Available online on 15 Jun, 2026 at https://ijdra.com/index.php/journal

International Journal of Drug Regulatory Affairs

Published by Diva Enterprises Pvt. Ltd., New Delhi
Associated with Delhi Pharmaceutical Sciences & Research University

Review Article **Open Access**

Lifecycle Continuity Through Regulatory Compliance: A Comparative Evaluation of Post-Approval Change Strategies for APIs and Drug Products Under the Regulatory Frameworks of Saudi Arabia, the United States, Australia, and Eurasia

Sharlee Krunalkumar Shah [a], Vinit Movaliya[a], Zuki Patel[a], Maitreyi Zaveri[a], Akshita Parekh[b], Niranjan Kanaki[a,*]

[a]*Department of Pharmaceutical Regulatory Affairs, K. B. Institute of Pharmaceutical Education and Research (KBIPER), a college of Kadi Sarva Vishwavidyalaya (KSV), Sector-23, Gandhinagar 382023, Gujarat, India.*

[b]*Intas Pharmaceuticals Ltd., Corporate House, Near Sola Bridge, SG Highway, Thaltej, Ahmedabad – 380054. Gujarat. India*

Abstract

The paper presents a parallel assessment of after-clearance change demands for drug substances between the regulatory structures of Saudi Arabia, US, Australia, and the Eurasian Economic Union. The regulatory structures that steer these changes in each area are fundamental for the upkeep of drug safety, usefulness, and standards as healthcare advances. The research strategy calls for a careful study of relevant standards, rules, and case assessments from all named realms. Key aspects such as the nature of amendments, data demands, clearance pathways, and treatment schedules are analyzed to understand the challenges of regulatory adherence. Added to that, the effect of these demands on market ventures, advancement, and access to treatments has been evaluated.

Conclusion: In conclusion, The Review also explain that this comparative analysis demonstrates that while Saudi Arabia, US, FDA, Australia, and Eurasian Economic Union regulations on API and drug product post-approval change management are all risk-based and critical to continued safety, efficacy, and quality, these regulations also vary with respect to classification, data, and timelines.

Keywords: Post approval changes, SFDA, USFDA, TGA, EAEU

Article Info: Received 21 Mar 2026; Review Completed 17 May 2026; Accepted 14 May 2026

Cite this article as:
Shah SK, Zaveria M, Kanaki N, Parekh A. Lifecycle Continuity Through Regulatory Compliance: A Comparative Evaluation of Post-Approval Change Strategies for APIs and Drug Products Under the Regulatory Frameworks of Saudi Arabia, the United States, Australia, and Eurasia. Int. J. Drug Reg. Affairs [Internet]. 2026 Jun 15 [cited 2026 Jun 15]; 14(2):54-59. Available from:
http://ijdra.com/index.php/journal/article/view/891

DOI: https://doi.org/10.22270/ijdra.v14i2.891
*Corresponding author. E-mail address: niranjan.kanaki@kbiper.ac.in (N. Kanaki)

1. Introduction

Drug Cycle Management spans the full management of a drug substance at every stage, from early advancement to market entry and the after-sales phase. At every stage of the cycle, several adjustments to the substance and related steps are executed to spur enhancements. These amendments may relate to substance results, manufacture means, standard checks, package setups, steadfastness parameters, or management steps, among further areas.

After a substance gets sales clearance, amendments may turn necessary for several reasons, such as tech-based advancement, adherence to updated regulatory standards, or enhancement of means. Any suggested amendment must be carefully evaluated to ensure that the substance's standard, safety, or usefulness stays unaffected. Regulatory bureaus have repeatedly rejected amendments that may threaten these key parameters. Due to the gap in the way separate regulatory bureaus place changes, a "change management" system has been set up to track all substance and step changes at drug makers. The Regulatory team examines each suggested change by a full expert assessment matched to the relevant regulatory standards. (1)

After a substance gets sales clearance, the MAH may detect the need to alter exact elements of the cleared paper. When such changes are expected to affect the substance's key features—namely standard, safety, or usefulness—after clearance from the relevant regulatory agency becomes mandated. These changes, largely termed "after-clearance changes," are relayed by change-type entries or parallel means.

Every amendment must be evaluated for the extent of effect and entered as needed. Based on the relevance of the change, regulatory stated demands may range from mere deep entry-management to full change-type entries or fully new sales clearance requests. As a result, manufacturers are demanded to keep to the exact regulatory mandates set by each agency to ensure steady adherence. (1)

2. Post-Approval Changes Requirement in Saudi Arabia

Regulatory Authority: Saudi Food and Drug Authority

When a drug substance gets sales clearance from the Saudi Food and Drug Authority (SFDA), the substance may need changes at later stages of the cycle. These are termed after-clearance changes and can demand adjustments to the manufacture means, raw matter sellers, substance package, labels, or manufacture place. Such changes are executed to guarantee that the substance's standard, safety, and usefulness stay unaffected.

Table 1. Global Classification of Country

Country	Regulatory Authority	Type of change
Saudi Arabia	Saudi Food & Drug Authority (SFDA)	Type IA, IAIN, IB, & II
USA	Food and Drug Administration (FDA)	PAS, CBE, AR
Australia	Therapeutic Goods Administration (TGA)	Cat 3, SARS, SRRS…
Eurasia	Eurasian Economic Union (EAEU)	Type IA, IAIN, IB, & II

In Saudi Arabia, the SFDA steers these after-clearance changes by the relevant standard rules on change-types to sales clearance. The standard rules are structured well, matched to global usages, and match key bureaus such as the EMA and WHO.

The SFDA places change-types under separate classes based on the related threat level and effect on the substance, and each class that demands exact data, entry due dates, and pre-enactment clearance.

The regulatory structure safeguards general health by carefully assessing all changes made after the early clearance. In the drug realm, even apparently small changes can present large threats to the well-being of the treated, and hence stern assessment stays fundamental. The SFDA uses a threat-based strategy to manage these changes, thereby that ensures steady substance standards.

For sales clearance holders, adherence to rules extends past mere legal demands—the duty to fully relay and back up after-clearance changes stands as a research-based duty. All entries must have clear and full data. (1)

Table 2. Types of Variation in Saudi Arabia

Variations types	Description	Regulatory Requirement
Type IA	These small changes don't need to be approved before being implemented (the "Do and tell" procedure).	Notification after implementation
Type IAIN	Type IAIN change must be submit right away, within 14 days of implementation.	Must be submitted 14 days post-implementation
Type IB	Submit before making change	Submit before making the change, if no objection during review it can be done
Type II	Require prior approval before implementation	Require prior approval before implementation

3. Post-Approval Changes Requirement in US Regulatory

Regulatory Authority: USFDA

The Food and Drug Administration (FDA) stands as a federal agency under the United States Department of Health and Human Departments. The FDA bears the duty of that safeguard and advances general health by the management and rule-upkeep of food safety, drugs, supplements, vaccines, and related health substances.

An entrant may enact after-clearance amendments to the New Drug Application or Abbreviated New Drug Application after after clearance, as these changes are relayed to the FDA by the apt entry types.

Under the Federal Food, Drugs, and Cosmetic Act and 21 CFR 314.70, the stated classes for after-clearance amendments are as beneath:(2)

-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 large amendment refers to a change that has a large chance to adversely affect the nature, strength, standard, pureness, or effect of a drug substance, thereby threatening safety or usefulness. Such changes are entered by PAS supplements.

Moderate Change: A mid-level amendment may affect the nature, strength, standard, pureness, or effect of a drug substance, and hence the safety or usefulness. Such amendments usually demand the entry of a CBE-30 supplement or a CBE-0 supplement to the FDA.

Minor Change: Small amendments generally carry a small chance to adversely affect the nature, strength, standard, pureness, or effect of a drug substance, and hence are not expected to greatly change safety or usefulness. These are entered by yearly relays. (2)

4. Post-Approval Changes Requirement in Australia

Regulatory Authority: Therapeutic Goods Administration

The management of drugs after market entry serves a key part in the drug realm, as the pathway guarantees that substances keep to set benchmarks for safety, usefulness, and standard at every stage. In Australia, the duty falls to the TGA, the federal regulatory agency that manages drugs and health apparatus. The TGA uses a clear and structured strategy for the management of after-clearance amendments by the change-type structure, and hence manufacturers can carry needed changes as regulatory checks and general health are preserved.

A further key element of the Australian regulatory structure is the ARTG, a central database that has full regulatory data on all drugs cleared for supply in Australia. When a drug substance gets entered in the ARTG database, the data used at entry—such as makeup data, manufacture steps, substance standard parameters, and substance data—turns the cleared reference matter for that substance. As a result, any amendment made to the substance after entry, be the change to the drug, manufacture place or step, makeup blend, labels, or substance data, must get TGA clearance before enactment. The demand enhances the regulatory pathway by that ensures that no uncleared or unassessed changes are made to the substance that may adversely affect the standard or the health of the treated.

To help the enactment of needed amendments at the after-clearance phase as full standard benchmarks are upheld, the TGA has developed a full, threat-based strategy for change-types. The strategy places after-clearance amendments by the level of effect and sets a regulatory pathway for assessment and clearance.

The placement system takes the effect on substance standard, safety, and usefulness as the key aspects. The placement sets the extent of needed data and the depth of the regulatory assessment by the TGA. (3)

Table 3. Application Category and Level of Assessment

Application Category	Level of Assessment
Correction or completion in ARTG entry	Verification of data provided
Modification request to vary an ARTG entry	No assessment
Self-assessable request to vary ARTG entry	Verification of data provided
Safety-related request	Verification of data provided
Category 3 request – variation to ARTG entry	Quality data evaluation
Safety-related request with data	Evaluation of data submitted to TGA
Category 1 application: Variation to ARTG entry with consequential PI change	Full evaluation of quality, bioequivalence, clinical and nonclinical data

5. Post-Approval Changes Requirement in Eurasia (EAEU)

The Eurasian Economic Union (EAEU) was set up through a Treaty penned on May 29, 2014, that began effect on January 1, 2015. The EAEU merges 5 member states: Russia, Kazakhstan, Belarus, Armenia, and Kyrgyzstan, and represents a people tally past 185 M and a merged trade strength past $5 trillion. The EAEU makes up a large and fast-enlargement drug market, and Russia's drug realm assessed separately at nearly $39 B as of 2021.

To set up a merged drug market, the member states reached agreement on shared tenets for drug spread. In late 2014, they drafted the "Agreement on shared tenets and rules for the spread of drugs in the Eurasian Economic Union." That fundamental agreement was then succeeded by fuller "Rules for the entry and expert assessment of drugs for human use," accepted by Decree No. 78 by the EEC Assembly on November 3, 2016. These Rules became enacted as at May 6, 2017, a key change from separate state-level clearance steps to a set area-based structure. The full transfer to the merged system happened on January 1, 2021, when all member states began under these aligned steps.

A key regulatory benchmark mandated that all drugs cleared before December 31, 2020, must transfer to adhere to the updated EAEU standards by December 31, 2025. The due date guarantees that the full drug market runs under steady rules. **(4)**

The EAEU runs through a structured setup that has well-set tasks. The Supreme Eurasian Economic Assembly, made up of the heads of all member states, acts as the peak level and sets the path for all tenets. The EEC serves as the management arm tasked with enactment of these tenets, and that demands the management of drug entry rules and standards.

Registration Pathways: Two Main Routes to Market Approval

1. Mutual Recognition Procedure
2. Decentralized Registration Procedure

Variations types for Eurasia

The EAEU change-type structure has 5 key classes:

1. Minor variations of Type IA
2. Minor variations of Type IA requiring immediate notification (IAIN)

3. Minor variations of Type IB
4. Major variations of Type II
5. Extensions of marketing authorization

Table 4. Types of Variation in Eurasia (4)

Variations types	Description	Impact on Product	Regulatory Requirement
Type IA	Small change with very low or no effect on the medicine	Low	No prior approval required
Type IAIN	Same as IA but more time-sensitive, so the authority must be told quickly	Low	Implement, then notify the reference authority immediately as an urgent minor change; no prior approval.
Type IB	Medium-level change that is not IA/IAIN, not major type II, and not an extension.	Moderate	Submit a variation application and wait for a positive decision from the reference authority before implementation.
Type II	Major change that can clearly affect quality, safety, or efficacy	High	Change can be implemented only after approval

6. Case Study

APIs:

6.1 US

a) Proposed change: Change to comply with reference pharmacopeia-API

b) Procedure Type/Category of Variation: Annual reportable-only notification is required

c) Documents Requirement:

- Updated drug substance extraction/Method of Analysis (MOA).
- Equivalency study results between the in-house and compendial method, when a compendial method exists and in-house analytical method is used.
- Testing confirmation
- Method verification for the compendial methods
- Relaxation of acceptance criteria or deletion of a test to comply with an official compendium must be reported in a changes-being-effected-in-30-days supplement (CBE-30).

d) Implementation/Approval timeframe: Immediately implementation

6.2 Kingdom of Saudi Arabia

a) Proposed change: Change to comply with reference pharmacopeia-API

b) Procedure Type/Category of Variation: Type IAIN

c) Documents Requirement:

- Substitution of the pertinent pages of the file that are influenced by the difference.
- Comparison chart of existing and suggested extraction.
- Three Batch analysis information (in a comparative table layout) on two production lots of the pertinent material for all assessments in the updated exactation and also, when suitable, comparative dissolution profile information for the final product on at least one test batch. For herbal medicinal products, comparative evaluations data on disintegration might be considered acceptable.

d) Implementation/Approval timeframe: Type IAIN variations should be submitted immediately, within 14 days following implementation

6.3 Australia

a) Proposed change: Change to comply with reference pharmacopeia-API

b) Procedure Type/Category of Variation: Notification

c) Documents Requirement:

- The updated collection of requirements for the API.

d)Implementation/Approval: No statutory framework [automatic approval upon e-form submission and complete fee payment]

6.4 Eurasia

a) Proposed change: Change to comply with reference pharmacopeia-API

b) Procedure Type/Category of Variation: Type IAIN

c) Documents Requirement:

- Replacement of the relevant pages of the dossier that are affected by the variation.
- Comparative table of current and proposed extraction.
- Three Batch analysis data

d) Implementation/Approval timeframe: Type IAIN variations should be submitted immediately, within 14 days following implementation

Drug product:

6.5 US

a) Proposed change: Change in batch size-Finish product (Up to 10-fold increase compared to the currently approved batch size)

b) Procedure Type/Category of Variation: AR or CBE-30 or PAS

c) Documents Requirement:

- Relevant impacted drug product sections (Batch formula, three consecutive production scale batches have been successfully validated, BMRs, COAs, Stability data)

d) Implementation/Approval timeframe: Implement at 30 days after submission

6.6 Saudi Arabia

a) Proposed change: Change in batch size-Finish product (Up to 10-fold increase compared to the currently approved batch size)

b) Procedure Type/Category of Variation: TYPE IB

c) Documents Requirement:

- Replacement of the relevant pages of the dossier that are affected by the variation.
- Two Batch stability study report for long term and accelerated study
- Copy of current spec

d) Implementation/Approval timeframe: Notify before implementation

6.7 Australia

a) Proposed change: Change in batch size-Finish product (Up to 10-fold increase compared to the currently approved batch size)

b) Procedure Type/Category of Variation: Cat 3

c) Documents Requirement:

- A detailed description of the changed manufacturing process, including in-process controls (MPCR/BPCR)
- Process validation data
- Batch analytical data (3 batches)
- Stability data (LT & ACC)

d) Implementation/Approval timeframe: No statutory framework [automatic approval on submission of e-form and full payment of fee]

6.8 Eurasia

a) Proposed change: Change in batch size – Finished product (Up to 10-fold increase compared to the currently approved batch size)

b) Procedure Type/Category of Variation: Type IA

c) Documents Requirement:

- Amendment to relevant dossier section(s)
- Validation protocol (plan).

d)Implementation/Approval timeframe: Such minor variations do not require prior approval before implementation ("Do and Tell" procedure)

Table 5. Comparative post approval changes of filing category in Saudi Arabia, US, Australia & EURASIA (1-4)

SrNo	Changes	Saudi Arabia	US	Australia	Eurasia
Comparative Post Approval Regulatory Requirement of Manufacturing sites					
1	Move to a separate manufacturing site for a drug substance intermediate (site never inspected for type/move results in restart of discontinued operation)	Type II Variation	PAS	Cat 3	Type II Variation
2	Move to a separate manufacturing site for drug substance intermediate (site lacks CGMP inspection for type)	Type II Variation	PAS	Cat 3	Type II Variation
3	Move to separate manufacturing site for primary packaging, processing/modifies delivery or rate of drug, or for in-process materials with modified-release characteristics	Type II Variation	PAS	Cat 3	Type II Variation
4	Transfer manufacture of aseptically processed sterile drug substance or product (new/refurbished/other site)	Type IB Variation	PAS	Cat 3	Type IB Variation
5	Transfer manufacture of finished drug product sterilized by terminal processes to newly constructed facility	Type IB Variation	CBE-30	Cat 3	Type IB Variation
Comparative Post Approval Regulatory Requirement of Manufacturing process					
1	Changes that may affect the controlled/modified release…	Type II Variation	PAS	Cat 3	Type II Variation

2	Changes in virus or adventitious agent removal…	Type II Variation	PAS	Cat 3	Type II Variation
3	Changes that may affect drug product sterility assurance	Type II Variation	PAS	Cat 3	Type II Variation
4	For drug substance: Changes in synthesis affecting impurity profile	Type II Variation	PAS	Cat 3	Type II Variation
5	For drug products: Any change in process	Type IA Variation	CBE-30	Notification	Type IA Variation
Comparative Post Approval Regulatory Requirement of Specification					
1	Relaxing an acceptance criterion	Type II Variation	PAS	Cat 3	Type II Variation
2	Deleting any part of an exactation	Type II Variation	PAS	Cat 3	Type II Variation
3	Change outside the approved exactation limits range	Type II Variation	PAS	Cat 3	Type II Variation
4	Tightening of acceptance criteria	Annual report	Ann. report	Notification	Type IA Variation
5	Addition of new test and limits	Type IA Variation	CBE-0	Notification	Type IA Variation
Comparative Post Approval Regulatory Requirement of Container closure system					
1	For liquid and semisolid…: change to polymeric materials…	Type IB	PAS	Cat 3	Type IB Variation
2	For liquid and semisolid… permeable container… new ink/adhesive	Type IB	PAS	Cat 3	Type IB Variation
3	Change in primary packaging components… control dose delivered	Type II	PAS	Cat 3	Type II Variation
4	For sterile drug products, any change… sterility assurance	Type II	PAS	Cat 3	Type II Variation
5	Deletion of secondary packaging… affect impurity profile	Type II	PAS	Cat 3	Type II Variation

7. Conclusion

In conclusion, it can be said that this comparative analysis demonstrates that while Saudi Arabia, USA, Australia, and Eurasian Economic Union regulations on API and drug product post-approval change management are all risk-based and critical to continued safety, efficacy, and quality, these regulations also vary with respect to classification, data, and timelines. While SFDA uses Type I-II variations with electronic submission through SDR, FDA uses prior approval, CBE, and annual reports depending on impact levels, TGA uses a risk tiered approach for minor and major changes, and finally, EAEU uses a harmonized approach with a set of guidelines similar to ICH principles.

Acknowledgements

I would like to express my sincere gratitude to my guide, mentor, and Head of the Department for their valuable guidance and support throughout this work. I also extend my heartfelt thanks to my colleagues for their encouragement and cooperation. Additionally, I would like to thank the International Journal of Drug Regulatory Affairs (IJDRA) for publishing my article.

Conflict of Interest

The author declares that there is no conflict of interest regarding the publication of this article.

Financial Disclosure statement:

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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