INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

Review Article

Comparative Post Approval Changes Requirement Of Pharmaceutical Drug Product And Drug Substance In USA And Canada

Renish S. Pethani*, Dr. Maitreyi Zaveri, Dr. Niranjan Kanaki

[1]*K.B. Institute of Pharmaceutical Education and Research, Kadi Sarva Vishwa Vidyalya, Gandhinagar, Gujarat.*
[2] *HOD of Pharmacognosy & Regulatory Affairs, K.B Institute of Pharmaceutical Education and Research, Kadi Sarva Vishwa Vidyalya, Gandhinagar, Gujarat.*
[3]*Associate Professor of Pharmacognosy Department, K.B Institute of Pharmaceutical Education and Research, Kadi Sarva Vishwa Vidyalya, Gandhinagar, Gujarat.*

ARTICLE INFO

Received: 19 June 2024
Accepted: 23 June 2024
Published: 01 July 2024

Keywords:
Post approval, post NOC approval; Canada, drug substance changes, prior approval supplement, annual report, annual notification, comparative post approval changes.

DOI:
10.5281/zenodo.12609178

ABSTRACT

This article presents a comparative examination of the post-approval changes requirements governing pharmaceutical drug products and drug substances in the United States (USA) and Canada. Regulatory frameworks in both countries are crucial for ensuring the safety, efficacy, and quality of pharmaceuticals while facilitating innovation and access to healthcare. the research methodology involves a thorough examination of relevant guidelines, regulations, and case studies from both countries. Key factors such as the types of changes, submission requirements, approval processes, and timelines will be scrutinized to understand the intricacies of regulatory compliance. Additionally, the impact of these requirements on industry practices, innovation, and patient access to medicines will be explored.

INTRODUCTION

Once the drug's regulatory authority (RA) in a given nation has approved its commercialization, the manufacturer may recognize the need for adjustments to a registered dossier and make such suggestions. The concerned RA must provide their prior approval if the proposed modification is believed to have an impact on the drug's quality, safety, or efficacy. Through the submission of an application known as a "post approval change submission," these modifications are communicated to the relevant authority for review of the suggested changes. For submissions of post-

***Corresponding Author:** Renish S. Pethani
Address: *K.B. Institute of Pharmaceutical Education and Research, Kadi Sarva Vishwa Vidyalya, Gandhinagar, Gujarat*
Email ✉: pethanirenishkumar2000@gmail.com
Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

market changes, numerous nations have their own regional laws. Information about post-approval changes is available in the United States of America through the Scale up and post-approval changes" guidance and in Canada known as post NOC guidance as per health Canada authority. (1)(2)

DISCUSSION:

USA:

Post approval filing category in USA

1. Major changes: A major change refers to a modification that has a substantial potential to adversely affect the identity, strength, quality, purity, or potency of a drug product, thereby impacting its safety or effectiveness. Filing category: prior approval supplement Time line: 06 to 08 months
2. Moderate changes: A moderate change refers to a modification that has a moderate potential to adversely affect the identity, strength, quality, purity, or potency of a drug product, thereby impacting its safety or effectiveness. Filing category: CBE-0, CBE-30 Timeline: 30 days
3. Minor changes: A minor change refers to a modification that has minor or less effect to the identity, strength, quality, purity, or potency of the drug product. Filing category: annual report Timeline: Submit within 60 days after annual period time (1)

Common annual report format in USA.

Forms require for annual report: 2252

1.1 FDA form (356h)
1.2 cover letter
1.13.1 non clinical
1.13.2 summary of clinical study
1.13.4 labelling
1.13.5 summary of manufacturing changes
1.13.7 summary of significant information
1.13.11 distribution data
1.13.12 post market commitment
1.13.13 status of other post market study
1.13.14 log of out standard business Attachment
3.2.s.2.1 DMF amendment
3.2.s.4.1 API specification
3.2.s.4.2 STP API
3.2.p.3.3 trend data, equipment documents
3.2.p.4.1 product specification
3.2.p.4.2 product standard testing procedure
3.2.p.4.4 impurity document
3.2.p.7 container closure system specification
3.2.p.8.3 stability data

CANADA:

There are 4 categories of post-notice of compliance (NOC) changes

1. Level I (major changes)

This type of modification has a substantial potential to adversely affect the identity, strength, quality, purity, or potency of a drug product, thereby impacting its safety or effectiveness.

Filing category: supplement

supporting document should be submitted to health Canada for review prior to implementing the change.

2. Level II (moderate changes):

This type of modification has a moderate potential to adversely affect the identity, strength, quality, purity, or potency of a drug product, thereby impacting its safety or effectiveness.

Filing category: notifiable changes

supporting document should be submitted to health Canada for review prior to implementing the change.

(not applicable to human pharmaceutics)

3. Level III (minor changes):

A minor change refers to a modification that has minor or less effect to the identity, strength, quality, purity, or potency of the drug product.

Filing category: annual notification

Supporting document should not be submitted, but should be available to health Canada upon request.

4. Level IV (minor changes):

supporting document should be kept record by the sponsor or manufacturer. (2)

Annual report format in Canada:

Forms for annual report-3011

- In Canada supporting data should not be submitted, but should be available to health Canada within thirty calendar days if requested at any time.
- Notify agency at a implement time or during notification period time
- Submit only annual report form (3011)

The following documents should be including, where applicable, with the sponsor's annual drug notification. A listing of all level III changes for each new drug that has received a NOC and that have occurred in the preceding 12 months compiled using the level III form or format. A copy of the most recent revised label inner and outer) if a level III labels change has been made (7)

COMPARATIVE POST APPROVAL CHANGES IN USA & CANADA

Drug product changes

Table 1. Components and composition changes (4,5)

Country	Type of change	Filing category	Major documents	Other common documents
USA	Change in excipients composition, expressed as percentage (w/w) of total formulation, greater than 10% and qualitative change in the formulation For example: Filler 10%	PAS	01 batch with 03-month stability data of Accelerated and long-term stability data.	• Dissolution document • Bioequivalence study • Stability summary and commitment • Labelling (PI, medication guide) • Intended & exhibit BMR, BPR
Canada	Change in excipients composition, expressed as percentage (w/w) of total formulation, greater than to 10% (the proposed change affects the solubility and absorption)	supplement	Minimum 02 batches with 03-month stability data of Accelerated and long-term stability data.	

Table 2. Manufacturing site changes (1,2)

country	Type of change	Filing category	Major documents	Other common documents
USA	Move to different site for primary packaging of IR solid oral dosage form New site has never been inspected and not satisfactory GMP	PAS	01 batch with 03-month stability data of Accelerated and long-term stability data.	• Administrative document (GMP, debarment certificate) • Exhibit BMR, BPR • Intended BMR, BPR • Product specifications and STP • COA-FPP, Raw material, in process, packaging.
Canada	Move to different site for primary packaging of IR solid oral dosage form New site has never been inspected and not satisfactory GMP	supplement	Minimum 02 batches with 03-month stability data of Accelerated and long-term stability data. Bio equivalence data	

Table 3. Manufacturing process changes (1,2)

Country	Type of change	Filing category	Major documents	Other common documents
USA	Changes in equipment with different design that does not affect the process methodology	CBE-30	01 batch with 03-month stability data of Accelerated and long-term stability data.	• Detailed justification • Intended and exhibit BMR, • Bioequivalence report • Batch formula of proposed dosage form • Stability commitment • Raw material specs • Working standard and impurity standard COA • Method validation report
Canada	Changes in equipment with different design that does not affect the process methodology& same principles if not then filing supplement	Annual notification	Minimum 02 batches with 03-month stability data of Accelerated and long-term stability data.	

Table 4. Specification changes (1,2)

Country	Type of change	Filing category	Major documents	Other common documents
USA	Relaxing of an acceptance criterion as per USP monograph	CBE-30	Proposed drug product Specification Standard testing procedure	• Detailed justification • Trend data of 10 commercial batches • Validation reports • Description of the batches and summary of results
Canada	Relaxation of an acceptance criterion as per Canadian reference product	Annual notification	Proposed drug product specification Standard testing procedure Description of the proposed batches and summary of results at least one batch	

Table 5. Container closure system changes (1,2)

Country	Type of change	Filing category	Major documents	Other common documents
USA	For liquid, semisolid dosage forms change to in polymeric materials (e.g., plastic, rubber)	PAS	01 batch with 03-month stability data of Accelerated and long-term stability data.	• Detailed justification • Updated post approval stability protocol and commitment • Information on the proposed container closure system • FPP-COA • Intended BPR • Exhibit BPR • Specs container
Canada	For liquid, semisolid dosage forms change to in polymeric materials (e.g., plastic, rubber)	supplement	Minimum 02 batches with 03-month stability data of Accelerated and long-term stability data. Data demonstrating the suitability of the container closure system. Evidence of process validation	

Drug substances changes

Table 6. Manufacturing site changes (1,2,6)

Country	Type of change	Filing category	Major documents	Other common documents
USA	Move to a manufacturing site for the manufacture or processing of drug substance Where the site has never never been inspected by FDA	PAS	GMP certificate EIR report 03 lot equivalency data of pre change batch and post change batch	• Updated COA • Impurity document • Updated specification • Updated STP
Canada	Move to a manufacturing site for the manufacture or processing of drug substance Where not valid or approved CEP	supplement	CEP certificate Drug Establishment License of new site Stability data at least 03 month of accelerated	

Table 7. Specifications changes (1,2,6)

Country	Type of change	Filing category	Major documents	Other common documents
USA	Relaxation of an acceptance criteria other than USP monograph.	PAS	Rational for the proposed change. Updated Spec and STP	• Detailed justification • Updated COA • Impurity profile • Justification of proposed parameter
Canada	Relaxation of an acceptance criteria other than Canadian reference	supplement	Comparative multipoint dissolution profile of one batch Updated Spec/STP	

Table 8. Container closure system changes for drug substance (1,2,6)

Country	Type of change	Filing category	Major documents	Other common documents
USA	Change in primary container closure system for the storage and shipment of the drug substance	PAS	01 batch with 03-month stability data of Accelerated and long-term stability data.	• Evidence of process validation if product is sterile • Proposed container closure system information • Information about suitability • Stability protocol and commitment • COA • justification
Canada	Change in primary container closure system for the storage and shipment of the drug substance	supplement	Minimum 02 batches with 03-month stability data of Accelerated and long-term stability data.	

CASE STUDIES

USA

Change proposed: change in the API sources/ alternate API sources

Question: can we file CBE-30?

Answer: No

Yes, if API source change within organizations

Required category: PAS

Required documents:

- Debarment certificates
- Letter of authorization
- Summary of biopharmaceutics
- Certificate of analysis finished product and raw material
- Stability protocol and commitment
- Accelerated and long-term stability data
- Justification of specification
- Finished product specification

- STP finished product
- In process specification and standard testing procedure

CANADA

Change proposed: change in the API sources/ alternate API sources

Question: Can we file annual notification?

Answer: Yes

Justification: health Canada require only valid CEP,

If API specific site associated with valid CEP has been previously approved either API manufacturing site listed on your company's DEL.

Required documents:

- A copy of certificate of suitability (CEP) issued by EDQM which is current and valid CEP.

Annexes as well as attestations from drug substance manufacture in accordance with the guidance document "use of certificates of suitability as supporting information in drug submission

CONCLUSION

- USA well define and specific guideline for various type of change compare to Canada.
- Applicant should have scientific rationale to any change pertaining to Approved product in USA and Canada.
- While there are similarities in the post-approval filing categories between the USA and Canada, there are also differences in terminology, processes, and specific requirements. Understanding these similarities and differences is essential for companies seeking to market regulated products in both countries to ensure compliance with regulatory requirements and facilitate timely approvals.
- Both the FDA and Health Canada 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.

Financial Disclosure statement

The author received no specific funding for this work.

Conflict of Interest

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

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HOW TO CITE: Renish S. Pethani*, Dr. Maitreyi Zaveri, Dr. Niranjan Kanaki, Comparative Post Approval Changes Requirement Of Pharmaceutical Drug Product And Drug Substance In Usa And Canada, Int. J. of Pharm. Sci., 2024, Vol 2, Issue 7, 138-143. https://doi.org/ 10.5281/zenodo.12609178