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COMPARATIVE ANALYSIS OF POST -APPROVAL CHANGE APPLICATION SUBMISSION AND APPROVAL PROCESS IN THE USA, EUROPE AND INDIA-REGULATORY INSIGHTS

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Abstract:

The aim of this research is to examine the significance of post approval change management in addressing non-compliance issues. The study primarily focuses on identifying the existing policies and procedures in this field and gaining a deeper understanding of the underlying concepts related to post approval compliance for marketing authorization licenses. By comparing and contrasting the policies and procedures of regulatory authorities in India, US, EU, Saudi Arabia, and Singapore, the study reveals that change management plays a crucial role in the pharmaceutical lifecycle. However, the lack of a defined framework and understanding of this process has led to increased compliance costs and a lack of attention towards compliance and license maintenance. The introduction of ICH Q12 guidelines by the ICH is seen as a positive step that may assist the pharmaceutical industry in complying with regulations.

Key words: *Product Life Cycle Management, Post Approval Changes, Non-Compliance, ICH.*

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INTRODUCTION:

Product lifecycle management (PLM) involves overseeing a product's journey from creation to disposal, serving as a crucial information hub for a company and its partners. It encompasses various components such as foundational technologies, information tools, core functions, functional applications, and business solutions, all aimed at optimizing product development and management processes. [1]

Post-approval change management focuses on implementing specific modifications throughout a product's lifecycle in a systematic manner, ensuring that changes are thoroughly prepared and validated. This methodical approach is designed to streamline the implementation of changes post-approval by securing agreement from Regulatory Authorities on proposed strategies and quality testing procedures. [2]

Product and process lifecycle management (PPLM) is a distinct type of PLM that emphasizes the importance of the manufacturing process in addition to the product itself. This approach is commonly used in the life sciences and advanced specialty chemicals industries. The process involved in creating a specific compound is a crucial aspect of the regulatory filing for a new drug application. PPLM aims to effectively manage the information related to process development, similar to how baseline PLM manages information about product development. One example of PPLM implementations is the use of Process Development Execution Systems (PDES), which oversee the entire development cycle of high-tech manufacturing technologies, from initial conception to production. PDES bring together individuals with diverse backgrounds, data, information, knowledge, and business processes from different legal entities. [3,4]

The ICH concept aims to harmonize drug regulatory requirements through collaboration between authorities and industry. The founders, representing Europe, the United States, and Japan, work together to develop guidelines for safe and effective drug registration. In addition to the founding members, other countries like Canada, Switzerland, Brazil, and South Korea are also part of the association. The formal harmonization process for an ICH guideline involves five steps: expert group consensus, regulatory member actions, consultation and discussion, finalization of the draft guideline, and adoption by regulatory members. [10-17]

Guidelines have been standardized on four main topics: safety, quality, efficacy, and multidisciplinary. Chemistry, Manufacturing, and Control (CMC) topics for medicinal products are regulated in the quality guidelines. The harmonization achieved so far includes defining impurity thresholds, conducting stability studies, and implementing risk management. However, despite the implementation of harmonized guidelines, member states of the International Council for Harmonisation (ICH) still maintain their own national regulations on various topics, indicating that harmonization efforts are still ongoing.

POST APPROVAL CHANGES IN USFDA:

The reporting categories given under section 506A of the Act and CFR 314.70 are outlined in the followingsections.

A. Major change
B. Moderate change
C. Minor change

Different Categories of Changes: Major changes require a prior approval supplement under 21 CFR 314.7(b). Moderate changes fall under 21 CFR 314.70(c)(5) and can be implemented within 30 days. Changes being affected without prior approval are covered by 21 CFR 314.70(d)(6). Minor changes can be reported through an annual report or notification as per 21 CFR 314.70(d).

1. Type IA variations refer to minor changes that do not need approval beforehand but require the Marketing Authorization Holder (MAH) to notify the relevant authority within 60 days after implementing the change.
2. Type IB variations, on the other hand, are also minor changes that need to be notified to the authority by the MAH before implementation. Although they do not require formal approval, the MAH must wait for a period of 120 days to ensure that the authority denies or accepts the change.
3. Moving on to major variations, Type II variations involve significant impacts on the quality, safety, or efficacy of a medicinal product. These changes require prior approval before implementation to ensure the product's integrity.

According to 21 CFR 314.70, changes to the production process, quality control, facilities, product, equipment, or labeling in an approved NDA/ANDA should be reported using one of three reporting categories based on the potential risk of the

change affecting the product's performance, strength, identification, potency, or purity, which can impact safety or efficacy. The three categories are: minimal potential (change can be implemented and distributed without prior FDA review), moderate potential (change requires a prior notification to FDA), and substantial potential (change requires a prior submission to FDA for approval before distribution).

Table 1: Reporting categories of changes and estimated timeline for approval according to USFDA regulations

Change	Major Change	Moderate Change		Minor Change
Supplement to be filed	Prior approval supplement (Tell, wait and do after getting approval procedure)	CBE-30 (Tell, wait and do procedure)	CBE-0 (Tell do procedure)	Annual report (Do and tell the report)
When to Notify to Agency	Before implementing the change	Before implementing the change	Can implemented simultaneously	List of changes should annually be reported from the approval date till withdrawn from the market.
Estimated timeline approval (6)	· 6 months (no pre-approval inspection) · 10 months (withpre-approval inspection)	30 days (Timeline may vary based on queries addressing to agency in due course)	Change can be implemented very next day after notifying to agency, but wait for 15 days)	NA

Post approval changes in europe:

In order to facilitate dossier life-cycle maintenance, Type IA variations can be submitted by the marketing authorization holder within months after implementation, while Type IAIN variations must be immediately notified to the National Competent Authorities or the European Medicines Agency, and Type IB variations must be notified before implementation and waited upon for the National Competent Authority or the Agency's approval, whereas Type II and Type II Extension variations, which may have a significant impact on the quality, safety, or efficacy of the medicinal product, must be submitted accordingly.

A comprehensive overview of the anticipated implementation dates for the variations in Europe reveals a range of timelines, from as little as days before submission for administrative variations to up to months for major variations, highlighting the need for innovative planning and coordination.

TABLE 2: Summary of variations and anticipated implementation dates in Europe

variation	Type	Anticipated implementation time	Guideline approval timeline
Admin	TypeIAIN	14 days beforesubmission	N/A
	Type IA	Up to 1 year beforesubmission	N/A
Minor	Type IB	Up to 3 months after submission	30 days
Major	Type II	Up to 5 months after submission	60 days

Post approval changes in India:

In India, the post approval change submission system for new chemical entities does not have a science-based and risk-based classification. However, there is a classification system available for biologics. This lack of a formal risk-based classification for changes that impact the safety and efficacy of new chemical entities is a major drawback. It creates confusion for industries regarding which changes need to be reported before implementation. By classifying changes based on risk, regulatory authorities can prioritize tasks that require an extensive review before implementing high-risk changes to commercial products. With the implementation of ICH Q12 in India, there is a possibility of categorizing changes based on risk for new chemical entities. This will streamline the procedure for submitting changes and help the agency in faster review and approval without hindering the steady supply of medical products.

The current post approval change submission system in the Sugam portal provides a list of changes that can be implemented by submitting checklists of documents online. Changes that are not listed online are submitted offline through hard copies to CDSCO or zonal state food and drug administrations. Some of the listed changes do not require extensive review times as they do not affect the safety and efficacy of the drug. With the implementation of ICH Q12 and the risk-based categorization of changes, it is expected that there will be changes on the portal. Different sections will address different changes based on the risk classification, and each section will have a different review timeline. This will simplify and expedite the process of post approval change submission. However, making changes to the newly established Sugam portal may require significant resources and time due to website development and government procedures.

SUMMARY:

In the US, post approval changes are classified into three levels: Level I (minor), Level II (moderate), and Level III (major). The reporting category for these changes includes annual reports, CBE-30 days, and prior approval supplements. The application format should comply with 21 CFR 314.70(b), 314.70(c), and 314.70(d), and can be submitted electronically through Gateway FDA eSubmitter. The timelines for these changes range from 30 to 210 working days, depending on the type of change. The dosage forms covered in the US include OSDs, biologics, and medical devices. In the EU, post approval changes are classified as Type I (annual report), Type IA (immediate notification), Type IB (30 days before distributing the product), and Type II (prior approval supplement). The application format in the EU does not have a specific format, but may require a DMF and supporting justifications or undertakings. The application can be submitted electronically through the eSubmission Gateway or the eSubmission Web Client. The timelines for these changes are 180 days for Level I and 90 days for Level II. The dosage forms covered in the EU include OSDs, biologics, and medical devices. In India, post approval changes are classified into three levels: Level I (major), Level II (moderate), and Level III (minor). The reporting category for these changes includes supplements, notifiable changes, and annual reports. The notification type in India is Level I. The application format in India requires paper submission. The dosage forms covered in India include biologics.

CONCLUSION:

The pharmaceutical sector undergoes constant changes, leading to advancements in technology and evolving marketing authorization applications and legal frameworks. A detailed examination of regulations in the EU, US, and India was conducted for post-approval application submissions and approval processes under GMP standards. The European Medical Agency offers detailed guidance with set timelines, while the US FDA has limited information on this matter. In India, guidelines are primarily focused on biologics, with only timelines provided and the process lacking clear definition.

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