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Regulatory Procedure of Post Approval Changes and Comparative Requirements of EU and USA Regulatory Regions

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Aim: The current research paper describes the "Regulatory procedure of post approval changes and comparative regulatory requirement of EU and USA regulatory regions".
Study Design: The present study is a type of Retrospective analysis of Regulatory requirements and the reviewed data was subjected to systemic review. Understanding of the same led to several observations regarding regulatory requirements of EU and USA regulatory regions.
Place and Duration of Study: The present study was carried out at Amneal Pharmaceutical Ltd., Ahmedabad, Gujarat, India from January, 2021 to April, 2021.
Methodology: Several guidelines were profoundly reviewed to compare the requirements of post approval changes in EU and USA regulatory regions. Various regulatory review aspects were focused i.e. requirements for manufacturing sites addition/or Transfer, process parameters,

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container and closures, packaging and labelling of medicinal products.
Results: The post approval changes in manufacturing sites of solid or semisolid dosage form considered as a major change for USA while considered as Moderate change for EU. The transfer of manufacturing section is major variation for USA while it is a minor but immediate inform type for EU. Change in manufacturing processes, containers, labelling section of sterile products considered as major variation for both. Semisolid and solid categories are falling under the same type of variation for EU and USA regulatory regions.
Conclusion: This work demonstrated that the drug approvals in US, EU are the most demanding globally and the available guidance and procedures for the triggered changes are clear in both countries. Applicant should have scientific rationale to any change pertaining to Approved product ; Since the all change control are falling under the scope of Audit, so Applicant should maintain the all the records online.

Keywords: Post approval management; audit, change control evaluation; lifecycle management; post-approval; variations; harmonization; Europe; US; Type IA/Type IB/Type II variations; line extensions, US; CBE-30, PAS and Annual reportable IR (Information request) and CR (Complete Response).

ABBREVIATIONS

CBE : Changes Being Effected
PAS : Prior Approval Submission
USA : United States of America
USFDA : United States Food and Drugs Administration
EU : European Unions
EMEA : European Medicines Agency
Type IA_{IN} : Immediate Implementation
e-CTD : Electronic Common Technical Dossier
CMC : Chemistry, Manufacturing and Control
NDA : New Drug Application
ANDA : Abbreviated New Drug Application
CFR : Centre For Research
MAH : Marketing Holder
SUPAC : Scale up and Post Approval Changes
QA : Quality Assurance
CMDh : Heads of Medicines Agencies
Rapporteur : a person who is appointed by an organization to report on the proceedings of its meetings i.e."the UN rapporteur"
IR : Information request
CR : Complete Response
IR dosage form : Immediate Release Dosage Form
cGMP : Compliance to Good Manufacturing Procedures

1. INTRODUCTION

Specific changes in those a corporation would like to apply during the product's lifecycle, as well as how they would be prepared and verified, are described in a post-approval change management; Because the Marketing Authorization Holder (MAH) will have obtained agreement from the Regulatory Authorities about the proposed strategy and tests to verify the effect of the change on product quality, such a stepwise approach can lead to faster and more predictable implementation of changes after approval [1].

Post Approval Change Management is involved in business-driven decision to meet on going Regulatory guideline updations to adhere product's life cycle management.

In the current post-market change management system, different jurisdictions have distinct methods for change management as well as various approaches for reporting proposed changes to the relevant health authorities. Each country's diverse mechanisms make it difficult for producers to maintain a consistent supply of the same product in different countries. Post Approval Change is an unavoidable part of product's life cycle management, and it can be happen for a assortment of reasons, including regulatory changes, changes in manufacturing process due to the development of more efficient and cost-effective methods, changes in business triggered requirements and product models, changes in analytical and formulation specifications, and so on. All of these modifications are aimed to enhance the safety and quality of healthcare supplements provided to the customers globally.

For post-market change submissions, several countries have their own regional regulations.

The 'Scale up and post approval changes' (SUPAC) advices in the United States of America gives information on many elements of post approval changes pertaining to quality, safety and efficacy of product. This guidance includes suggestions on post-approval changes, recommended tests, and documentation for CMC changes for new drug applications or abbreviated new drug applications. The implementation of this guideline has led to faster approval times and incorporation of the post approval changes of an already marketed product whenever applicable [2,3].

Proper Change control form (CCF) evaluation is necessary while accessing the proposed changes from each department. The Regulatory Affairs Post Approval Team plays a critical role to finalize the CCF. The CCF form should be mentioned in such a way that each countries' regulatory requirement should be fulfilled. The final copy of CCF should mention each of department's task, actions and target date for it's completion. The CCF is very crucial document and is falling under the scope of Audit so monitoring of each CCF completion and close task is the big challenge to QA department.

In this Article; we are focusing on best regulatory practices-specifically Post approval changes evaluation and comparative regulatory requirements for EU and USA regulatory regions.

2. METHODOLOGY

The present study is a type of Retrospective analysis of regulatory requirements and the reviewed data was subjected to the systemic review. Understanding of the same led to several observations regarding regulatory requirements of EU and USA regulatory regions. Internet databases were searched including Wikipedia, Google, Google scholar and Yahoo. The search words that were used included EU and USA, Post approval changes in EU, Post approval changes in USA, Change control Evaluation, Post-approval Variations, Type IA/Type IB/Type II variations; Line extensions, US; CBE-30, PAS and Annual Report. Thirteen references were identified which were used to write the article.

3. RESULTS AND DISCUSSION

3.1 European Medicines Agency (EMEA/ EU)

The EMEA/EU has established regulatory standards for post-approval changes, referred in Europe as a variation filing, and has classified the variations. Type 1A variations are modest changes that are submitted once a year and do not need to be reported to the competent authority right away. Whereas the Type IA_{IN} variations need to be notified immediately. The Type IB variations are moderate level changes that must be notified to the competent authority. Type II or major variations are high risk changes for which prior approval from competent authority must be taken before implementation of the change [4].

3.1.1 Types of variation in EMEA/EU [5]

1. Type IA – "Do and tell" for changes implemented in previous 12 months.
2. Type IA_{IN} - "Do and tell" and requires immediate notification after implementation.
3. Type IB – "Tell, wait and do" and requires notification before implementation. (wait 30 days after submission of procedure)
4. Type II – More detailed changes ("Tell and do") and requires approval before implementation (usually 60 day review; range 30-90 days)
5. Extension applications – e.g. additional strengths, pharmaceutical form and route of administration (up to 210-day review)

3.1.2 Guidelines to follow

1. ***Variations Regulation (1234/2008)*** *as amended by (712/2012)*
2. ***Variations Guidelines*** *(2013/C 223/01)*

3.1.3 Review Process

The Agency will review the Type IA/IA_{IN} variation(s) within 30 calendar days following receipt. By day 30 the Agency will inform the MAH by Eudralink about the outcome of the review (favorable or unfavorable). During the review, the Agency will verify the documentation against the validation checklist and in particular:

- Whether the application form has been properly filled in;
- The presence and correctness of the required documentation and
- Compliance with the required conditions, in accordance with the Classification Guideline.

In exceptional cases, during the review process the Agency may issue a request for

supplementary information (VSI) in case deficiencies have been identified in the submission, responses to which are due within 4 working days as part of a new e-CTD sequence.

3.1.4 For Type IB variation

"Tell, Wait and Do" – upon acknowledgment of receipt of a valid notification MAH must wait 30 days to ensure notification is deemed acceptable by Agency.

Variation Guidelines contains examples of changes which are considered Type IB.

When one or more conditions for Type IA/IA$_{IN}$ variations are not met, such change should be classified as IB unless explicitly listed as type II.

Unforeseen variations (Change is not specifically classified in Variation Regulation or as CMDh Art 5 recommendation) should be submitted as Type IB or Type II, depending on the impact of the change(s) on the quality, safety and efficacy of the finished product.

The Rapporteur is involved in assessment of changes.

3.2 USFDA [6-13]

Any post approval changes to an approved NDA/ANDA must be notified to USFDA as per section 506A of the *Federal Food, Drug, and Cosmetic Act (the Act) and § 314.70 (21 CFR 314.70).*

"…the applicant must notify FDA about each change in each condition established in an approved NDA/ANDA beyond the variations already provided for in the NDA. The notice is required to describe the change completely.

Depending on the type of change, the applicant must notify FDA about the change in a supplement…"

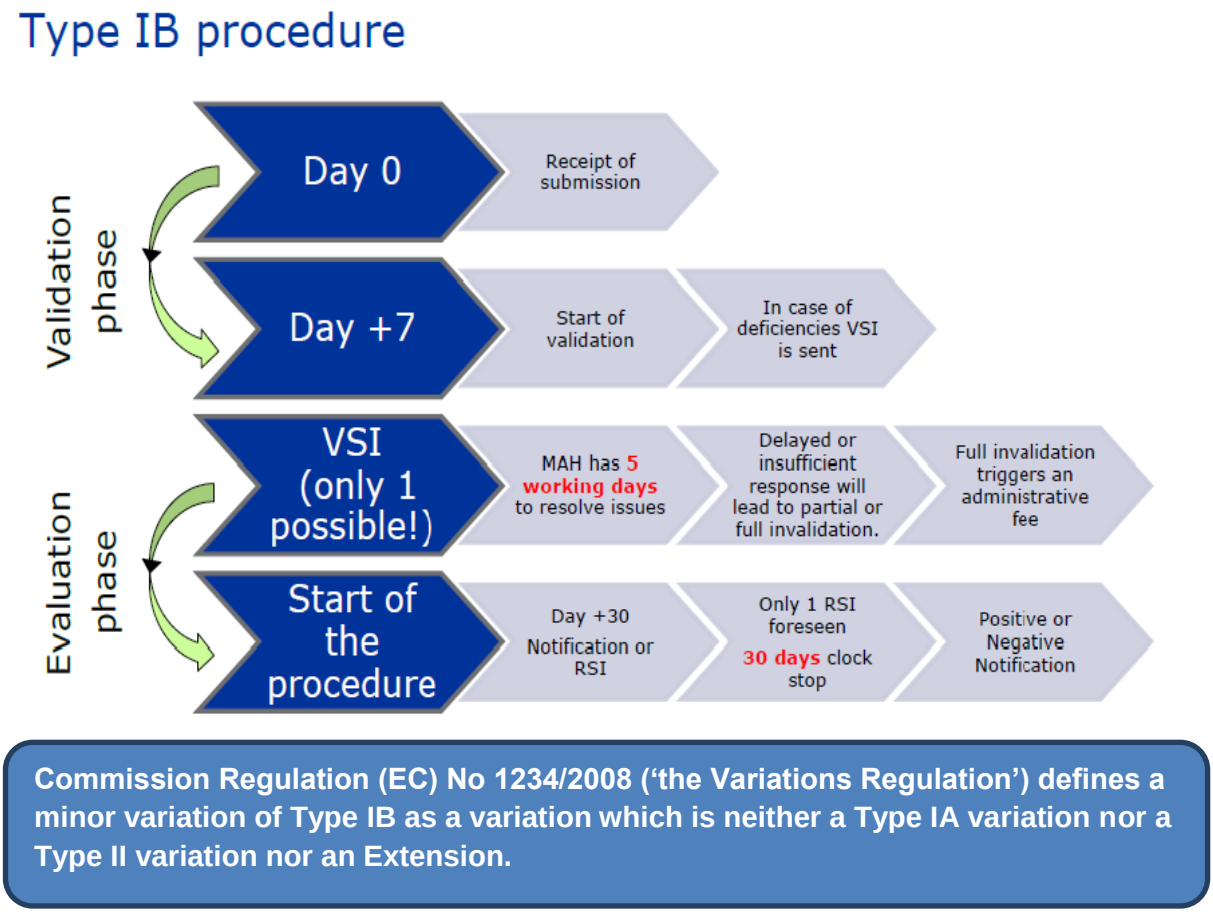

Fig. 1. Procedure of Type IB Variation

"The NDA/ANDA holder must assess the effects of the change before distributing a drug product made with a manufacturing change."

According to FDA, any change in approved ANDA is classified as below:

1) **Major Changes**
   - Prior Approval Supplement
2) **Moderate Changes**
   - CBE- 0 and CBE - 30
3) **Minor changes**
   - Annual Reportable

1. Major Changes - Prior Approval Supplement (PAS)

- A large change is the one that has the potential to have a significant negative impact on the identity, strength, quality, purity, or potency of a drug product, as these variables may affect the medicine's safety or effectiveness. A major modification necessitates the submission of a supplement and FDA clearance before the drug product created with the change can be distributed. This type of supplement is called, and should be clearly labeled, a **Prior Approval Supplement.**

2. Moderate Changes

- A moderate change 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. There are two types of moderate change.
- 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 should be clearly labeled, a Supplement - **Changes Being Effected in 30 Days (CBE-30).**
- 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 labeled, a Supplement - **Changes Being Effected (CBE-0).**

3. Minor changes - Annual Reportable (AR)

- 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 (i.e. Once in a year) **Annual Report.**

3.2.1 Review Process

USFDA has separate CFR for the Post Approval Supplements as mentioned in below table.

- Annual Reports are moderate change and can be file after one year of Product approval date.
- CBE (Changes Being Effected) are can be granted after 30 days followed by Approval from FDA. Based on granting Confirmation from FDA, Company can implement the change with assessment of Risk based approach.
- PAS is generally have goal date of 6 month. Generally, it took 7-8 month for approval.
- For all above supplement FDA can send the queries inform IR (Information request) and CR (Complete Response) depending on the submission done by Applicant.

Table 1. Types of CFR for Post Approval Supplement of USFDA

Type of Submission	Type of CFR
Annual Report	*21 CFR314.70$_{(d)}$ and 21 CFR 314.81$_{(b)(2)}$*
CBE-0	*21 CFR 314.70$_{(c)(6)}$ and 21 CFR 601.12$_{(c)(5)}$*
CBE-30	*21 CFR 314.70$_{(c)}$ and 21 CFR 601.12$_{(c)}$*
PAS	*21 CFR 314.70$_{(b)}$ and 21 CFR 601.12$_{(b)}$*

Table 2. Comparative Post Approval Regulatory Requirement of Manufacturing sites [5-13]

Sr no	Changes[@]	US	EU
1.	A move to a different manufacturing site, except one used to manufacture or process a drug substance intermediate, when the new manufacturing site has never been inspected by FDA for the type of operation that is being moved or the move results in a restart at the new manufacturing site of a type of operation that has been discontinued for more than two years.	PAS	Type II
2.	A move to a different manufacturing site, except one used to manufacture or process a drug substance intermediate, when the new manufacturing site does not have a satisfactory CGMP inspection for the type of operation being moved.	PAS	Type II
3.	A move to a different manufacturing site for (1) the manufacture, processing, or primary packaging of drug products when the primary packaging components control the dose delivered to the patient or the formulation modifies the rate or extent of availability of the drug, or (2) the manufacture or processing of in-process materials with modified-release characteristics.	PAS	Type II
4.	Transfer of the manufacture of an aseptically processed sterile drug substance or aseptically processed sterile drug product to (1) a newly constructed or refurbished aseptic processing facility or area or (2) an existing aseptic processing facility or area that does not manufacture similar (including container types and sizes) approved drug products.	PAS	Type IB
5.	Transfer of the manufacture of a finished drug product sterilized by terminal processes to a newly constructed facility at a different manufacturing site.	CBE-30	Type IB
6.	A move to a different manufacturing site for the manufacture or processing of any drug product, in-process material, or drug substance	CBE-30	Type IB
7.	For aseptically processed sterile drug substance or product, a move to an aseptic processing facility or area at the same or different manufacturing site	CBE-30	Type IB
8.	A move to a different manufacturing site for the primary packaging of (1) any drug product that is not otherwise listed as a major change and (2) modified-release solid oral dosage form drug products.	CBE-30	Type IA_{IN}
9.	A move to a different manufacturing site for testing.	CBE-30	Type IA
10.	A move to a different manufacturing site for the manufacture or processing of the final intermediate	CBE-0	Type IB
11.	A move to a different manufacturing site for secondary packaging.	Ann. report	Type IA_{IN}
12.	A move to a different manufacturing site for labelling	Ann. report	Type IB
13.	A move to a different manufacturing site for the manufacture or processing of drug substance intermediates other than the final intermediate.	Ann. report	Type IB
14.	A change in the contract sterilization site for packaging components when the process is not materially different from that provided for in the approved application	Ann. report	Type IB
15.	A transfer of the manufacture of a finished product sterilized by terminal processes to a newly constructed building or existing building at the same manufacturing site.	Ann. report	Type IB
16.	A move to a different manufacturing site for the ink imprinting of solid oral dosage form drug products.	Ann. report	Type IB

Table 3. Comparative Post Approval Regulatory Requirement of Manufacturing process [5-13]

Sr no	Changes[@]	US	EU
1.	Changes that may affect the controlled (or modified) release, metering or other characteristics (e.g., particle size) of the dose delivered to the patient, including the addition or deletion of a code imprint by embossing, debossing, or engraving on a modified-release solid oral dosage form.	PAS	Type II
2.	Changes in the virus or adventitious agent removal or inactivation methods. For drug substance and drug product, changes in the source material (e.g., microorganism, plant) or cell line. For drug substance and drug product, establishment of a new master cell bank or seed.	PAS	Type II
3.	Changes that may affect drug product sterility assurance.	PAS	Type II
4.	For drug substance: Changes in the synthesis or manufacture of the drug substance that may affect its impurity profile and/or the physical, chemical, or biological properties.	PAS	Type II
5.	For drug products, any change in the process, process parameters, and/or equipment.	CBE-30	Type IA
6.	For natural protein drug substances and natural protein drug products: Any change in the process, process parameters, and/or equipment An increase or decrease in production scale during finishing steps that involves different equipment. Replacement of equipment with equipment of different design that does not affect the process methodology or process operating parameters.	CBE-30	Type IA
7.	For sterile drug products, drug substances, and components: Changes in dry heat depyrogenation processes for glass container systems, Changes to filtration parameters for aseptic processing, Filtration process changes that provide for a change from single to dual sterilizing filters in series, or for repeated filtration of a bulk. Changes from one qualified sterilization chamber to another for in-process or terminal sterilization that result in changes to validated operating parameters (time, temperature, F0, and others). Changes in scale of manufacturing for terminally sterilized drug products that increase the bulk solution storage time by more than 50 percent beyond the validated limits.	CBE-30	Type II
8.	A change in methods or controls that provides increased assurance.	CBE-0	Type IA
9.	For sterile drug products, elimination of in-process filtration.	CBE-0	Type IA
10.	For drug products, changes to equipment of the same design and operating principle and/or changes in scale	Ann. report	Type IA
11.	A minor change in an existing code imprint for a dosage form.	Ann. report	Type IA
12.	Addition or deletion of a code imprint by embossing, debossing, or engraving on a solid dosage form drug product other than a modified-release dosage form.	Ann. report	Type IA
13.	For natural protein drug products and natural protein drug substances: An increase or decrease in production scale during finishing steps that does not involve an equipment change. Replacement of equipment with equipment of the same design, operating principle, and capacity with no change in production scale.	Ann. report	Type IA

Table 4. Comparative Post Approval Regulatory Requirement of Specification [5-13]

Sr. no	Changes[@]	US	EU
1.	Relaxing an acceptance criterion	PAS	Type II
2.	Deleting any part of a specification	PAS	Type II
3.	Change outside the approved specification limits range	PAS	Type II
4.	Tightening of acceptance criteria	Ann.report	Type IA
5.	Addition of new test and limits	CBE-0	Type IA
6.	Addition or replacement of a specification parameter as a result of a safety or quality issue	CBE-0	Type IB
7.	Deletion of a non-significant specification parameter	CBE-0	Type IA
8.	A change in an analytical procedure that does not provide the same or increased assurance of the identity, strength, quality, purity, or potency.	CBE-30	Type IB

Table 5. Comparative Post Approval Regulatory Requirement of Container closure system [5-13]

Sr no	Changes[@]	US	EU
1.	For liquid and semisolid dosage forms, a change to or in polymeric materials of primary packaging components	PAS	Type IB
2.	For liquid and semisolid dosage forms in permeable or semipermeable container closure systems, a change from an ink and/or adhesive used on the permeable or semipermeable packaging component to an ink or adhesive that has never been used in an approved drug product of the same dosage form and same route of administration ***and*** with the same type of permeable or semipermeable packaging component.	PAS	Type IB
3.	A change in the primary packaging components for any drug product when the primary packaging components control the dose delivered to the patient.	PAS	Type II
4.	For sterile drug products, any change that may affect drug product sterility assurance, such as: A change from a glass ampule to a glass vial with an elastomeric closure. A change to a flexible container system (bag) from another container system. A change to a prefilled syringe dosage form from another container system. A change from a single unit dose container to a multiple dose container system. Changes that add or delete silicone treatments to container closure systems Changes in the size and/or shape of a container for a sterile drug product	PAS	Type II
5.	Deletion of a secondary packaging component intended to provide additional protection to the drug product or a change in the composition of, or the addition of, a secondary packaging component that may affect the impurity profile of the drug product.	PAS	Type II
6.	A change to a new container closure system if the new container closure system does not provide the same or better protective properties than the approved container closure system.	PAS	Type II
7.	A change in a container closure system that does not affect the quality of the drug product.	CBE-30	Type IB

Sr no	Changes[@]	US	EU
8.	Changes in the size or shape of a container for a sterile drug substance.	CBE-30	Type IB
9.	A change in the number of units (e.g., tablets, capsules) or labeled amount (e.g., grams, milliliters) of a nonsterile drug product in a unit-of-use container	CBE-30	Type IA_{IN} (within the range) Type IB (outside the range)
10.	A change in the size and/or shape of a container for a nonsterile drug product, without a change from one container closure system to another	CBE-0	Type IA
11.	A change in the labeled amount (e.g., grams, milliliters) of drug product for a nonsterile drug product in a multiple-unit container, except for solid dosage forms	CBE-0	Type IB
12.	A change in or addition or deletion of a desiccant	CBE-0	Type IA
13.	A change in the container closure system for a nonsterile drug product.	Ann. report	Type IA
14.	A change in the size and/or shape of a container for a nonsterile solid dosage form	Ann. report	Type IA
15.	A change in the number of units (e.g., tablets, capsules) or labeled amount (e.g., grams) of nonsterile solid dosage form in a multiple-unit container	Ann. report	Type IA_{IN} (within range) Type IB(outside range)
16.	Changes in the container closure system of drug products as long as the new package provides the same or better protective properties. • Adding or changing a child-resistant closure, • Changing from one plastic container to another of the same type of plastic. • Changes in packaging materials used to control odour. • Changes in bottle filler without changes in the type of filler. • Increasing the wall thickness of the container. • A change in or addition of a cap liner. • A change in or addition of a seal. • A change in an antioxidant, colorant, stabilizer, or mould releasing agent for production of the container and/or closure. • A change to a new container closure system when the container closure system is already approved in the NDA or ANDA for other strengths of the drug product	Ann. report	Type IA
17.	A change in the flip seal cap colour as long as the cap colour is consistent with any established colour coding system for that class of drug products	Ann. report	Type IA_{IN} (if affect product info.) Type IA (if not affect product info.)

Table 6. Comparative Post Approval Regulatory Requirement of Labelling [5-13]

Sr no	Changes[@]	US	EU
1.	Changes based on post marketing study results, labeling changes associated with new indications and usage.	PAS	Type II
2.	Change in, or addition of, pharmacoeconomic claims based on clinical studies.	PAS	Type IB
3.	Changes to the clinical pharmacology or the clinical study section reflecting new or modified data.	PAS	Type IB
4.	Changes based on data from preclinical studies	PAS	Type II
5.	Revision (expansion or contraction) of population based on data	PAS	Type II
6.	Claims of superiority to another drug product.	PAS	Type II
7.	Change in the labeled storage conditions	PAS	Type IB
8.	Addition of an adverse event due to information reported to the applicant or Agency	CBE-0	Type II
9.	Addition of a precaution arising out of a post marketing study	CBE-0	Type IB
10.	Clarification of the administration statement to ensure proper administration of the drug product	CBE-0	Type IA
11.	Changes in the layout of the package or container label without a change in the content of the labeling.	Ann. report	Type IA
12.	Editorial changes, such as adding a distributor's name	Ann. report	Type IA

Table 7. Comparative Post Approval Regulatory Requirement of Miscellaneous changes [5-13]

Sr no	Changes[@]	US	EU
1.	Addition of a stability protocol or comparability protocol.	PAS	Type II
2.	Changes to an approved stability protocol or comparability protocol	PAS	Type IA
3.	An extension of an expiration dating period based on (1) data obtained under a new or revised stability testing protocol that has not been approved in the application or (2) full shelf life data on pilot scale batches using an approved protocol	PAS	Type IB
4.	Reduction of an expiration dating period to provide increased assurance of the identity, strength, quality, purity, or potency of the drug product. Extension of an expiration date that has previously been reduced under this provision should be submitted in a changes-being-effected-in-30-days supplement.	CBE-30	Type IA_{IN}
5.	An extension of an expiration dating period based on full shelf life data on production batches obtained under a protocol approved in the application	Ann. report	Type IB
6.	Addition of time points to the stability protocol or deletion of time points beyond the approved expiration dating period	Ann. report	Type IB
7.	A change from previously approved stability storage conditions to storage conditions recommended in International Conference on Harmonization (ICH) guidances	Ann. report	Type IB
8.	Replacement of an in-house reference standard or reference panel according to procedures in an approved application	Ann. report	Type IA
9.	Tightening of acceptance criteria for existing reference standards to provide greater assurance of drug product purity and potency	Ann. report	Type IA

[@] *To access change accurately please refer the change with different condition in guidance.*

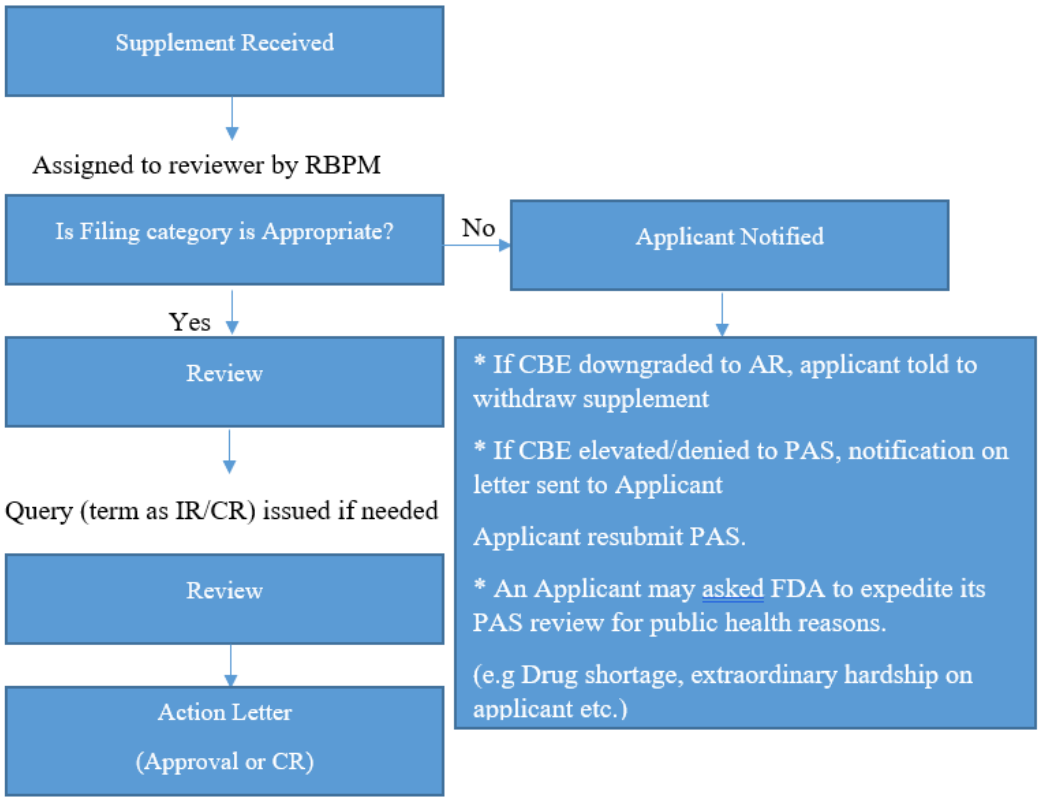

Fig. 2. Submission of Post Approval Supplement

For both countries EU and USA have different procedures for assessment of supplement. If change category is not properly assign in the submission then submission either will be rejected or elevated to the next category.

1. Case Study for EU/EMEA :

For Europe data available for Analysis of Type IA/IA_{IN} applications submitted between Sept. 01, 2015 to Sept. 01, 2016:

- 48% of submissions triggered either a request for clarifications or additional information;
- most common validation issues: Incorrect update/missing Annex A/PI: 24%
- Incorrect update/missing Module(s): 22%
- Application Form incorrectly filled in: 22%
- Discrepancy in details of contact person: 9%
- Guideline page missing, conditions/ documentation not ticked: 6%
- Incorrect or missing

In EU submission, most of the common mistakes are due to Implementation of date due to trigerred change. Below is the brief detail of Implementation dates.

Implementation date:

The implementation date is dependent on the type of change(s) being applied for and should be intended as follows:

- **Quality Changes:** when the company makes the change in its own quality system (to allow to manufacture conformance batches and generate any needed stability studies to support a Type IA_{IN} variation before making an immediate notification).
- **Product Information (PI):** when the company internally approves the revised PI, which will then be used in the next packaging run.
- **Change in name of the MAH:** the date when the new name is reflected by the Chamber of Commerce.
- **Change in the address of the MAH:** the date of the physical move.

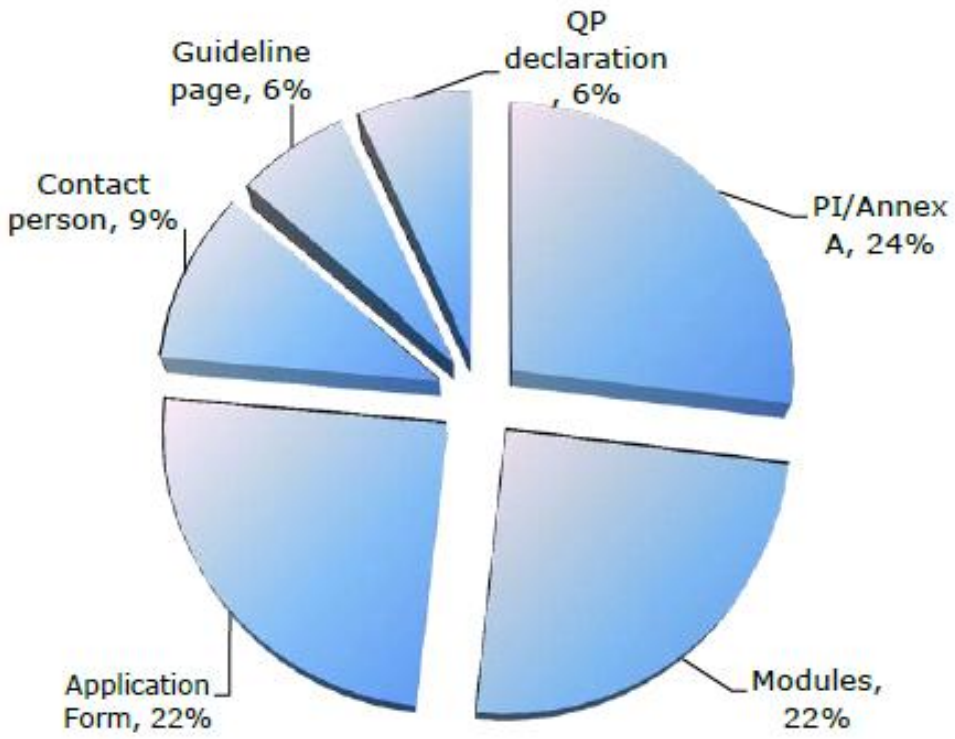

Fig. 3. Pie chart of Type IA/IA$_{IN}$ applications submitted between Sept. 01, 2015 to Sept. 01, 2016

2. Case study USFDA:

a. CBE-30 elevated to PAS:

Proposed change: Alternate drug product manufacturing site for an IR dosage form product
Supplement submitted as CBE-30 *(VI.C.1.a CANADA guidance)*
[CANADA :Changes to an Approved NDA or ANDA]
Decision: FDA denied Supplement to PAS
Reason: Proposed site did not have a satisfactory cGMP inspection *(PAS per VI.B.2 in CANADA Guidance)*
A move to a different manufacturing site, except one used to manufacture or process a drug substance intermediate, when the new manufacturing site does not have a satisfactory CGMP inspection for the type of operation being moved.
Modified release (MR) solid oral dosage forms include both delayed and extended release drug products as per SUPAC-MR, alternate drug product manufacturing site is a PAS (Level 3 change), with the bioequivalence study.

b. CBE-30 Elevated to PAS

Proposed Change: Delete blend uniformity analysis (BUA) testing for a low dose drug (0.5 mg)
- Supplement submitted as CBE-30
Decision: Supplement elevated to PAS by FDA
Reason: *Active drug represents 0.5 mg or only 0.6% of total tablet weight of 80 mg.*
Deletion of BUA is high risk. (PAS per VIII. B.2 in CANADA guidance.)
Deleting any part of a specification except as otherwise provided for in this guidance (e.g., *section VIII.D.2*).

Common Deficiencies in Supplements:
1. Comply with the current USP monograph for DS (Drug Substance) and/or DP (Drug Product) - e.g., Assay, and Specified Impurities
2. Demonstrate method equivalency to USP (United States Pharmacopoeia)
3. DMF (Drug Master File) is inadequate; provide revised API specification and method Validation/verification
4. Provide tablet splitability data for scored tablets for Level 2/3 changes in

SUPAC IR/MR - e.g., Change in equipment to a different design and different operating principles; alternate drug product manufacturing site, etc.

4. CONCLUSION

The Drug approvals in the US, Europe the most demanding globally. The guidance and procedure are clear in both the countries. Applicant should have scientific rationale to any change pertaining to Approved product. Since the all change control are scope of Audit, so Applicant should maintain the all record online.

Following are the tips for the good supplement filing:

1. Use regulations and guidance to determine the appropriate reporting category for the change and provide sufficient supporting data (e.g. As per SUPAC, Tablet scoring guidance)

✓ Do not rely on data to justify classification, but instead justify reporting category based on cited guidance applicable sections and nature of proposed change(s). If multiple related changes, most restrictive filing category will apply.

✓ clearly list all proposed changes in the cover letter.

2. Keep track of USP (United States Pharmacopoeia) updates.
3. Work with your DMF(Drug Master File) holder closely.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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