug substance and drug product. The analysis highlights the level of regulatory convergence or divergence between them.

Europe - CMC changes	Drug substance	Drug product
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 Guideline*[1]:

- **Low convergence** (1 or none of the 3 parameters are aligned),
- **Medium convergence** (2 parameters are aligned),
- **High convergence** (all 3 parameters are aligned).

5. Conclusions and recommendations

The analysis of PACs regulations across 22 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, 59% 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, 86% 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 nine countries also accepting eCTD. Scientific advice is available in 55% of the countries, and reliance mechanisms are present in 50%. Additionally, 59% 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 Guideline*[1]. The following country groupings can be identified based on their alignment:

- Countries that have adopted the *WHO Reference Guideline*[1] (Egypt, Thailand, Jordan)
- Countries with PACs frameworks similar to the current EU's Variations Guidelines[10], 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 Guideline*[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 Guideline*[1] (major or moderate categorization).

These survey results related to PACs regulatory framework are aligned with those from an earlier industry survey[15] on PACs and reliance.

Main highlights:

- 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 3-tier categorization, requirements, and timelines allows predictability and consistency in the handling of changes without the need for additional local requirements. The selection of the reference guideline should be based on a careful assessment of NRA resources and capabilities.
  - Partial alignment and/or adoption of national variants with WHO[1] or EMA[9] guidelines limits the applicability of reliance strategies and change management, making them less feasible.
  - Notification categories (e.g "Do &Tell" for minor changes, and "Tell, Wait & Do" for moderate changes) can help reduce administrative burden and ensure timely implementation of changes with no or minimal impact on quality, safety, and efficacy of the product.
- Expanding reliance practices to include life cycle management—supported by reliance pilots that facilitate end-to-end harmonization—will accelerate the approval of changes, thus patient access to innovative, high-quality, and safe products.
- Convergence of categorization, requirements, and timelines as well as leveraging adoption of the ICH CTD format/content (including M4Q) drives toward a harmonized dossier and further enables reliance process.

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

- Adopting grouping of multiple changes or multi-products submissions enables efficient management of changes across products, reducing duplicative assessment, thus accelerating the implementation of changes worldwide.
- To reduce shortage risk and improve supply continuity when changing manufacturing sites, we advocate for risk-based strategies—such as reliance on GMP inspection, enabling multisite registrations, minimizing duplicative data requirements, and Q12 implementation (e.g. PACMP adoption).

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 NRAs 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 PACs.

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
European Union
Draft EU Variations Guidelines 2025
EU Variation Guidelines 2013
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

7. Annex 1. European Union

Analysis of PAC CMC scenarios

A detailed review of these 10 common CMC PACs under the *Draft EU Variation Guidelines 2025*[9] shows that the EC applies a risk-based approach. The comparison between *Draft EU Variation Guidelines 2025*[9] and *WHO Reference Guideline*[1] for PACs in biologics shows a generally aligned regulatory framework, particularly in terms of technical requirements and evaluation timelines. However, though applying a risk-based approach, the *Draft EU Variation Guidelines 2025*[9] is generally more granular in the categorization of the changes with several scenarios still categorized as Type II (major) for biologicals.

Although the technical requirements outlined by WHO and EC exhibit substantial similarities, the *Draft EU Variation Guidelines 2025*[9] lacks explicit provisions (supportive data required) for major PACs. Similarly, some changes may be downgraded as type IB by default, if not part of the listed categories. Thus, this level of interpretation may limit its applicability and transferability to regulatory authorities in less mature NRAs. The *Draft EU Variation Guidelines 2025*[9] also introduces flexibility through the incorporation of more advanced regulatory tools—such as extrapolation, modelling approaches aligned with ICH Q1 draft revision, and the use of pilot batches—which collectively contribute to more efficient submission timelines.

In addition, according to EMA post-authorization procedural advice for users of the centralized procedure[16], certain changes may be managed within the company's Quality Management System (QMS) without the need for a variation to the marketing authorization. This distinction highlights that while EMA maintains a stricter categorization for many changes to biologics, some operational modifications may still be handled flexibly under QMS, depending on their impact on the dossier.

In terms of regulatory timelines, the *Draft EU Variation Guidelines 2025*[9] issued by EMA are broadly aligned with *WHO Reference Guideline*[1]. For Type II variations—classified as major changes—both frameworks foresee evaluation periods ranging from approximately 30 to 90 working days (3 to 6 months and up to 10 months for safety and efficacy changes as per *WHO Reference Guideline*[1]), depending on the complexity of the changes and the impact on the Product Information. For Type IA (minor) and Type IB (moderate) changes, which do not require prior approval, EMA typically processes notifications of Type IB changes within 1 to 3 months in practice, similar to WHO's expectations.

The tables below show the alignment between *Draft EU Variation Guidelines 2025*[9] and *WHO Reference Guideline*[1] for the ten CMC changes for drug substance and drug product across three parameters: categorization of the changes, associated requirements, and timeframes. Alignment is color-coded as follows: red indicates low alignment, yellow indicates moderate alignment, and green

[16] European Medicines Agency post-authorisation procedural advice for users of the centralised procedure

indicates high alignment. *Total convergence level* row is the level of regulatory convergence or divergence of the change, color-coded as light blue for less aligned (1 or none of the 3 parameters are aligned), medium blue for moderately aligned (2 parameters are aligned), and dark blue for very aligned.

Europe - Manufacturing Facility changes		
Parameters	**Drug substance**	**Drug product**
Categorization		
Requirements		
Timeframes		
Total convergence level		

Legend:
Alignment level of country vs WHO guidance (parameters: categorization, requirements and timeframes):
- Less aligned **(red),**
- Moderately aligned **(yellow),**
- Very aligned **(green).**

Convergence level of country vs WHO guidance (global: summary of the three parameters):
- **Low convergence** (1 or none of the 3 parameters are aligned),
- **Medium convergence** (2 parameters are aligned),
- **High convergence** (all 3 parameters are aligned).

When analysing **manufacturing facility changes** for Drug Substances where the active substance is a biological substance, EMA applies more stringent criteria than WHO. Specifically, the addition or replacement of a manufacturing process is classified as Type II variation (major change) by the *Draft EU Variation Guidelines 2025*[9] while it may be a moderate change in *WHO Reference Guideline*[1] (under specified conditions). Only addition or replacement of a manufacturing site responsible for sterilization of the active substance using a Ph. Eur. method and addition or replacement of a batch control/testing site are classified as type IB. On the other hand, the duplication of line (frequent variation type) within the same facility in EMA is considered GMP. However, EMA and WHO are aligned in classifying the deletion of a manufacturing site as a Type IA variation (minor change).

For Drug Product, EMA adopts a risk-based approach to the categorization of changes, generally applying less stringent requirements than WHO. However, the level of stringency varies depending on the nature of the change. For example, the addition or replacement of sites with novel or complex manufacturing processes is classified as type II variation (major change) by EMA, being more stringent, while the addition of a site responsible for any manufacturing operation is categorized as type IB, which aligns with *WHO Reference Guideline*[1] but entails less stringent conditions and requirements. The deletion of a manufacturing site is aligned between both guidelines as a Type IA variation (minor change).

The conversion of a manufacturing facility for Drug Substance or Drug Product from single-product to multi-product facility is not explicitly addressed in EMA guideline. This type of change is considered a GMP-related matter and is expected to be managed within the Company's PQS.

Europe - Manufacturing Process changes		
Parameters	**Drug substance**	**Drug product**
Categorization		
Requirements		
Timeframes		
Total convergence level		

Alignment level of country vs WHO guidance (parameters: categorization, requirements and timeframes):
- Less aligned **(red),**
- Moderately aligned **(yellow),**
- Very aligned **(green).**

Convergence level of country vs WHO guidance (global: summary of the three parameters):
- **Low convergence** (1 or none of the 3 parameters are aligned),
- **Medium convergence** (2 parameters are aligned),
- **High convergence** (all 3 parameters are aligned).

For **manufacturing processes changes** of Drug Substances involving biological products, minor modifications are classified by EMA as Type IB variations. This classification is not fully aligned with WHO, which may consider certain manufacturing process changes as minor. Major changes with potential impact on product quality are classified by EMA as Type II variations (without specific conditions), which is aligned with WHO's approach to critical changes.

For Drug Product manufacturing processes changes, EMA applies a risk-based approach with no specific limiting conditions for biologics, focusing primarily on changes to the manufacturing process itself, rather than on scale changes, equipment changes or the addition of process steps (as in WHO). EMA details also three specific types of changes not included in WHO classification. EMA distinguishes between changes in manufacturing process and changes in batch size, treating them separately, as type IB (when no associated process change). Like-for-like equipment changes are typically managed as GMP within the EU and do not require variation submission. *WHO Reference Guideline*[1] would benefit from alignment by adapting a category related to process changes, rather than focus on equipment changes and addition of steps.

Additionally, WHO requires more extensive supportive data, including stability data for three commercial-scale batches, whereas EMA may accept data from a single pilot-scale batch.

Europe - Pharmacopoeia standard/monograph changes		
Parameters	Drug substance	Drug product
Categorization		
Requirements		
Timeframes		
Total convergence level		

Legend:
Alignment level of country vs WHO guidance (parameters: categorization, requirements and timeframes):
- Less aligned **(red),**
- Moderately aligned **(yellow),**
- Very aligned **(green).**

Convergence level of country vs WHO guidance (global: summary of the three parameters):
- **Low convergence** (1 or none of the 3 parameters are aligned),
- **Medium convergence** (2 parameters are aligned),
- **High convergence** (all 3 parameters are aligned).

Changes related to **Pharmacopoeial standards and monographs** for both Drug Substance and Drug Product are categorized as minor changes by EMA and WHO, showing alignment in their classification approach. However, EMA requires compliance with the European Pharmacopoeia (Ph. Eur.) or the pharmacopoeia of an EU Member State, whereas WHO accepts compliance with any recognized pharmacopoeia.

Europe - Specification and/or Analytical methods changes		
Parameters	**Drug substance**	**Drug product**
Categorization		
Requirements		
Timeframes		
Total convergence level		

Legend:
Alignment level of country vs WHO guidance (parameters: categorization, requirements and timeframes):
- Less aligned **(red),**
- Moderately aligned **(yellow),**
- Very aligned **(green).**

Convergence level of country vs WHO guidance (global: summary of the three parameters):
- **Low convergence** (1 or none of the 3 parameters are aligned),
- **Medium convergence** (2 parameters are aligned),
- **High convergence** (all 3 parameters are aligned).

EMA applies a risk-based approach to **changes in specification and analytical methods** for Drug Substance and Drug Product, classifying the deletion of specification attribute with impact on quality as Type II variation, as well as changes outside the approved specification acceptance criteria, showing higher stringency than WHO. Similarly, introduction, replacement, or substantial changes to a biological/immunological/immunochemical analytical procedure for biological Drug Substances and Drug Products are also considered Type II, reflecting also a more stringent approach.

For analytical method changes for Drug Substance and Drug Product not involving biological, immunological, or immunochemical methods, EMA classifies the introduction or replacement of a method as Type IB variation, while minor changes are considered Type IA. This aligns with WHO, which uses only minor and moderate categories for all changes to analytical methods and does not distinguish between changes to chemical vs biological/immunological methods (except for potency).

Europe - **Shelf-life extension/changes**		
Parameters	**Drug substance**	**Drug product**
Categorization		
Requirements		
Timeframes		
Total convergence level		

Legend:
Alignment level of country vs WHO guidance (parameters: categorization, requirements and timeframes):
- Less aligned **(red),**
- Moderately aligned **(yellow),**
- Very aligned **(green).**

Convergence level of country vs WHO guidance (global: summary of the three parameters):
- **Low convergence** (1 or none of the 3 parameters are aligned),
- **Medium convergence** (2 parameters are aligned),
- **High convergence** (all 3 parameters are aligned).

For **shelf-life changes** in Drug Substance, EMA classifies the extension of the retest/storage period supported by extrapolation in accordance with ICH Q1E as a Type IB variation. In contrast, WHO only allows this categorization under exceptional circumstances. When extension is based on extrapolation or stability modelling, not in accordance with relevant stability guidelines (pending ICH Q1 revision), EMA considers it a Type II variation, whereas WHO does not permit such an approach. In this regard, EMA is less stringent than WHO.

For Drug Product shelf-life changes, both EMA and WHO classify the extension of shelf-life supported by extrapolation in line with ICH Q1E as a Type IB variation, showing alignment. However, EMA allows the use of extrapolation/modelling and accepts data from pilot-scale batches, while WHO

seems to allow only real-time data and commercial-scale batches. This reflects EMA's comparatively less stringent data requirements and acceptance of modern approaches.

Conclusions and recommendations

The EMA adopts a risk-based approach to the management of PACs, which facilitates a more efficient regulatory process. However, most changes related to biological products remain classified as Type II variations under the *Draft EU Variation Guidelines 2025*[9], despite the potential for reclassification to Type IB under defined conditions or by default when no specific category provisioned. Such reclassification could accelerate implementation timelines and reduce regulatory burden without compromising product quality or patient safety.

The *Draft EU Variation Guidelines 2025*[9] provides greater regulatory flexibility by allowing the use of PACMP, extrapolation and modelling approaches, as well as the acceptance of pilot-scale batches to support certain variations. These provisions reduce the data generation burden on manufacturers while maintaining regulatory oversight compared to *WHO Reference Guideline*[1] requirements, which typically mandate real-time data from three commercial-scale batches.

Overall, continued alignment of global regulatory frameworks—particularly in the classification of variations and data requirements—would support more agile and harmonized PAC management, benefiting both regulators and industry stakeholders.

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