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POST APPROVAL CHANGES: REGULATED AND SEMI-REGULATED MARKET PERSPECTIVE

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ABSTRACT

The functioning of pharmaceutical company does not stop when a drug product is approved and its marketing starts. When a product is first approved, its manufacturing process represents the current technology standard for manufacturing and follows the cGMP standard for regulatory compliance. After approval, market demand, technological advances, GMP standards, raw material sourcing or manufacturing experience may require that the approved process or product needs to be modified. Therefore, Post Approval Change management plays an important role in maintaining the marketing status of a drug product. For the purpose of carefully assessing and successfully implementing the changes in a pharmaceutical company, the company should have an efficient and well-defined change control system in place. Complying post approval requirements enables FDA and the pharmaceutical industry to make sure that the drug product is consistent in its quality, efficacy and safety throughout its lifecycle.

KEYWORDS: United State Food and Drug Administration (USFDA), Scale Up Post Approval Changes (SUPAC), Common Technical Document (CTD), Medicines Control Council (MCC),European Medicines Agency (EMA), Association of South East Asian Nations (ASEAN).

INTRODUCTION

During the life cycle of Products, medicinal products are generally having many changes. The products rarely stay the same in original condition. The driving forces for changes are many, e.g., the need to introduce process and production improvements, market demands, the continuously evolving requirements of regulatory bodies. These are many reasons for making change to pharmaceutical products after the original regulatory approval is obtained. For each change, it is necessary to find out the acceptability of the proposed changes, in order to prove that the specified change does not have an adverse effect on the product. Some of these changes may be significant and require a substantial amount of stability data while others are minor and may only require a stability commitment. Change Control procedure in pharmaceuticals is an inherent part of a pharmaceutical product. Change control is a procedure that ensures changes are

implemented in a coordinated manner. The purpose of change control is to prevent the unintended consequences that are sometimes encountered when making a change to product or a system. Changes can happen anytime during a products life cycle.

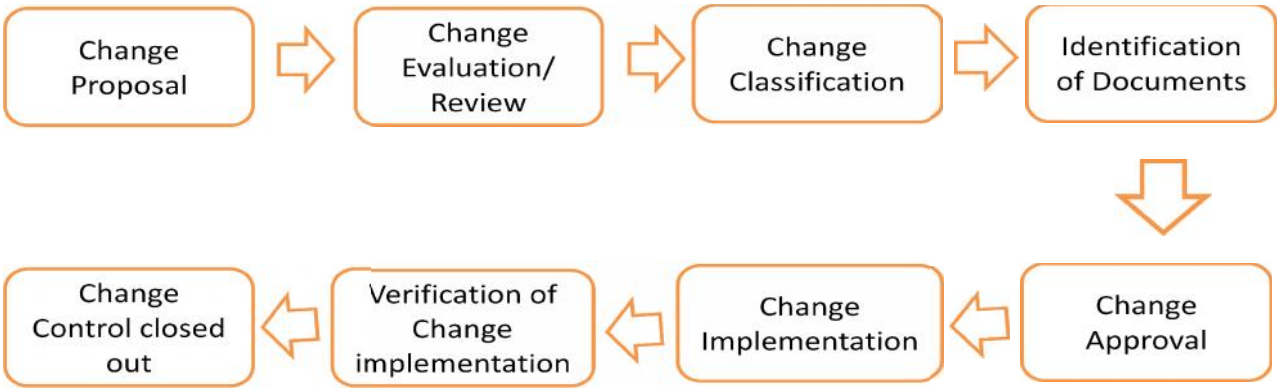

Figure 1: Change Control Process Flow

In US, the post approval changes are to be in accordance with section 506A of the Federal Food, Drug and Cosmetic Act and 21 CFR 314.70.The post approval changes are categorically reported as Major, Moderate [CBE-0 (Changes Being Effected) and CBE-30 (Changes Being Effected in 30 days) Supplements) and Minor changes.

Fees: Annual Report, CBE-0 and CBE-30 supplement: No fees

PAS (Prior Approval Supplement) : 38,020 U.S.D

Application format: eCTD

Application Submission: Electronic Submissions Gateway, FDA eSubmitter

Basic Elements of Comparability Protocol:

- Description of Planned Changes
- Specific Tests and Studies to be performed
- Analytical Procedures to be used
- Acceptance Criteria
- Data to be reported under or included with the comparability protocol
- Proposed Reporting Category
- Equivalence not demonstrated using the Approved Comparability Protocol
- Commitment

General Requirements:

- Excluding editorial changes in priory submitted information (e.g., correction of spelling or typographical errors, reformatting of batch records), an applicant must notify FDA

about each change in each condition established in an approved application beyond the variations already provided for in the application.

- A supplement or annual report must include a list of changes contained in the supplement or annual report. FDA recommends that the applicant describe each change in enough detail to allow FDA to quickly determine whether the appropriate reporting category has been used. For supplements, this list must be provided in the cover letter.
- In annual reports, the list should be included in the summary section. The applicant must describe each change fully in the supplement or annual report.

Variations in Europe:

Type of Variations:

1) Type IA variations requiring immediate notification (‘IAIN’)

   Type IA variations NOT requiring immediate notification (‘IA’)

2) TYPE IB Variations (Prior permission before 30 days)
3) TYPE II Variations (Major variations)

Fees: Type IA and IAIN: 3000 Euros

Type IB: 7000 Euros

Type II: 83,500 Euros

Application format: eCTD (electronic Common Technical Document)

Application submission: Electronic Submissions Gateway, eSubmission Web Client

Timelines (Review Period): Type IAIN: 30 days

Type IB: 30 days

Type II: 30, 60, 90 days

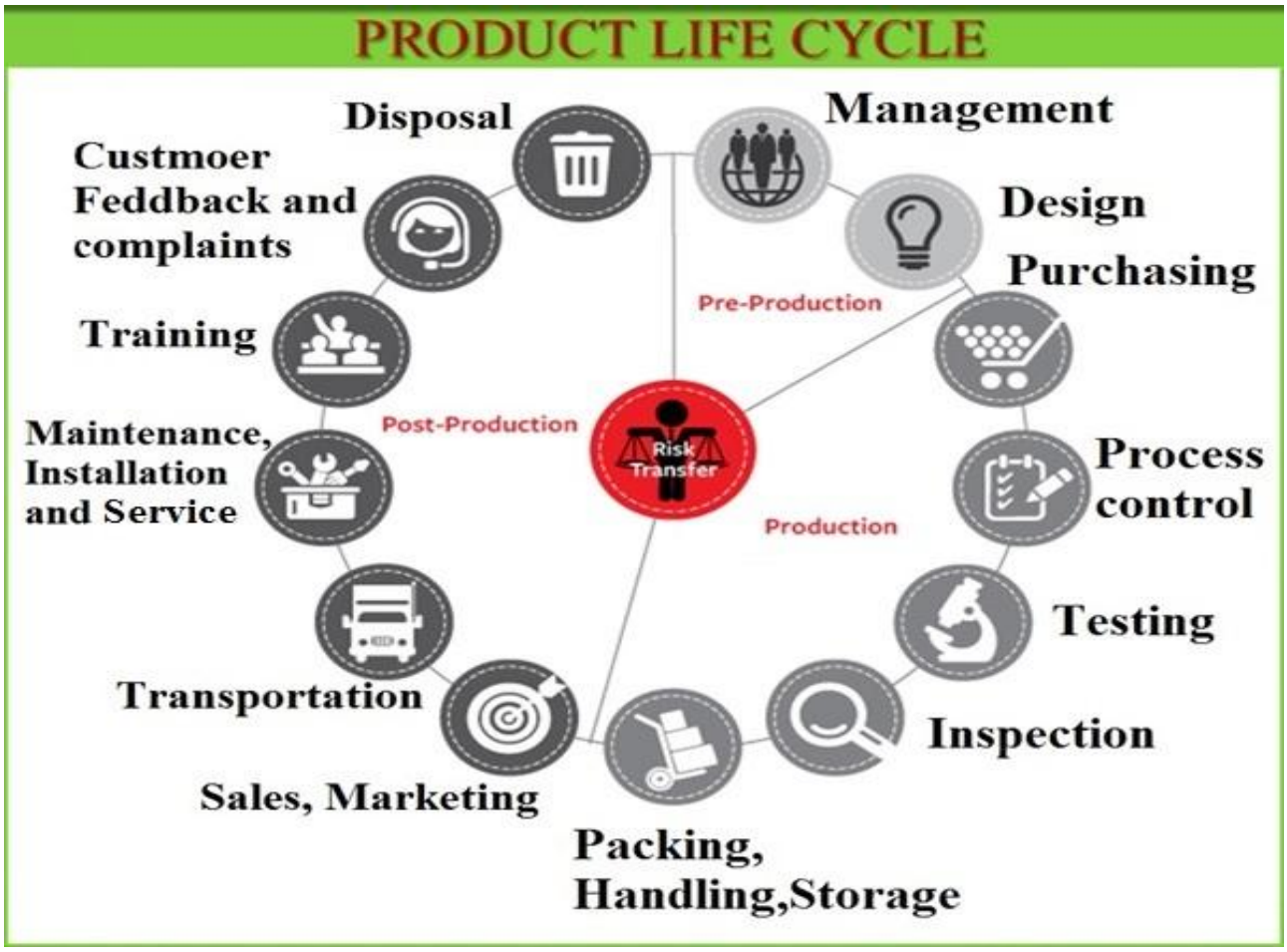

Figure 2: Product Life Cycle

Amendments in South Africa

Four different types of amendments are identified:

Type A - Amendments that may be implemented without interference of or prior notification to Council

Type B - Amendments that require prior notification

Type C - Amendments that require prior approval

Type D -Amendments that should be considered new applications.

Application Format: eCTD(Common Technical Documents)

Application Submission: The Registrar of Medicines

Medicines Control Council

Room NG090, Civitas building

42 Andries Street (Thabo Sehume Street)

Pretoria, South Africa.

Variations in ASEAN:

Major variation (MaV)

Variation to a registered pharmaceutical finished product that may affect significantly and/or directly the aspects of quality, safety and efficacy and it does not fall within the definition of minor variation and new registration.

Minor Variation (MiV-N & MiV-PA)

Variation to a registered pharmaceutical finished product in terms of administrative data and/or changes with minimal/no significant impact on the aspects of efficacy, quality, and safety.

Application Format-ACTD (ASEAN Common Technical Documents)

Application Submission: 70 A Jalan Sisingamangaraja
Jakarta 12110.

CONCLUSION

Changes are inevitable in pharmaceutical industry in fact they are very much necessary for the continuous Quality improvement of the product. By a thorough understanding of the relevant regulatory requirements stated in the act and the related guidance documents, the applicant can plan the necessary changes to the approved NDA. The applicant should think back the impact of the change on the Quality attributes of the final product and should report the changes for an approved NDA for regulatory authorities in a timely manner to be in compliant with FDA. This ultimately beneficiates the manufacturers in preventing the 483's and warning letters from the FDA and also can give the best possible quality Medicines that would be compliant both for patients and FDA as well.

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