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Comparison of post approval changes & requirements of US, Brazil & Mexico

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Abstract

Once the medicine's regulatory authority (RA) in a given country has approved its commercialization, the manufacturer or market authorization holder (MAH) may recognize the need for adaption to a registered dossier and make similar suggestions. If the expected modifications are thought to affect the medicine's quality, safety and efficacity, the responsible RA must provide their previous authorization. These modifications may take the form of administrative or chemical manufacturing and controls (CMC) tweaks. Through the submission of an operation known as a "post approval change submission," these variations are communicated to the relevant authority for review of the suggested changes. A change is described as "A modification in every aspect of a medicinal product. In that 3 countries classification of PAC based upon risk. In USA, the Food and Drug Administration (FDA) provide four reporting categories for post-approval adjustments are provided under Section 506 A of the Federal Food, Drugs, and Cosmetic Act and 21 CFR 314.70. In Brazil, National Health Surveillance Agency - ANVISA provide Resolution (RDC73/2016) for filing guidance of post approval change. In Mexico, Mexican health authority or COFEPRIS provide criteria to define the classification of modifications to the conditions of sanitary registry of medicines. In conclusion, USA well define and specific guideline for various type of change compare to Brazil and Mexico. While there are similarities in the post-approval filing categories between the USA, Brazil and Mexico, there are also differences in terminology, processes, timeline for approval and specific requirements. Understanding these similarities and differences is essential for companies seeking to market regulated products in 3 countries to ensure compliance with regulatory requirements and facilitate timely approvals. These timelines can vary based on the complexity of the submission and the type of product.

Keywords: CMC, SUPAC, FDA, Post Approval changes, ANVISA, COFEPRIS, MAH

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1. Introduction

Once the medicine's regulatory authority (RA) in a given country has approved its commercialization, the manufacturer or market authorization holder (MAH) may recognize the need for adaption to a registered dossier and make similar suggestions. If the expected modifications are thought to affect the medicine's quality, safety and efficacity, the responsible RA must provide their previous authorization. These modifications may take the form of administrative or chemical manufacturing and controls (CMC) tweaks. Through the submission of an operation known as a "post approval change submission," these variations are communicated to the relevant authority for review of the suggested changes.

A change is described as "A modification in every aspect of a medicinal product, including, however not restricted to, modifications in the composition, procedure and place of manufacture, specifications of the final product and constituents, packaging and it's labeling and product information."

Changes to approved items should be calculated for their impact on quality, safety, and efficacy/effectiveness, and documented accordingly. Depending on the level of impact, certain adjustments may only need the organization to document the change being estimated. Authorities use several strategies to report changes, such as annual reports, modification/variation applications, and new license applications. Manufacturers should provide authority-specific instruction documents to ensure effective compliance.

The medicinal product's entire life cycle involves industrial creation, development of products, manufacturing, and dossier submission to regulatory agencies, commercial approval, post-approval compliance, post-approval adjustments, and license renewal (after expiration).

"Specific changes that a company would like to enforce during the lifecycle of the product and how these would be

made and justified" is the definition of post-approval change management. Since the market authorization holder (MAH) will have obtained agreement from the Regulatory Authorities (RA) regarding the intended strategy and procedures to validate the impact of the change on product quality, it is hoped that this cumulative approach will result in a quicker and more predictable implementation of changes after approval. (1)

Different country classified these changes in different type based upon risk. And based upon type of change applicant have to follow procedure for approval of product change for commercialization. (1)

Table 1. US, Brazil & Mexico Regulatory authority & PAC type

Country	Regulatory authority	Known as	Type of change
USA	FDA (Food and Drug Administration)	SUPAC (Scale Up and Post Approval Changes)	Level I (Major change) Level II (Moderate change) Level III (Minor change)
Brazil	ANVISA (Agência Nacional de Vigilânci Sanitária)	Post Registration Changes	Major, Moderate & Minor Chang
Mexico	COFEPRIS (Comisión Federal para la Protección contra Riesgos Sanitarios)	Post Registration Modification	Major, Moderate & Minor modification

II. Post approval changes requirement in US

Regulatory authority: USFDA

"The Food and Drug Administration (FDA), a federal executive agency in the United States, is part of the Department of Health and Human Services". The FDA is responsible for protecting and promoting public health through the regulation and supervision of food safety, tobacco products, nutritional supplements, prescription and over-the-counter pharmaceutical drugs, vaccines, biopharmaceuticals, and blood transfusions.

The applicant may make post-approval modifications to their New Drug Application or Abbreviated New Drug Application after it has been approved, as long as they are notified to the FDA in the proper formats.

The following four reporting categories for post-approval adjustments are provided under Section 506 A of the Federal Food, Drugs, and Cosmetic Act and 21 CFR 314.70.

-21 CFR 314.70 (b): Prior Approval Supplement – PAS

-21 CFR 314.70 (3): CBE-30 (Modification to Accompany Change in 30 Days)

-21 CFR 314.70 (6): CBE-0 (Change Being Affected in 0 day)

-21 CFR 314.70 (7): Rejection Change Being Effected-0 and Change Being Affected -30

-21 CFR 314.70 (3): Yearly reports

Major Change: A major-modification is described as "an adjustment that has a significant potential of adversely affecting the identity, strength, quality, purity, or potency of a drug product, consequently impacting its safety or efficacy." It files under prior approval supplements.

Moderate Change: A moderate change that could potentially affect the identity, strength, quality, purity, or potency of a drug product, and subsequently its safety or effectiveness, typically requires the submission of either a Changes Being Affected in 30 Days (CBE-30) supplement or a Changes Being Affected (CBE-0) supplement to the FDA."

Minor Change: "Minor changes typically have minimal potential to adversely affect the identity, strength, quality, purity, or potency of a drug product, and therefore are unlikely to impact its safety or effectiveness significantly." It files under annual reports. (2)

III· Post approval changes requirement in Brazil

Regulatory authority: National Health Surveillance Agency - ANVISA

This Resolution (RDC73/2016) has the aim of categorizing the modification done after registration of medicines, demonstrating the criteria and the minimal mandatory documentation, foreknowing direct liabilities of the companies and demonstrating the simplified process for post-registration modification of instant implementation according to the category of the modification established in this rule, aiming to guaranty the quality, safety and effectiveness of these drugs.

Major Change: A major-modification is described as "an adjustment that has a significant potential of adversely affecting the identity, strength, quality, purity, or potency of a drug product, consequently impacting its safety or efficacy."

Moderate Change: A moderate change that could potentially affect the identity, strength, quality, purity, or potency of a drug product, and subsequently its safety or effectiveness.

Minor Change: "Minor changes typically have minimal potential to adversely affect the identity, strength, quality, purity, or potency of a drug product, and therefore are unlikely to impact its safety or effectiveness significantly."

General provisions relating to documentation:

- The documentation required for each change is listed in annex I.
- All requests for post-registration changes and cancellation of drug registration must be accompanied by the following documents:

I - Federal Government Payment Guide regarding the Health Surveillance Inspection Fee (TFVS) accompanied

by the respective payment receipt or exempt GRU, when applicable;

II - Petition forms duly filled in;

III - Justification of the request, including the detailed description and rationale of the proposal, as per Annex II; and

IV- Company Technical Analysis Opinion (PATE)

- Stability study data
- Stability study protocol
- Validation protocol
- Forms contained in annexes II and IV
- Package inserts and labelling according changes
- Technical document
- Production report
- Stability study
- Quality control report
- Evaluation GMP condition
- BA/BE study

Product Change History

The registered company is responsible for completing and attaching the necessary papers for each HMP process.

HMP contain following information

I – All immediate implemented post registration changes with or without protocol as well as previously approved by ANVISA.

II – Additional information

a) The list of all batches manufactured and imported in the year (date of manufacturing, batch number and size)

b) Latest tests, specification limit, analytical method of drug quality control

c) Report of complete follow up stability studies

HMP must be up to date and easily available in company.

HMP must be filed annually, in the month of drug registration anniversary.

HMP protocol must be carried out through electronic petition, no need to send paper document. (3)

IV. Post approval changes requirements in Mexico

Regulatory authority: The Mexican health authority or COFEPRIS (Comisión Federal para la Protección contra Riesgos Sanitarios)

Sanitary registration is the process of submitting a product for documentation evaluation and analysis before the country's competent health authorities.

Procedures and services are classified as,

1. HOMOCLAVE COFEPRIS-2022-022-011-A

-Minor modifications are those that have little to no effect on the drug's efficacy, safety, or quality.

-Certificate for minor modification is issued.

2. HOMOCLAVE COFEPRIS-2022-022-012-A

-Moderate modifications are those that could potentially affect the drug's efficacy, safety, and quality.

- Certificate for minor modification is issued.

3. HOMOCLAVE COFEPRIS-2022-022-013-A

-Major modifications are those that could significantly affect the drug's efficacy, safety, and quality.

-A revised sanitary registration document is provided, along with any necessary annexes. (4)

VI. Case studies

1. US: Proposed change: Modification in additive composition, greater than **10%** and qualitative change in the formulation.

Question: can we file CBE-30?

Answer: No

Required category: PAS

Justification: Significant impact on drug product safety and efficacy, FDA require filing category PAS. FDA also require cGMP inspection and comparative stability data.

Required documents:

- Debarment certificates
- Letter of authorization
- Detailed description of the change
- Detailed justification about change
- Batch record of updated formulation
- Updated drug product specification
- Comparative Biopharmaceutic Studies
- One batch with 03-month stability data of accelerated and long-term stability.
- Stability study report
- Dissolution profile of pre change batch and post change batch should match F2 criteria.
- Bioequivalence study
- Risk assessment data
- Labelling change

2. Brazil: Proposed change: Modification in additive composition, greater than 10% and qualitative change in the formulation.

Question: Can we file immediate implementation application?

Answer: No;

Yes, if change in excipients composition NMT ±5% W/W.

Required category: Individual application (Major change)

Justification: Major impact on drug product safety and efficacy, ANVISA require filing category individual application. ANVISA also require cGMP inspection and comparative stability data.

Table 2. Comparison PAC in USA, BRAZIL & MEXICO

Sr. No.	Post-approval changes	US	BRAZIL	MEXICO
Components & composition changes				
1	Reduction or removal of an excess from the batch formula.	Annual reportable		Notification
2	Modification in coating formulation.	Annual reportable		
3	Switch to a different supplier for the inactive ingredient.	Annual reportable		
4	Elimination or partial removal of a component that is meant to change the drug product's colour or flavour.	Annual reportable	Immediate-Implementation require favourable opinion of ANVISA	
5	Replacing the printing ink's ingredient to one that has been approved.	Annual reportable	Immediate Implementation	
6	A change in the composition of the excipients that is less than or equal to ± 5%, represented as a percentage (w/w) of the entire formulation.	Annual reportable	Immediate Implementation	Notification
7	A change in the composition of the excipients that is less than or equal to ± 10% of the overall formulation, represented as a percentage (w/w).	Annual reportable	Immediate Implementation	Requires notification and supporting documentation, COFEPRIS review
8	More than 10% change in the composition of the excipients, represented as a percentage (w/w) of the entire formulation, and a qualitative shift in the formulation.	Prior Approval supplement	Individual application	Prior approval Required.
9	Each qualitative and quantitative modification in excipient or change in excipient range in product.	Prior Approval supplement	Individual application	Prior approval Required.
Manufacturing site change				
10	Alter the major package manufacturing location. For both modified release and immediate release solid dose forms.	Prior approval supplement	Immediate Implementation and it require favourable opinion from ANVISA	Prior approval Required.
11	Alter the basic packaging manufacturing location. For solid dose forms with immediate release	CBE-30	Immediate Implementation and it require favourable opinion from ANVISA	Prior approval Required.
12	Manufacturing of a pharmaceutical product that has undergone aseptic processing is moved to a newly built facility.	Prior approval supplement	Individual application	
13	A transfer to a new manufacturing location for drug product or substance testing.	CBE-30	Immediate implementation	Requires notification and supporting documentation, COFEPRIS review
14	A transfer to a manufacturing facility in order to produce the last intermediate.	CBE -0	Immediate implementation	
15	For secondary packaging, relocate to a separate manufacturing location.	Annual reportable	Immediate implementation	Notification
16	Moving the labeling to a new location.	Annual reportable		Notification
17	Change of corporate name of the API manufacturing site		Immediate implementation	
18	Change of manufacturing site within the previously authorized establishment.			Notification
Manufacturing process change				
19	Modifications that could impact metering, controlled release, or other features include adding or removing a code imprint through engraving, debossing, or embossing.	Prior approval supplement		Prior approval Required.
20	Change in sterilization method.	Prior approval supplement	Individual application	Prior approval Required.
21	Equipment for lyophilization of a different size may be added or replaced.	Prior approval supplement		
22	Any significant modifications to the applicant's present production process. For example, a medication Granulation from dry to wet	Prior approval supplement	Individual application	Prior approval Required.

Sr. No.	Post-approval changes	US	BRAZIL	MEXICO
23	During the final stages that require various pieces of equipment, the production size for natural medicine products might be increased or decreased.	CBE-30		
24	Increasing or decreasing the production scale and replacing equipment are two options for natural medicinal products.	CBE-30	Immediate Implementation and it require favourable opinion from ANVISA	Requires notification and supporting documentation, COFEPRIS review
25	Modifications to the flow rate, pressure, time, or volume of the filtration process for aseptic processing.	CBE-30		
26	In-process filtration is eliminated for sterile medicinal preparations.	CBE-0		
27	Modifications to equipment with the same design and functionality.	Annual reportable	Immediate Implementation	Notification
Specification change				
28	Relaxing of acceptance criteria these changes are other than USP.	Prior approval supplement	Individual application	Prior approval Required.
29	Relaxing of acceptance criteria these changes are as per USP.	CBE-30		Requires notification and supporting documentation, COFEPRIS review
30	Deleting a test these changes are as per USP.	CBE-30		Requires notification and supporting documentation, COFEPRIS review
31	specification addition that enhances confidence in the drug's or product's substance.	CBE-0		
32	Tightening of acceptance criteria.	Annual reportable	Immediate implementation	
33	Change in analytical method	Prior approval supplement	Individual application	Prior approval Required.
Container Closure System changes				
34	primary/secondary Packaging components change for topical and parenteral.	Prior approval supplement	Individual application	Prior approval Required.
35	Semisolid dosage forms transform into polymeric compounds for liquids. (As an example, rubber or plastic)	Prior approval supplement	Individual application	Requires notification and supporting documentation, COFEPRIS review
36	The sterility of the medication product is impacted by changes to the container closing system. For example, glass vial to glass ampule.	Prior approval supplement	Individual application	Prior approval required.
37	For sterile drug product: Change from glass ampule to glass vial.	Prior approval supplement	Individual application	
38	Primary and secondary packaging components are altered for solid orals.	CBE-30	Individual application	Requires notification and supporting documentation, COFEPRIS review
39	A desiccant's addition, modification, or removal.	CBE-0		
Labelling change				
40	Change in labelled storage conditions.	PAS	Individual application	Prior approval Required.
41	Strength addition.	PAS	Individual application	Prior approval Required.
42	Precautionary measure added as a result of a post marketing analysis.	CBE-30		
43	To assure correct drug product administration, the administration statement should be clarified.	CBE-30	Immediate Implementation and it require favourable opinion from ANVISA	Requires notification and supporting documentation, COFEPRIS review
44	RLD revision.	CBE-0		
45	Modifications to the container label or package layout that comply with rules.	Annual reportable	Immediate implementation	Notification
46	Editorial modifications, such the distributor's name.	Annual Reportable	Immediate implementation	Notification

Required documents:

- The relevant documents emphasize the possible effects on product performance by contrasting the authorized and suggested production processes.
- Analytical Report physical-chemical and microbiological quality control
- Comparative dissolution profile
- One batch's stability research report is part of the HMP.
- After approval, the first two industrial batches and one batch must have long-term stability data.
- Photostability study report.
- Comparability data between the drug component, new excipient and packaging.
- Specification of excipient.
- For first-time excipient usage in a medicine or new administration route, include production details, characterisation, and controls, along with bibliographic references to support safety data.
- BA/BE study
- Process validation protocol
- Additional information for excipients of animal origin
- Validation report for analytical method

3. Mexico: Proposed change: Modification in additive composition, greater than **10%** and qualitative change in the formulation.

Question: can we file COFEPERIS-2022-022-013-A?

Answer: No

Required category: COFEPRIS-2022-022-012-A (Moderate change) Requires notification, supporting documentation and COFEPRIS review

Justification: Potential impact on drug product safety and efficacy, COFEPRIS require filing category COFEPRIS-2022-022-012-A. COFEPRIS also require cGMP inspection and comparative stability data.

Required documents:

Legal administrative:

- Certificate of GMP or equivalent document
- CLV, CPP or equivalent document

Technical documents:

- Drug control part 3.2.S.4, 3.2.S.5 and 3.2.R
- Medication qualitative and quantitative formula
- Manufacturing information of additives
- Control of additive document
- Validation of analytical methods
- Stability study
- Report of comparative dissolution profile

7. Conclusion

USA well define and specific guideline for various type of change compare to Brazil and Mexico.

Applicant should have scientific rationale to any change pertaining to Approved Product.

While there are similarities in the post-approval filing categories between the USA, Brazil and Mexico, there are also differences in terminology, processes, timeline for approval and specific requirements. Understanding these similarities and differences is essential for companies seeking to market regulated products in 3 countries to ensure compliance with regulatory requirements and facilitate timely approvals.

The FDA, ANVISA and COFEPRIS have target review timelines for different types of post-approval submissions. These timelines can vary based on the complexity of the submission and the type of product.

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Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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