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sustained release (SR), delayed release (DR), and multi-particulate systems are dosage forms designed to maintain therapeutic plasma concentrations over prolonged periods of time.^[4] Their therapeutic efficacy is largely dependent on well-designed release controlling mechanisms such as diffusion-controlled polymer barriers, hydrophilic matrix systems, membrane-coated pellets, and osmotic pump tablets.^[4-5]

In the United States, the management of PAC is primarily governed by 21 CFR 314.70, which classifies variations based on their impact significance on product quality.^[1] The U.S. Food and Drug Administration (FDA) has provided additional guidance for MR SODFs under SUPAC-MR, which utilizes a three-level risk categorization system covering changes in composition, site, scale, and process.^[2] These frameworks are further supported by guideline on changes to an approved NDA or ANDA that defines reporting categories and data requirements, providing a structured and predictable approach to PAC submissions.

In the Republic of Korea, pharmaceutical lifecycle regulation is overseen by the Ministry of Food and Drug Safety (MFDS) under the Pharmaceutical Affairs Act.^[3] PACs are handled through a variation-based system, with modifications classified according to their impact on quality, safety, and efficacy, reflecting growing alignment with international risk-based lifecycle management principles.^[6]

In contrast, the GCC Drug Registration Committee regulates variations through the "Guideline for Variation Requirements Version 6.2," which applies to all dosage forms and does not provide MR-specific scientific stratification (GCC-DR, 2024).^[7]

This study provides a comparative analysis of regulatory approaches to PACs for MR SODFs in the United States, Republic of Korea, and GCC regions.

Scientific Foundations Of Mr Dosage Forms

MR SODFs are intended to control the rate and extent of drug release to maintain therapeutic plasma concentrations, decrease dose frequency and enhance patient compliance. In contrast to immediate release formulations, MR systems are based on developed release-controlling mechanisms such as membrane-coated reservoir systems, hydrophilic matrix polymers or osmotic pump technologies. Drug release from these systems is controlled by diffusion, erosion, swelling or osmotic pressure mechanisms depending on the formulation design.^[1, 3]

The performance of modified-release (MR) products is highly dependent upon critical material attributes and manufacturing parameters. Variations in polymer grade, excipient content, coating thickness, compression force or curing conditions may alter the in vivo drug exposure. Thus, dissolution testing is the main in vitro

tool to evaluate release behaviour and comparability after formulation or process change, with the similarity factor (f_2) being commonly used for quantitative profile comparison.^[8]

MATERIALS AND METHODS

Literature sources and search design

Extensive literature survey of both academic (PubMed, Scopus, Web of Science, and Google Scholar) and official sources (Agency websites) was conducted to gather reliable information on how MR formulations are regulated in USA, Korea and GCC w.r.t. life cycle management. By using terms such as modified-release formulations, Post-approval change; SUPAC-MR; MFDS; GCC Variation Guideline, a considerable amount of information was gathered. Since this information mostly referred to journal publications, it did not seem to be entirely satisfactory as a secondary form of data, which led to checking experts' views on existing rules. Official web pages of the authorities in the respective countries were browsed, where the most up-to-date regulations and circulars were obtained.

Screening of the gathered data

The post approval regulatory requirements for MR formulations were examined through a qualitative and comparative lens to capture both shared features and key differences among the three national systems. Data has been provided to give a clearer view of each authority's specific expectations. A structured screening process was conducted to ensure the applicability and validity of the collected data. The selection of literature followed a qualitative approach, which included three major stages: identification, screening, and inclusion.

RESULTS AND DISCUSSION

Regulatory Framework in the USA

In the US, pharma products are regulated by the FDA under the Federal Food, Drug, and Cosmetic Act. PACs to approved drug products are addressed under 21 CFR 314.70, which categorizes modifications according to the potential risk they may introduce to critical product quality attributes, such as purity, identity, strength, quality, and potency. This framework provides for the appropriate evaluation and reporting of product changes to ensure continued product efficacy and safety.^[9]

For MR SODFs, the central interpretive document is the SUPAC-MR guidance, issued in 1997.^[10] SUPAC, an acronym for Scale-Up and Post-Approval Changes, was developed to provide industry with predictable regulatory expectations for changes involving composition, manufacturing site, scale, and process/equipment.

The SUPAC-MR framework categorizes post-approval

modifications into three levels based on their potential impact on product performance and quality. Changes categorised under Level 1 are expected to have little or no effect on product characteristics, Level 2 changes may moderately influence product performance, while Level 3 changes possess a greater likelihood of significantly affecting drug release behavior and therapeutic performance.

Another guidance, 'Guidance for Industry: Changes to an Approved NDA or ANDA,' was issued by the FDA in 2004, which provides a risk-based framework for categorizing post-approval changes into major, moderate, and minor levels. This guidance provides a regulatory framework for reporting post-approval modifications through mechanisms such as PAS, CBE-30/CBE-0, and AR, depending on the potential impact of the change on product quality attributes. It serves as a foundational complement to the SUPAC-MR guidance by establishing uniform regulatory principles and facilitating a harmonized approach to post-approval change management.

Types of Post-Approval Changes under USFDA Guidelines

Composition changes

Changes in composition include both qualitative and quantitative changes in the excipients. Changes to non-functional excipients within defined limits may be classified as Level 1 or Level 2 depending on the size. Changes to excipients that control release (e.g. type, grade or concentration of polymer) are usually considered to be Level 3 as they have a direct impact on dissolution kinetics. Changes in Level 3 composition normally require submission as a Prior Approval Supplement (PAS) and may require comparative bioequivalence study or established IVIVC.^[9]

Manufacturing site changes

Level 3 manufacturing site changes involve the transfer of manufacturing, processing, or primary packaging operations to a different facility when such activities have a direct influence on product performance. This includes situations where the primary packaging system regulates the dose administered to the patient or where the formulation affects the rate and extent of drug release and absorption. Additionally, relocating the manufacture or processing of intermediates that possess MR properties is also classified as a Level 3 change due to its potential impact on the quality of the final product.

A move to a different manufacturing site, responsible for the primary packaging of a drug product, is generally classified as a Level 2 change when the packaging components play a role in controlling the dose delivered to the patient. In contrast, relocating operations related

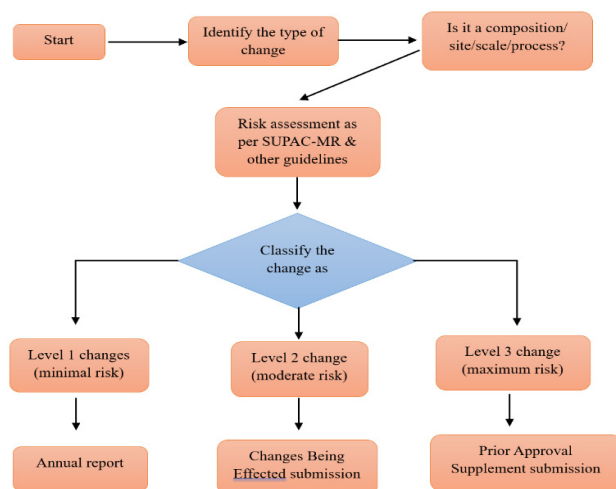


Fig. 1: Post-Approval Change Classification: United States

solely to the ink imprinting of MR SODFs is considered a Level 1 change, as such modifications are unlikely to affect the product's quality, performance, or release characteristics.^[11]

Batch Size Changes

Batch size modifications are common during commercialization. SUPAC-MR provides defined ranges to determine classification. Changes that remain within validated design space may be categorized as moderate, whereas significant scale expansion affecting blending uniformity or compression dynamics may be considered major.^[9]

Manufacturing Process and Equipment Changes

Modification to processes are evaluated by whether or not the underlying operating principle is changed. A change in process like wet granulation to a process like direct compression is a major redesign that could impact drug distribution and release characteristics. These modifications are generally classified as level 3.^[9, 11] The change of code on a MR SODF by embossing, debossing or engraving is regarded as Level 3 change.^[11]

• Post-Approval Change Classification

Regulatory decision-making pathway for classification and reporting of PACs in MR SODFs according to the USFDA SUPAC-MR guidance is provided in Fig. 1.

Regulatory Framework in the Republic of Korea

In the Republic of Korea, the Ministry of Food and Drug Safety (MFDS) is the supervisory authority of pharmaceutical regulation. The Pharmaceutical Affairs Act and the 2024 Guideline on Post-Approval Change Management of Pharmaceutical Manufacturing Processes regulate and provide supplementary information on post-



approval changes. Interestingly, MFDS issued an English version of the guideline in January 2025 to make it more accessible for the global stakeholders.^[12] On February 20, 2024, the Pharmaceutical Affairs Act was further amended with provisions coming into effect on February 21, 2025, establishing a strengthened Risk management Plan (RMP) system that includes post-marketing safety into lifecycle oversight framework.^[13] The MFDS also implemented a major regulatory overhaul effective from January 2025, which aimed to reduce new drug approval timelines from about 420 days to 295 days through streamlining GMP inspection procedures and expanding rolling review mechanisms, among other measures.^[14]

The MFDS regulatory framework classifies post-approval changes based on the potential effect on product quality and the level of regulatory scrutiny. These changes are generally classified as Annual Reports (AR), Immediate Reports (IR) or Prior Approval Change Applications. Annual reports can be submitted for minor changes that are not expected to impact the quality, safety/efficacy of the product. Changes with little potential to affect the product quality shall be submitted as an Immediate Report prior to the introduction of the modified product to the market. On the other hand, any major change that can have a potential influence on product quality is subject to prior approval and must be supported by detailed scientific and regulatory documentation for evaluation by the authority.

Types of Post-Approval Changes in the Republic of Korea^[12]

Composition Changes

In the Republic of Korea, changes in composition are evaluated by their effect on product performance. Changes to release-controlling polymers, excipient substitution or grade changes are generally regarded as major variations

when they may affect dissolution behaviour. In such cases, MFDS requires comparative dissolution testing and stability data, and may require bioequivalence studies, if similarity cannot be sufficiently demonstrated *in vitro*.

Manufacturing Process changes

Manufacturing process variations include changes to the method of manufacture, process parameters or in-process control tests performed during manufacture of the drug product. The manufacturing process is particularly important for modified release products since changes in granulation, coating or matrix formation can significantly influence the drug release mechanism. Thus, regulatory authorities usually require supporting data like comparative batch analysis, process validation reports and dissolution profile comparisons to show that the changed manufacturing process results in a product equivalent to the previously approved formulation.

Manufacturing Site Changes

Submission of GMP documentation, process validation reports and stability data generated at the new site is required for site transfer. Analytical comparability needs to be demonstrated in the Common Technical Document (CTD) format.

• Post-Approval Change Classification

Regulatory framework for classification and reporting of PACs in MR SODFs in Republic of Korea is provided in Fig. 2.

Regulatory Framework in the GCC Region^[7]

The Gulf Health Council (GHC) regulates the pharmaceutical regulation in the Gulf Cooperation Council (GCC) by issuing unified regulatory guidelines for the member states. Post approval changes are governed by the GCC Guidelines for Variation Requirements (Version 6.2) based on a risk classification system consistent with European regulatory principles. The formal adoption of version 6.2 was communicated to the GCC member states by circular No. 153 of 2024, issued in October 2024, which confirmed the binding application of this version to all variation submissions.^[15]

In the GCC context, PACs are classified as minor variations (Type IA and Type IB) and major variations (Type II) based on the potential outcome on product quality, safety and efficacy. Type IA variances are minor changes that may be implemented before notification (“do and tell”). Type IB variances require prior submission and a waiting period before implementation (“tell, wait and do”). Major changes (Type II), which may significantly impact product quality, safety or efficacy, require approval from the regulatory authority based on extensive documentation and scientific evaluation prior to implementation.

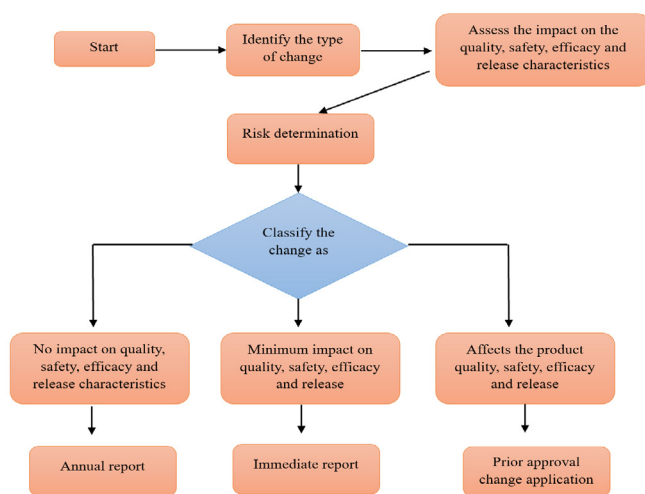


Fig. 2: Post-Approval Change Classification: Republic of Korea

Types of Post-Approval Changes in the GCC region:

Composition Changes

Changes in composition are carefully evaluated for modified release (MR) dosage forms as they affect the kinetics of drug release. Minor changes to non-functional excipients may be either Type IA or IB if dissolution is not affected. Changes to release controlling excipients are generally Type II variations and require supporting data such as comparative dissolution and, where applicable, bioequivalence or IVIVC studies.

Manufacturing Site Changes

Any changes to MR product manufacturing sites are evaluated for their potential impact on critical quality attributes, especially drug release characteristics. Type IA variations may also include minor changes to sites (e.g. noncritical packaging operations). Changes to sites that perform significant manufacturing steps (e.g. granulation, coating or compression) are generally classified as Type IB variations. However, changes to the site that may impact the MR performance, especially for complex formulations, are considered Type II variations and require prior approval with supporting process validation and comparative dissolution data.

Batch Size Changes

Changes in batch size for MR products were assessed with regard to their specific effect on blending uniformity, coating consistency and compression dynamics. Type IA variations can be considered to be minor scale adjustments in validated ranges, provided there are no changes in dissolution behaviour. Type IB variations: Moderate size changes in scale may be considered as Type IB variations. Type II variations: Large scale-up or scale-down which may impact on the drug release characteristics is usually

considered as a Type II variation and will require additional validation and comparative dissolution studies.

Manufacturing Process and Equipment Changes

The changes in the process for MR formulations are very critical, as they can have direct effect on drug release mechanisms. Minor changes to processes that do not impact critical process parameters (CPPs) or dissolution profiles may be Type IA or Type IB changes. However, major changes such as modification of the granulation method, coating process, change of coating weight, curing conditions or equipment that affect release characteristics are classified as Type II variations. These changes must be approved in advance and backed up by a lot of validation data, such as dissolution profiling, stability studies, and, when applicable, bioequivalence assessment.

• Post-Approval Change Classification

Regulatory decision-making pathway for classification and reporting of PACs in MR SODFs in GCC region is provided in Fig. 3.

Comparative regulatory analysis

The comparative regulatory framework for post-approval change management is provided in the Table 1. Insert table 1 here.

Influence of ICH and Global Harmonization

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use has significantly influenced PAC management through guidelines Q8, Q9, Q10, and Q12. [16-19]

In ICH Q12, established conditions and Post-Approval Change Management Protocols (PACMPs) allow for pre-defined regulatory reporting pathways for expected changes. Using these mechanisms can reduce regulatory burden and facilitate global lifecycle management. However, a global industry survey published in 2024 indicated that the implementation of ICH Q12 remains limited in most of the ICH member countries with only one country reporting the active use of the PACMP, and no country has fully implemented the Established Conditions or the product Life Cycle management (PLCM) document. [20] The survey still showed a positive trend of risk-based approaches to variation categorization as compared to the 2020 baseline, indicating a gradual regulatory convergence. The EMA updated its Q&A on PACMP's in December 2025 to account for the 2024 revision of the EU variation Regulation, reinforcing the relevance of ICH Q12 tools in evolving regulatory landscapes. [21]

Dissolution and Bioequivalence Considerations

Dissolution testing is the main surrogate for in vivo performance. The similarity factor (f_2) is a common way of comparing dissolution profiles. In the US, IVIVC models

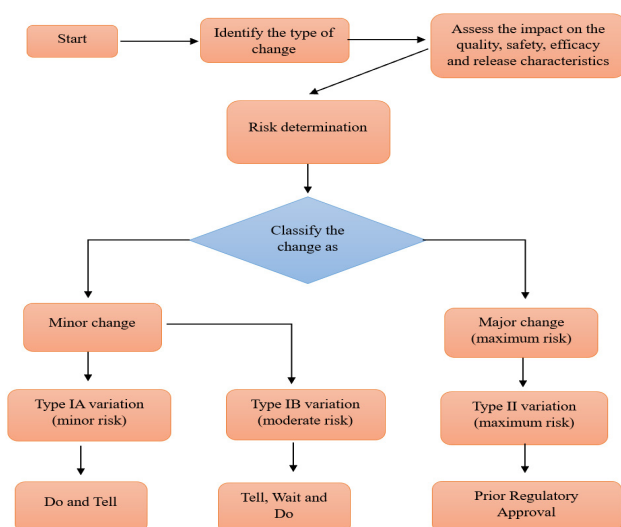


Fig. 3: Post-Approval Change Classification: GCC Region



Table 1: Comparative Regulatory Framework for Post-Approval Change Management

<i>Regulatory Aspect</i>	<i>United States</i>	<i>Republic of Korea</i>	<i>GCC Region</i>
Regulatory Authority	U.S. Food and Drug Administration	Ministry of Food and Drug Safety	Gulf Health Council (GHC)
Key Guidelines	SUPAC-MR Guidance for Industry and Guidance for Industry: Changes to an Approved NDA or ANDA	Guideline on Post-Approval Change Management of Pharmaceutical Manufacturing Process	GCC Guidelines for Variation Requirements (Version 6.2)
Legal Basis	21 CFR 314.70	Pharmaceutical Affairs Act	GCC Unified Pharmaceutical Regulatory Framework
Major	Prior Approval Supplement Prior approval required before implementation; full data submission (dissolution, stability, BE if needed)	Maximum Impact on quality, safety and efficacy requires Prior Approval Change Application	Type II Variation - Prior approval required; dissolution, stability, BE if applicable
Moderate	CBE-30 / CBE-0 Notify FDA; implement after 30 days (CBE-30) or immediately (CBE-0) with supporting data	Minimum Impact on quality, safety and efficacy requires Immediate Report	Type IB Variation Notification before implementation; review within short timeline ("tell, wait and do")
Minor	Annual Report No prior approval; reported annually with minimal data	No Impact on quality, safety and efficacy requires Annual Report	Type IA Variation Immediate notification ("do & tell"); minimal data required

can potentially allow for the waiver of *in vivo* studies if predictive relationships can be demonstrated.

Republic of Korea Most major variations require comparative dissolution testing. Bioequivalence studies are required if differences in dissolution exceed acceptable thresholds.

Dissolution testing is an important tool to assess *in vitro* performance and comparability of post-approval changes in the GCC region. Dissolution profiling comparison is needed for modified-release formulations and bioequivalence studies may be required if similarity criteria are not met.

Recommended Amendments to the Republic of Korea and GCC Guidelines

(Benchmarking Against US SUPAC-MR and Guidance for industry: Changes to an approved NDA or ANDA)

Introduction of Detailed Risk-Based Reporting Categories (similar to US FDA)

In the US, the FDA categorizes post approval CMC changes into well-defined reporting categories under 21 CFR 314.70 namely, PAS, CBE-0, CBE-30 and AR changes. These categories are clearly related to the risk associated with the change and its potential impact on product quality, safety, and efficacy.

By contrast, the Republic of Korea and the GCC use risk-based systems, but not to the same level of granularity. In Korea, Annual Report (AR), Immediate Report (IR) and Prior Approval are differentiated while in the GCC, Type IA, IB and Type II changes are differentiated. While effective, these systems do not offer intermediate paths like CBE-30 for moderate-risk changes.

Adoption of Comparability Protocols for Predictable Change Management

Under the US regulatory regime, sponsors may submit Comparability Protocols that pre-define the tests, acceptance criteria and documentation required to assess certain prospective manufacturing changes. "If approved, the sponsor will be able to make those changes with less regulatory burden."

At present, neither the Republic of Korea nor the GCC has formally incorporated any comparability protocols into its PAC regimes. Both regions are risk-based, but the lack of pre-defined change strategies may result in variability in regulatory expectations. The adoption of comparability protocols in both regions would improve regulatory predictability, support lifecycle management and enable the efficient implementation of planned changes.

Development of Specific Guidance for Modified Release Formulations

The US FDA offers detailed regulatory guidance for MR dosage forms including requirements for *in vitro* dissolution testing, *in vivo* bioequivalence studies and SUPAC-MR (Scale-Up and Post-Approval Changes for Modified Release products).

In contrast, both the Republic of Korea and the GCC deal with MR-specific issues in their general post-approval change guidance, but do not have dedicated, stand-alone guidance documents specifically dealing with MR formulations, such as the US FDA SUPAC-MR. The development of specific post-approval change guidelines for MR formulations including dissolution testing requirements, *in vitro-in*

vivo correlation (IVIVC) utilization, bioequivalence expectations and risk classification would be of benefit to both regions and increase scientific consistency and regulatory predictability.

Expansion of Low-Risk Changes Allowed via Notification or Annual Reporting

In the US, numerous low-risk changes such as minor equipment changes, editorial changes to specifications or certain changes to process parameters can be reported in Annual Reports rather than needing prior regulatory approval.

The Republic of Korea, on the other hand, provides for minor changes through annual reporting (AR), but only within a fairly narrow range. The GCC allows Type IA variations (“do and tell”) but again the range of such changes is limited. Extending the scope of low-risk, self-managed changes in both regions would reduce regulatory burden, increase operational efficiency and allow for more efficient lifecycle management.

CONCLUSION

The post-approval management of MR SODFs remains a scientifically and regulatory challenging area due to the critical reliance of these formulations on controlled drug-release mechanisms. The comparative review shows that the three regions, the United States, the Republic of Korea and the GCC, have risk-based principles in common, but the US has a more structured and detailed framework with SUPAC-MR and well-defined reporting categories. In contrast, Korea and GCC have broader variation-based systems with limited granularity, with less focus on MR-specific regulatory concerns.

Dissolution testing, supported by similarity factor (f_2) is a universal tool to assess comparability whereas bioequivalence studies are required when in vitro methods are not enough. ICH guidelines, particularly Q12, offer opportunities to improve regulatory flexibility and predictability through tools such as comparability protocols and established conditions.

The Republic of Korea and GCC are advised to increase regulatory efficiency and global harmonization by expanding their frameworks to include more detailed risk classification systems, comparability protocols, and specific guidance for modified release formulations. These advances would bring consistency in regulatory decisions, reduce unnecessary regulatory burden, and encourage innovation and life cycle management in the pharmaceutical industry.

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