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Overview of Post-approval Submissions Management in US, Europe and Canada

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Abstract

In today's business era & competition in pharmaceutical industries, post-approval evaluation & cGMP compliance plays an important role. Regulatory approval is a critical milestone in the lifecycle of pharmaceuticals and medical devices, ensuring their safety, efficacy, and quality before entering the market. A regulatory affair is a bridge between pharma industry and health authorities.

Post-Approval function in Regulatory Affairs department plays a major role in supporting continuous commercialization and facilitating for its implementation. This function are responsible to provide strategic regulatory inputs to plant team on their proposals and to facilitate smooth submission followed by acceptance/ approval. In the USA, the Food and Drug Administration (FDA) governs the regulatory process, employing a thorough and well-defined approach to submission evaluation. Europe, with the European Medicines Agency (EMA) at its helm, utilizes a centralized procedure for marketing authorization, harmonizing regulations across member states. Meanwhile, Health Canada oversees regulatory activities in Canada, emphasizing a risk-based approach to ensure public safety.

Post-approval submission management is equally vital in maintaining compliance and ensuring ongoing product safety. This paper delves into the strategies and best practices for handling post-approval changes, variations, and renewals. It examines the role of regulatory intelligence, life cycle management, and effective communication with regulatory agencies to navigate the evolving regulatory landscape.

By comparing and contrasting the regulatory processes in the USA, Europe and Canada, this overview aims to provide valuable insights for pharmaceutical and medical device companies seeking global market access. Understanding the intricacies of regulatory submission and post-approval submission management across these regions is essential for successful product development, commercialisation and long-term regulatory compliance.

Keywords: Post approval, EMA, FDA, cGMP, post-approval submission management.

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1. Introduction

Regulatory Affairs is a comparatively new profession which developed from the desire of governments to protect public health by controlling the safety and efficacy of products in areas including pharmaceuticals, veterinary medicines, medical devices, pesticides, agrochemicals, cosmetics and complementary medicines.

The companies responsible for the discovery, testing, manufacture and marketing of these products also want to ensure that they supply products that are safe and make a worthwhile contribution to public health and welfare.

It takes anything up to 15 years to develop and launch a new pharmaceutical product and many problems may arise in the process of scientific development and because of a changing regulatory environment. Regulatory professionals help the company avoid problems caused by badly kept records, inappropriate scientific thinking or poor presentation of data.

In most product areas where regulatory requirements are imposed, restrictions are also placed upon the claims which can be made for the product on labelling or in advertising. The pharmaceutical regulatory affairs professional's roles and responsibilities span all elements and stages of the drug development process including research and development, clinical trials, premarket approvals, manufacturing, labelling and advertising, and post market surveillance. Regulatory affair is a unique mixture of science and management to achieve a commercially important goal within a drug development organization.

In today's competitive environment the reduction of the time taken to reach the market is vital to a product's and hence the company's success. (1,2)

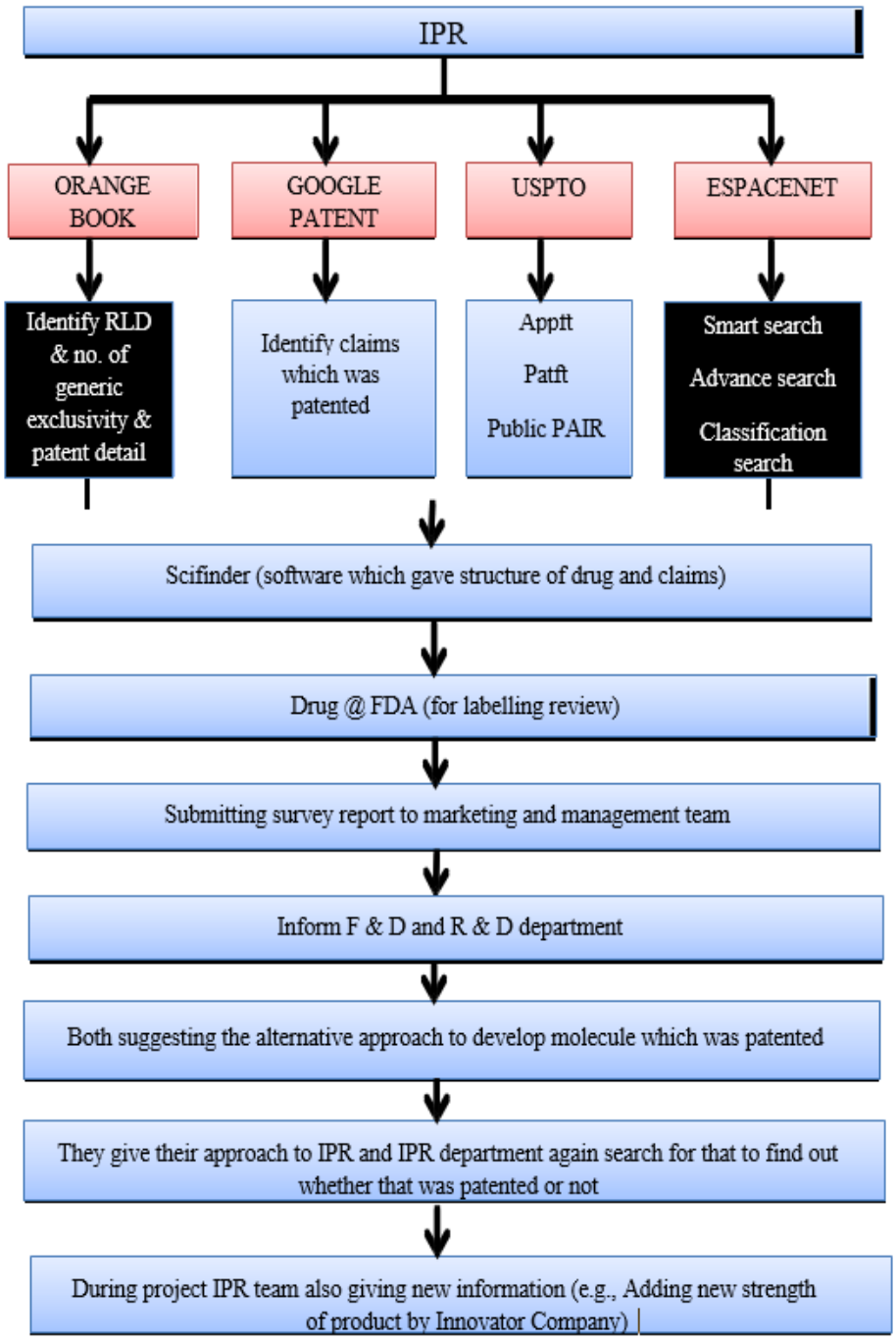
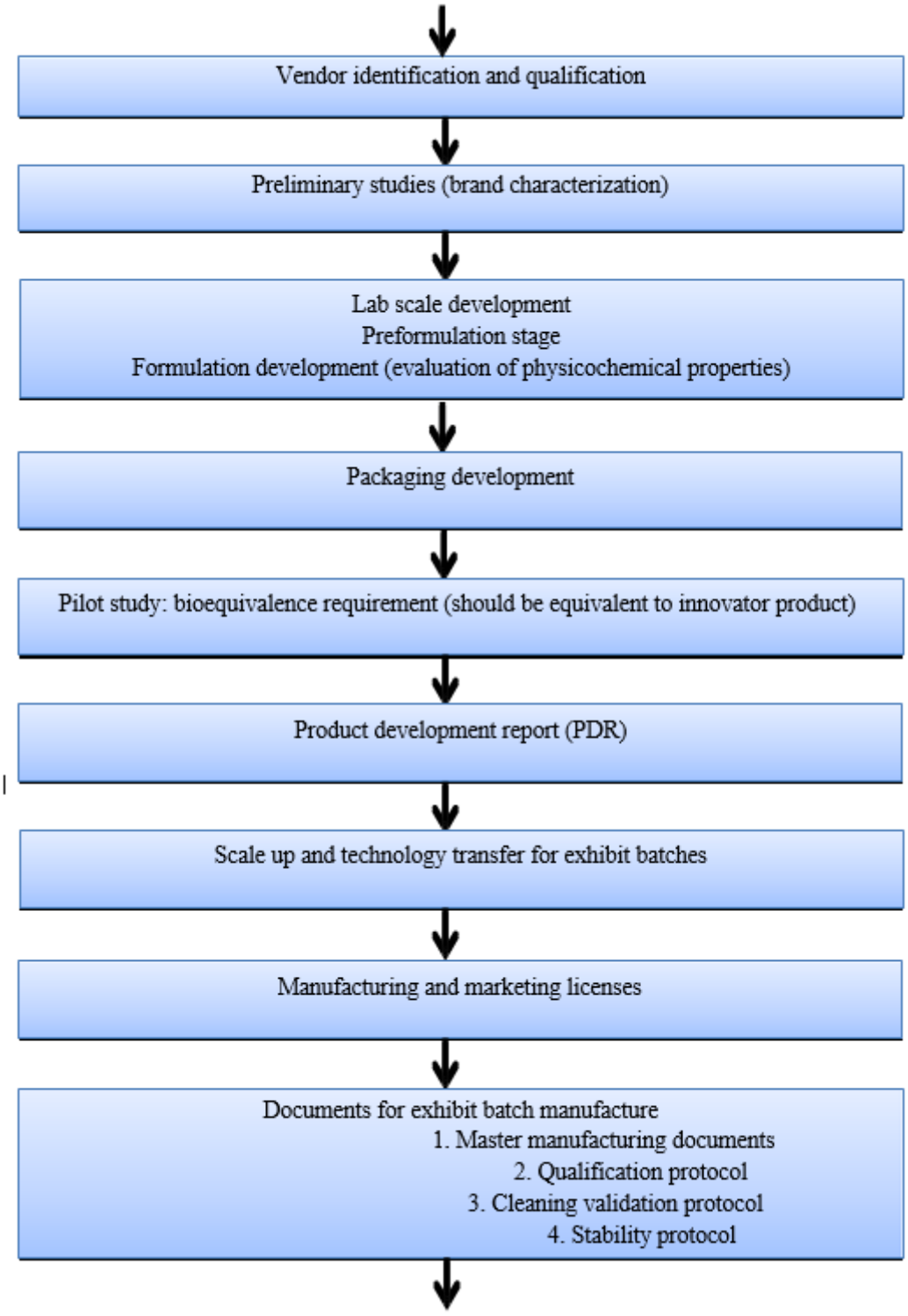


Figure 1. Generic Product Lifestyle Management



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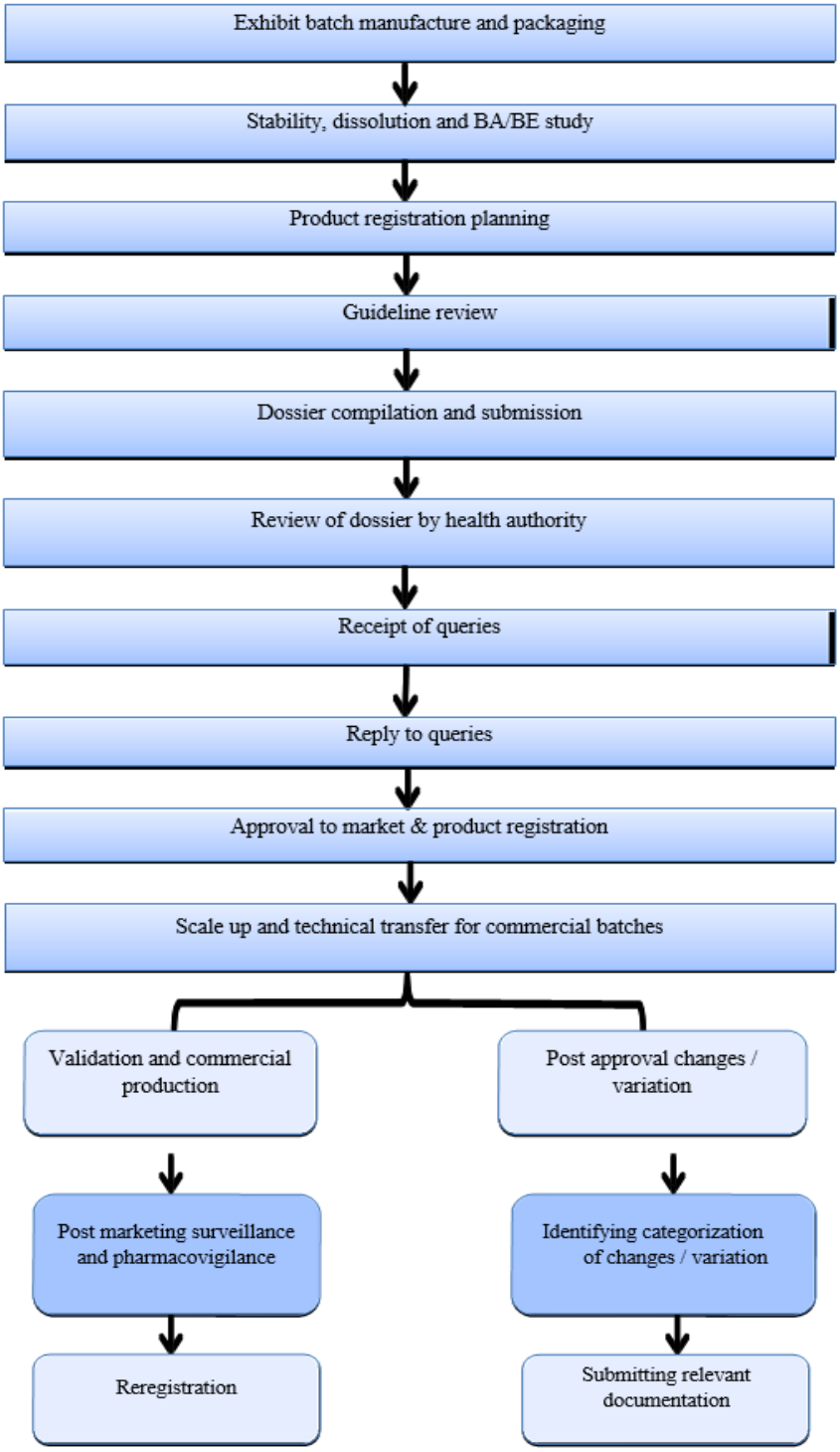

Figure 1. Generic Product Lifestyle Management

The proper conduct of its regulatory affairs activities is therefore of considerable economic significance for the company. Regulatory affair department is the crucial link between companies, drug products and regulatory authorities whose positive or negative standpoint foster the insight of the regulatory into the industry. So, better the scientific precision, the greater will be the chances for a product to come to the market within the expected time.

Responsibilities of regulatory affairs department are to keep in touch with international legislation, guidelines and customer practices, keep up to date with company's product range, ensure that a company's products comply with the current regulations, The regulatory affairs professional's job is to keep track of the ever-changing legislation in all the regions in which the company wishes to distribute its products. They also advise on the legal and scientific restraints and requirements, and collect, collate and evaluate the scientific data their research and development colleagues are generating, Formulate regulatory strategies for all appropriate regulatory submissions for domestic, international and/or contract projects, coordinate, prepare and review all appropriate

documents for example dossier and submit them to regulatory authorities within a specified time frame in conjunction with the organization, monitor the progress of all registration submission, maintain approved applications and the record of registration fees paid against submission of DMF's and other documents, respond to queries as they arise, and ensure that registration/ approval are granted without delay, impart training to R&D, pilot plant, ADI and RA team members on current regulatory requirement, manage review audit reports and compliance regulatory and customer inspection. (3,4)

2. Objective

A regulatory affair is a bridge between pharma industry and health authorities. Nowadays for generic drug holders, it is very important to launch the product immediately after getting approval. After approval of product post approval department is responsible for product launch. After receiving the approval or during commercialization of the drug product, if manufacturer propose any changes i.e. Administrative/ quality to the registered content (ANDA/ Dossier) those shall be informed to health authorities by filing supplements or variations which are known as post approval changes. In addition of this, post approval change management also helps generic companies to maintain end to end life cycle management.

Process of Post-Approval Change:

The present research endeavours to shed light onto the role that post approval change management in overcoming non-compliance. The present study has focused on identifying the existing policies and procedure in this area and understanding the underlying concepts for post approval compliance for licenses pertaining to marketing authorization. The study compared and contrasted policies and procedures of regulatory authorities in India, US, EU, Saudi Arabia and Singapore. The major finding of the study indicates that though change management plays a crucial role in the lifecycle of a pharmaceutical. However, lack of defined framework coupled with lack of comprehension of the same has increased the cost of compliance resulting step-motherly treatment being mitigated towards compliance and license maintenance. The initiatives by the ICH with drafting of ICH Q12 guidelines is a welcome step forward and may help the pharmaceutical industry to comply with the regulations.

Scale up and postapproval changes (supac):

In today scenario, as per market demand there is definitely carry out an increment or decrease in production, this is called SUPAC. Different guidelines are provided for those different types of SUPAC in by different regulatory authority for manufacturing of product. Here SUPAC guidelines for USFDA are elaborated for production in this review article. (5,6)

3. Post-approval submission in US

Different types of post approval changes:

1. Manufacturing changes
2. Component and composition
3. Manufacturing site changes
4. Specification change
5. Container closure change
6. Labelling changes

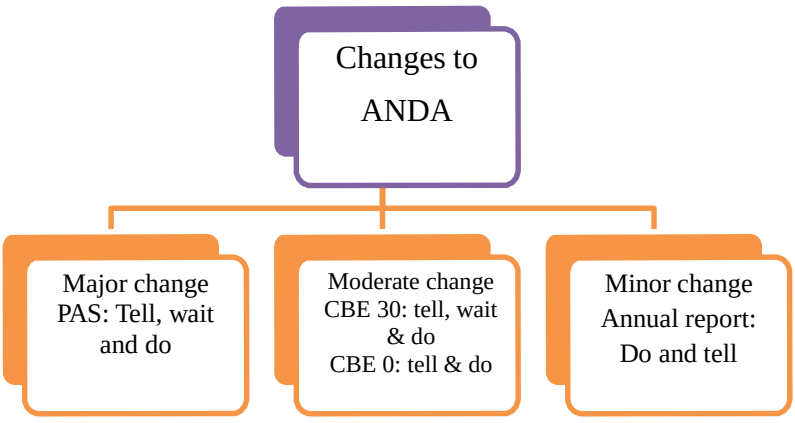

Figure 2. Reporting categories of post approval change management

Major changes

It is a change that has a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product. A major change requires the submission of a supplement and approval by FDA prior to distribution of the drug product made using the change. This type of supplement is called, and should be clearly labelled, a Prior Approval Supplement (PAS).

Moderate changes

It is a change that has a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product.

Two types of moderate changes

CBE 30: One type of moderate change requires the submission of a supplement to FDA at least 30 days before the distribution of the drug product made using the change. This type of supplement is called, and should be clearly labelled, a Supplement - Changes Being Effected in 30 Days. The drug product made using a moderate change

cannot be distributed if FDA informs the applicant within 30 days of receipt of the supplement that a prior approval supplement is required.

CBE 0: FDA may identify certain moderate changes for which distribution can occur when FDA receives the supplement. This type of supplement is called, and should be clearly labelled, a Supplement - Changes Being Effected.

Minor changes

A minor change is a change that has minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product. The applicant must describe minor changes in its next Annual Report.

Scale up and post approval changes (SUPAC)

Technology transfer of a pharmaceutical product from research to the production floor with simultaneous increase in production outputs is commonly known as scale - up. In simple terms, the process of increasing batch size is termed as scale- up. Conversely, scale- down refers to decrease in batch size in response to reduced market requirements.

Level of changes

1. Level 1 change: Those are unlikely to have any detectable impact on formulation quality and performance.

2. Level 2 change: That could have a significant impact on formulation quality and performance. Tests and filing documentation for a Level 2 change vary depending on three factors: therapeutic range, solubility, and permeability. Therapeutic range is defined as either narrow or non-narrow.

3. Level 3 change: Those are likely to have a significant impact on formulation quality and performance. Tests and filing documentation vary depending on the following three factors (7-9):

Table 1. Regulatory Submission Cost in US

User Fee Type		FY 2023	FY 2024
ANDA		$240,582	$252,453
DMF		$78,293	$94,682
Program	Large Size	$1,620,556	$1729,629
	Medium Size	$648,222	$691,852
	Small Size	$162,056	$172,963
Facility	Domestic API	$37,544	$40,464
	Foreign API	$52,544	$55,464
	Domestic FDF	$213,134	$220,427
	Foreign FDF	$228,134	$235,427
	Domestic CMO	$51,152	$52,902
	Foreign CMO	$66,152	$67,902
Backlog		$17,434	$17,434
PAS		NA	NA

4. Post-approval submission in Europe (10-16)

Reporting Categories:

- **Type IAIN:** This type of minor changes requires immediate notification after implementation.
- **Type IA:** This type of minor changes does not require any prior approval, but must be notified by the holder within 12 months following implementation ('Do and Tell' procedure).
- **Type IB:** This type of minor changes must be notified before implementation. The holder must wait a period of 30 days to ensure that the notification is deemed acceptable by the relevant authorities before implementing the change ('Tell, Wait and Do' procedure).
- **Type II:** This type of major variations requires approval of the relevant competent authority before implementation .

Table 2. Regulatory Submission Cost for EU

Fee Category		Fees
Marketing-Authorisation application		€ 345 800
Extension of marketing authorisation (level I)		€ 103 800
Extension of marketing authorisation (level II)		€ 77 900
Type IA Variation		€ 3 900
Type IB Variation		€ 8 600
Type II Variation	**Level I**	€ 103 800
	Level II	€ 77 900
	Level III	€ 26 200
Renewal of marketing authorisation		€ 17 000
Annual Fees (level I)	**Level I**	€ 123 900
	Level II	€ 62 000
	Level III	€ 31 000

Scientific Advice (Level I)	**Level I**	€ 51 800
	Level II	€ 77 900
	Level III	€ 103 800

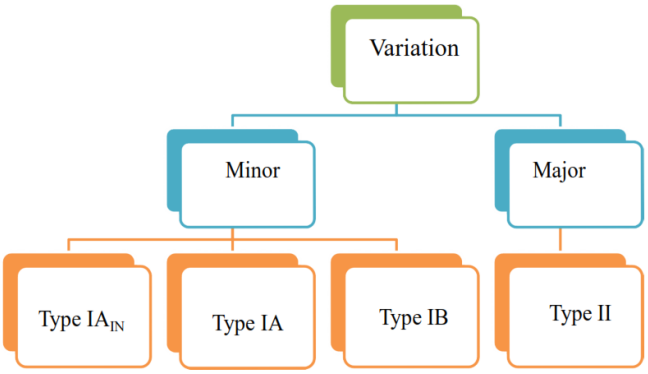

Figure 3. Reporting categories of post approval change management

5. Post-approval submission in Canada

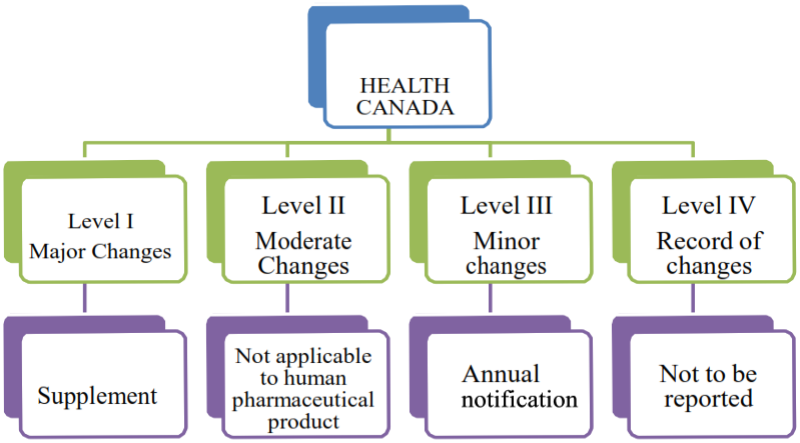

Figure 4. Reporting categories of post approval change management

Table 3. Regulatory Submission Cost in Canada

Fee Category	Fees as of April 1, 2023
New Active Substance	$565,465
Clinical or Non-Clinical Data and Chemistry and Manufacturing	$292,806
Clinical or non-Clinical Data only	$117,080
Comparative Studies	$65,985
Chemistry & Manufacturing Data only	$40,597
Clinical or non-clinical data only, in support of safety updates to the labelling	$21,429
Labelling only	$5,901
Labelling only (generic drugs)	$2,217
Administrative Submission	$933
Disinfectants full review	$12,297
Drug Identification Number application- Labelling Standard	$1,782

Types of Post-approval changes *(17-20)*

Level I – supplements:

Level I- Supplements (Major Quality Changes) are changes that have a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product. In general, a change that is supported by extensive documentation and/or requiring extensive assessment of the supporting documentation would be considered a Level I - Supplement (Major Quality Change) (e.g., a change supported by in vivo studies). This assessment will take into consideration any potential impact upon market availability as well as the adverse effects on the identity, strength, quality, purity, or potency of the drug product. The changes included in this reporting category

shall be filed, along with the recommended supporting data, to Health Canada as a Supplemental New Drug Submission (SNDS) or Supplemental Abbreviated New Drug Submission (SANDS). The change may not be implemented by the sponsor until a NOC has been issued.

Level II- notifiable changes:

Not applicable to human pharmaceutical product.

Level III- Annual Notification:

Level III - Annual Notification (Minor Quality Changes) are changes that have minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product. The changes included in this reporting category may be implemented by the sponsor without the prior review by Health Canada of the data supporting such a change. Supporting data for the Level III changes recommended in this guidance documents should not be submitted; however, the data should be available to Health Canada within thirty (30) calendar days, if requested at any time.

Level IV- record of changes:

Level IV (Quality only) changes are changes to a new drug that are not Level I, Level II or Level III and are not expected to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product. The changes included in this reporting category may be implemented by the sponsor without prior review by Health Canada.

6. Conclusion

In todays' business era and competition in harmaceutical industries, post-approval evaluation and cGMP compliance plays an important role. With the trend data of recent past where many companies have received warning letter, import alert, major observations (in terms of 483 issued by US-FDA), and business has stucked up. This has immensely impacted growth of companies and survival has become one of the questions in current situation. Looking at this scenario, prime requisite for any pharmaceutical company is to have continuous commercialization with cGMP compliant facility, which is mandatory to fulfil market requirements in generic world. In view of current condition, pharmaceutical companies are more emphasizing and revisiting their strategy "About how to ensure and subsequently implement post-approval changes". Apart from business revenue generation, basic objective behind continuous commercialization is to provide cost effective quality medicines uninterrupted supply at affordable price.

Post-Approval function in Regulatory Affairs department plays a major role in supporting continuous commercialization and facilitating for its implementation. This function / group are responsible to provide strategic regulatory inputs to plant team (which includes but not limited to, R&D, Quality, Mfg., etc.) on their proposals and to facilitate its smooth submission followed by acceptance / approval. Apart from this, this group is also actively involved in supporting cGMP and PAI audits / inspection. This group is responsible for maintenance of overall product life cycle throughout. Consequences of failure to comply with cGMP requirements includes but not limited to, warning letter, recall of products, field alert report etc. In nutshell, post-approval changes and submissions are having Direct and Significant impact on business and survival / growth of any company. (21-23)

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Conflict of Interest

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

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