Review Article

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Study on post approval source change of active pharmaceutical ingredient in the finished product and its regulatory requirements in EU and US

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ABSTRACT

Post approval changes are changes to any characteristic of pharmaceutical product after approval. Certificate of suitability of European pharmacopoeia (CEP) and drug master file (DMF) are two mechanisms for active pharmaceutical ingredient (API) registration. Regulatory requirements vary for each mechanism. This study focused on regulatory requirements for post approval API source change in the European Union (EU) and USA; and to delve on the mechanism of post approval API source changes in the USA and EU. To improve quality of the API, the most of the pharmaceutical industries concentrate on CEP certified source instead of DMF as CEP assures compliance to standard and compliance to good manufacturing practices as well. DMF to CEP source change is considered as minor change as it provides more assurance toward standard and quality whereas CEP to DMF source change is considered as major change because of no assurance of standard compliance in both countries. Differences observed by this study include approval procedure, timeline and fees for approval; similarities are observed classification of variation but the terms used for each class differ. In both the countries, CEP is preferred over DMF to improve quality of the product and to assure its safety.

Keywords: Variation, active pharmaceutical ingredient, regulations, European Union, USA

INTRODUCTION

Components of finished product consist of active pharmaceutical ingredient (API) and inactive ingredient (excipient). API is the central element of the formulation that causes "pharmacological activity." APIs are commonly manufactured by the company other than manufacturer of finished product. Pharmaceutical industry maintains documentation as an evidence of maintaining quality of the drug substance. European pharmacopoeia commission deals with unique procedure for the drug substance with defined quality specifications. In case, finished product manufacturer changes his API source, post approval/variation guideline is applied for it. Sponsor or holder of finished product can be applicant for the source change of API. The drug substance/active substance information generally submitted for obtaining Certification of suitability to the monograph of European pharmacopoeia (CEP) and Drug master file (DMF).

API Registration

There are two ways by which sponsor can provide information on drug substance

1. DMF
2. CEP delivered by European Directorate for the Quality of Medicines and Healthcare (EDQM).

DMF

DMF is used to provide confidential information about facilities, processing, packaging, and storing of drug substance. The submission of DMF is not mandatory, but it solely depends on the holder. The information submitted in DMF is used as supportive information for various types of application such as IND, new drug application (NDA), and abbreviated NDA (ANDA).[1]

Role of DMF Submission in API

1. Registered API is published online which helps in marketing API to manufacturer of drug product

2. To provide proprietary and confidential information
3. As supporting document in approval process.

There are two parts of DMF:

Open part: Applicant's part of a DMF. It normally includes brief outline of manufacturing process and information on potential impurities.

Closed part/restricted part of DMF: It includes detailed description on step by step manufacturing process, critical steps, validation, and quality control test. Such information is provided to authorities only.

Certificate of Suitability

The CEP applicant is responsible to conform that the substance is manufactured as per good manufacturing practices (GMP) requirements. EDQM issues CEP on the compliance of GMP for respective drug substance. It will not provide GMP certificate nor is GMP certificate equal to CEP.[2] Assurance of GMP in manufacturing of API and compliance to the standard laid down in European pharmacopoeia helps to meet end product specification resulted in diversion of API industries toward CEP certification.

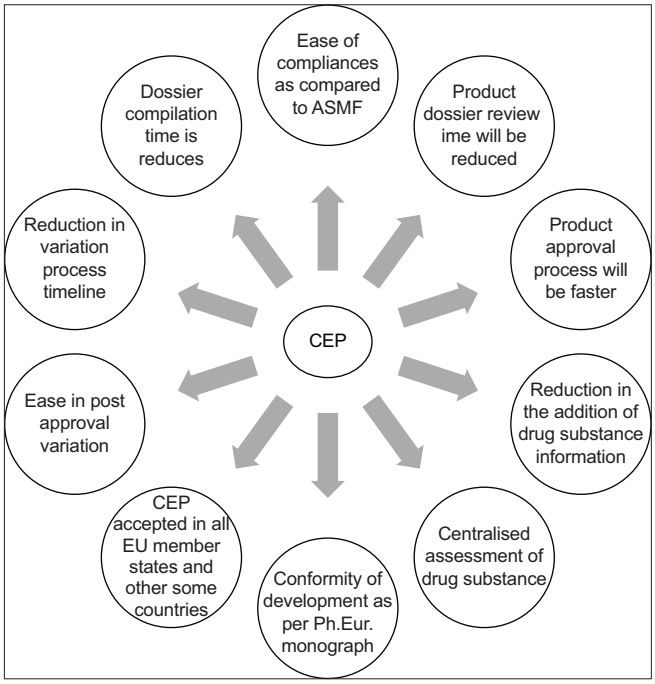

Figure 1: Advantages of Certificate of Suitability to the Monograph of European Pharmacopoeia[2]

CEP is submitted for both API and excipients. CEP is generally applicable for

a. Manufactured or extracted active substances (Organic or inorganic)
b. Gene products obtained from fermentation of microorganisms.
c. Products having risk of transmissible or bovine spongiform encephalopathy (BSE) agents.

Advantages of CEP [Figure 1]

As European Medicines Agency (EMA) and United States Food and Drug Administration have clearly defined regulations for variation and being part of a regulated market, the EU and USA is selected for the study. The objective of this study is to provide an insight on types of variations of API source, post approval procedure, and to compare regulatory requirements for approval of API variation in the EU and USA.

As CEP assures the compliance of API requirements to that of the monographs laid down under European pharmacopoeia, it is preferred by the industries over DMF that takes longer time for approval during source change of API. As this article is based on the source change of API, the timeline and fees required for it are based on the classification of variation. Details on timeline and fees required for each type of variation are provided in the EU and USA separately.

DISCUSSION

API Source Change

API source change is proposed and executed after product approval. It is necessary to ensure the impurity profile, chemical and physical properties, and other specifications to remain the same as they lead to change in quality of the drug product. This is ensured using appropriate methods such as NMR, X-ray powder diffraction, and assay.

Any change which has impact on physical characteristics of API or impurity data of the API is evaluated from the stability perspective and its potential effect on the finished product. Change in source of API includes more than location change. Differences observed during source change includes equipment change, change in route of synthesis, and modification in manufacturing procedure. Without thorough knowledge of old and alternate sources, an applicant cannot effectively describe the variances between the sources. If synthesis procedure is different in new API source, the complete safety evaluation of the API is mandatory.

Table 1: Types of Variation based on CEP

Source of active substance	Change		Type of variation
	Existing	Proposed	
Change within the organization	Non-CEP	Non-CEP	IA_{IN}
Outside the organization	Non-CEP	Non-CEP	II
For both within as well as outside the organization	Non-CEP	CEP	IA_{IN}
For both within as well as outside the organization	CEP	Non-CEP	II
For both within as well as outside the organization	CEP	CEP	IA

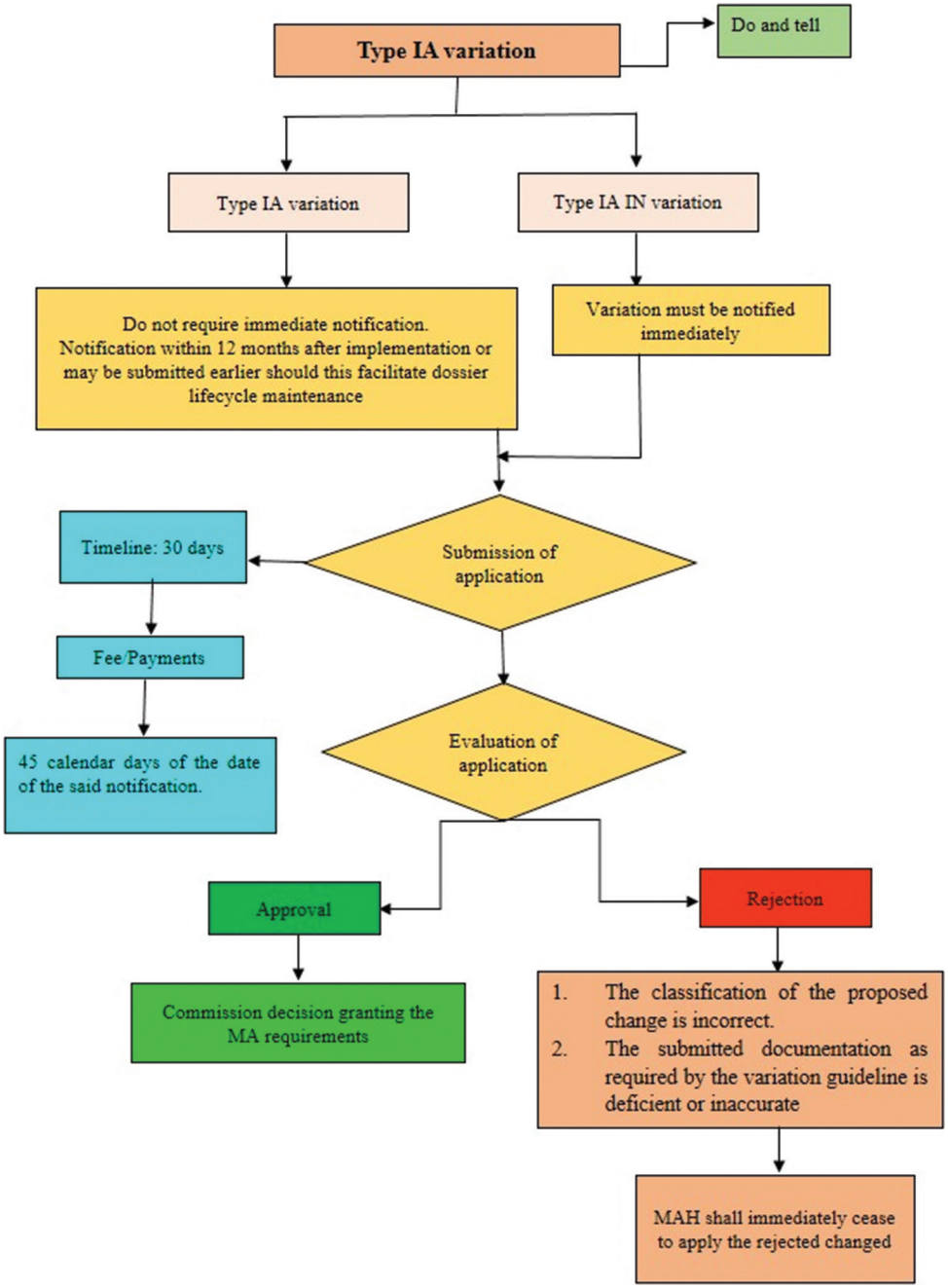

Figure 2: Approval procedure for Type IA variation[7] (Hoey B. 2017)

Classification of changes[3]

Classification is based on its effect on safety, quality, and purity of finished pharmaceutical product.

1. Minor changes: A change having minimal effect on safety, quality, and purity of the drug product. For example, change in the address of the manufacturer of finished product
2. Moderate changes: Change has moderate effect on the safety, quality, and purity of the finished product. For example, manufacturing site of drug product changes to the new location
3. Major changes: Change has significant effect on the quality, safety, and purity of the finished product. For example, change in specifications of drug product.

Need for changing API source[3]

The need may be either listed below or combination of them –

1. To improve drug product quality
2. To reduce the cost of material that ultimately reduces cost of finished product
3. To obtain higher quality materials (valid for product specific needs)
4. To search vendor with improved API quality

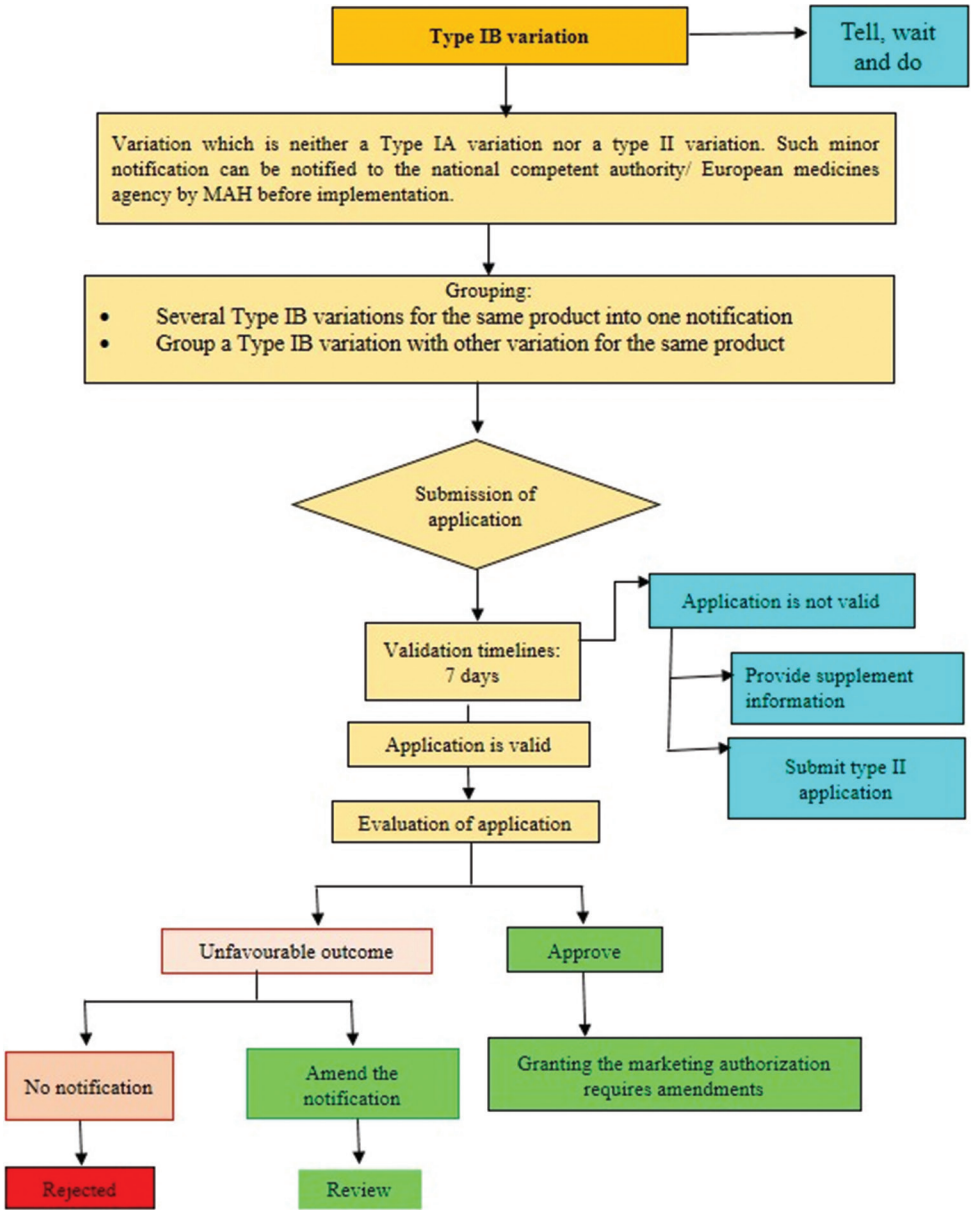

Figure 3: Approval procedure for Type IB variation[7] (Hoey B. 2017)

5. To reduce lead time for availability of material
6. To confirm presence of alternate source in case of unavailability of material from present source.

API supplier selection[4,5]

Manufacture of the API is subjected to the strict GMP regulations that are intended to assure the quality, purity, and safety of the API. GMP is the major criteria while selection of the API source. Before selecting the supplier, there is need of quality system evaluation. In this context, the following information from the supplier is requested for supplier evaluation:

- Specifications
- Details related to manufacturing process, packaging, labeling, etc.
- Safety data of raw materials
- Information related to supply of the product. For example, delivery time and lead time.
- Certificates regarding quality system, residual solvents, etc.
- BSE/Transmissible spongiform encephalopathy assessment
- Analytical assessment methods.

The following dimensions could be assessed: Assurance of supply, cost aspects, technical/innovation aspects, communication capabilities, and responsiveness.

API Source Change in EuropeanUnion (EU)

The EMA provides comprehensive procedural guidelines on the handling of variations (European Commission, 2013). The EU allows post approval API source change as a part of variation for approved pharmaceutical products. Variation is categorized based on its impact on quality, safety, and efficacy of medicinal products.

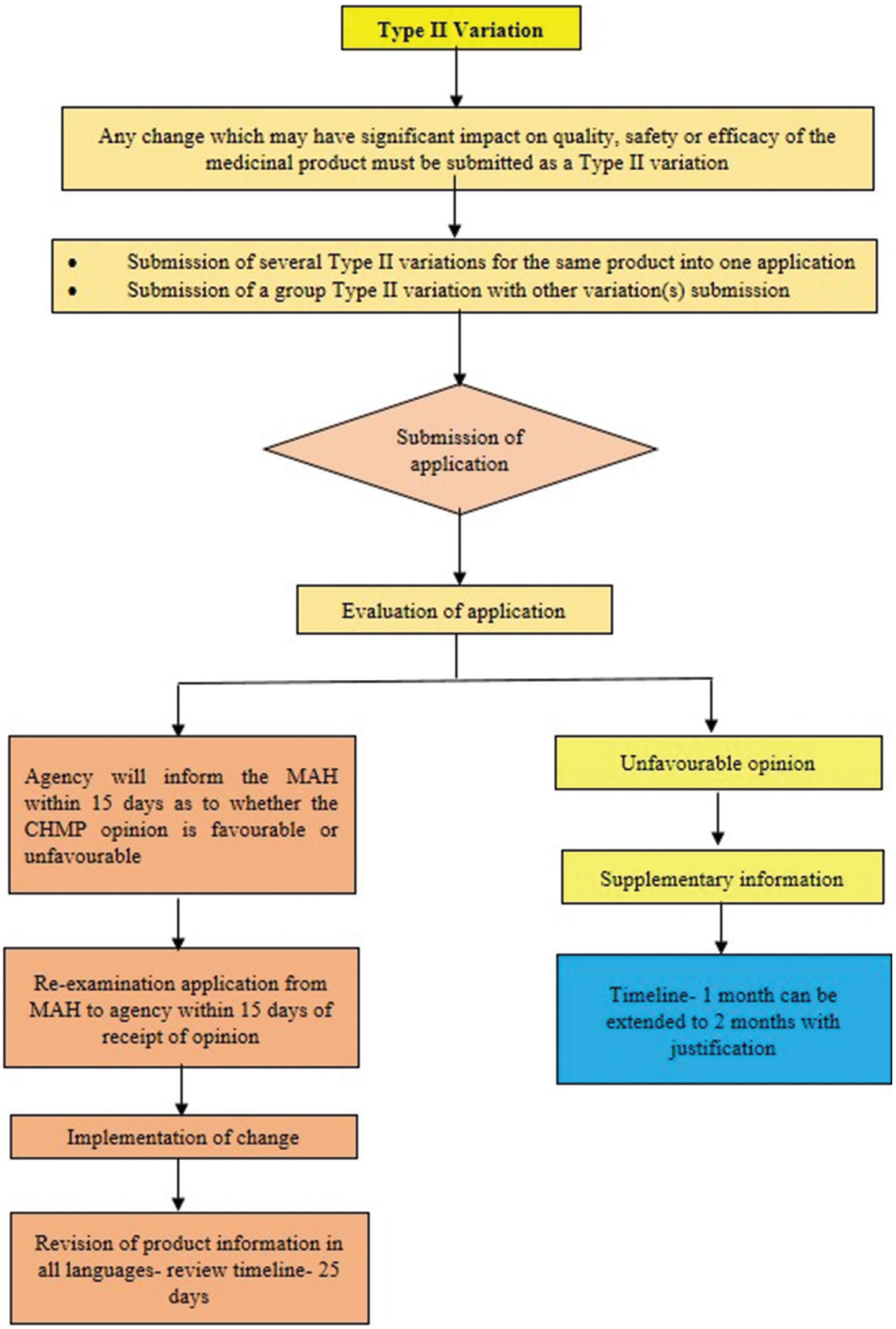

Figure 4: Approval procedure for Type II variation[7] (Hoey B. 2017)

Categories of variation[6]

1. Minor variations of Type IA: Minimum or no impact on quality, safety, and efficacy of drug product. No prior approval is needed
   - "Do and tell"
   - Notification within 12 months from amendment of variation
2. Minor variations of Type IB: Moderate impact on quality, safety, and efficacy of drug product
   - Notified before implementation of variation
   - "Tell, wait, and do"
   - Waiting period: 30 days
3. Major variations (Type II)
   - Major effect on the quality, safety, or efficacy of a drug product
   - Need prior approval before change implemented.

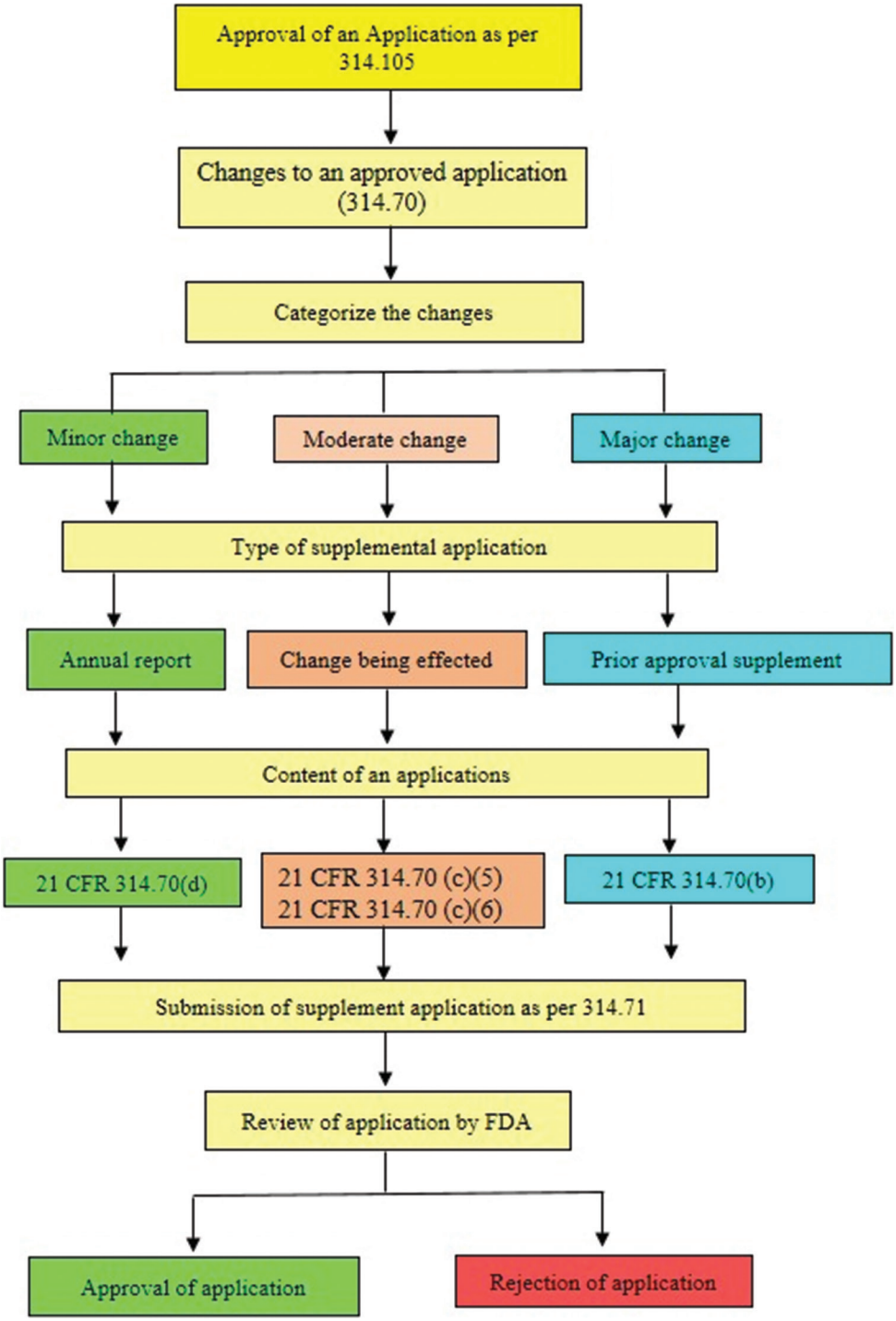

Figure 5: Flow chart for application submission and approval process[7]

Approval procedure of Type IA variation[7]

Type IA variation excludes prior inspection by the regulatory agency. However, the notification of relevant variation is sent within 12 months from date of execution to the agency. Agency reviews Type IA notification and informs applicant about outcome by day 30. Immediate rejection is applied in case applicant fails to provide supporting documents [Figure 2].

Approval procedure of Type IB variation

Type IB notification is notified before implementation. Thirty days wait period is applied to confirm that the notification is

Table 2: Conditions and documents for various types of changes in EU[6]

Source of active substance	Change		Type of variation	Conditions	Documents
	Existing	Proposed			
Change within the organization	Non-CEP	Non-CEP	IA_{IN}	1. Identical Specifications and complete route of synthesis as permitted 2. Viral safety assessment or compliance with Minimizing Risk of TSE agent for human or animal origin materials	1. Revision of relevant part of the dossier 2. Declaration of Marketing authorization holder or the Active substance master file holder: Synthetic route, quality control procedures and specifications of the active substance are the same as those already approved 3. Documentary evidence: 4. TSE risk substances has been previously evaluated by regulatory authority 5. Batch analysis data for active substance: minimum two pilot batches 6. Variation application form 7. Qualified person declaration: Manufacturing process in compliance with GMP
Outside the organization	Non-CEP	Non-CEP	II	No specific conditions for major changes	Complete DMF
For both within as well as outside the organization	Non-CEP	CEP	IA_{IN}	1. Same Finished product release and termination of shelf life specifications as approved 2. Identical impurity profile as approved 3. No use of human or animal origin material 4. Active substance will be tested immediately prior to use if no retest period is included in CEP 5. The active substance is not sterile 6. For herbal API: Synthesis process, physical form, extraction solvent and drug extract ratio have to be similar	1. Copy of CEP 2. Variation application form 3. Revision of the relevant part of the dossier 4. Document containing following information: Name of manufacturer, species and tissues from which the material is a derivative, country of origin of the source animals and its use. (if material falling under TSE agent) 5. Declaration by qualified person: Manufacturing process in compliance with GMP
For both within as well as outside the organization	CEP	Non CEP	II	No specific conditions for major changes	Complete DMF
For both within as well as outside the organization	CEP	CEP	IA	1. FP release and end of shelf life specifications remain the same 2. Same specifications for impurities and product specific requirements, if applicable 3. No use of human or animal origin material 4. Active substance will be tested immediately prior to use if no retest period is included in CEP 5. For herbal active substances: The manufacturing route, physical form, extraction solvent and drug extract ratio should remain the same	1. Copy of CEP 2. Variation application form 3. Amendment of the relevant section of the dossier 4. Document containing following information: Name of manufacturer, species, and tissues from which the material is a derivative, country of origin of the source animals, and its use. (if material falling under TSE agent) 5. Declaration by qualified person: Manufacturing process in compliance with GMP

Table 3: Approval timeline and fees for variation

Type of variation	Timeline for approval	Fees for approval
Type IA_{IN}	30 days	€ 3000
Type IB	1–2 months	€ 7000
Type II	5–7 months	€ 8300

considered to be acceptable by the relevant regulatory agencies before executing variation. After receiving notification, it is handled as follows:

Within 7 calendar days, agency evaluates application whether change is considered as Type IB variation or not. If not, application is rejected. If yes, applicant will be informed and procedure starts. Within 30 days following, the

Table 4: Conditions and documents for various types of changes in the USA[10]

Source of active substance	Change		Type of variation	Documents
	Existing	Proposed		
Change within the organization	DMF	DMF	CBE-30	Name, contact number, email id of contact person for the novel facility, its DUNS number, and FEI number, if available
				Elucidation of API development steps and brief of equipment variation and process parameter
				Statement: "synthetic pathway is identical at the new facility for a master file"
Change outside the organization	DMF	DMF	PAS	Name, contact number, email id of contact person for the novel facility, its Data Universal Numbering System number, and Facility Establishment Identifier number, if available
				Elucidation of API development steps and brief of equipment variation and process parameter
				Statement: "Synthetic pathway is identical at the new facility for a master file"

Table 5: Approval timeline and fees for variation in the USA[11]

Type of change	Timeline	Fees
CBE 30	30 days	$ 3752
PAS	4 months	$ 35,240

Table 6: Classification of variation/post approval changes in the EU and USA[12]

Type	EU	USA
Minor	Type –IA	Annual report
Moderate	Type –IB	CBE 0/CBE 30
Major	Type-II	PAS

Type-IA: Do & Tell; Type-IB: Tell, wait & Do; CBE 0: change being effected within 0 days; CBE 30: change being effected within 30 days; PAS: prior approval supplement

Table 7: API source change: Types of variation and documents required for change

Type of variation	EU	USA
Change within the organization	IA_{IN}	CBE-30
Change outside the organization	II	PAS

Documents	EU	USA
DMF/ACTD/CTD section	✓	-
Amendment of relevant section of dossier	-	-
Variation application form/summary of variation	✓	✓
QP declaration: GMP compliance	✓	-
GMP certificate	-	-
ASMF/Marketing Authorization holder declaration: synthetic route, Quality control procedure and remains same	✓	✓
Batch analysis data	✓	-

*Note: If variation is outside the organization, these countries has to submit complete DMF document for approval of variation

acknowledgment of receipt applicant receives opinion on the notification by regulatory authority. If applicant fails to get opinion from regulatory authority, then the notification is considered to be acceptable. For unfavorable opinion, within 30 days, applicant may amend the notification. Final approval or refusal of variation is sent to the applicant by the day 30. In case of centralized procedure, Rapporteur is involved for review process [Figure 3].

Approval procedure of Type II

Notification for major variation must be submitted to concerned member states, to national competent authority. The authority will accept receipt of valid application and evaluation process will start. Sixty days evaluation period will apply that can be decreased in case of emergency. If agency request for supplementary information, then 1-month suspension period is applied to justify request. In case of mutual recognition procedure, reference member state/s prepares a draft assessment report of variation and circulates them to the concerned member state to comment on variation within specified timeline. The final decision is taken by the reference member state by considering concerned member states opinion [Figure 4].

- Evaluation period of Type II variation: 60 days
- This period may be reduced to 30 days in case of urgency for safety issues or extended to 90 days for grouping of variation.

Change in API source

As the API source changes, it is necessary to consider whether the new API source contains certificate of suitability (CEP) or not. The conditions and documents required to submit for approval of variation depends on CEP of relevant source.

Variations can be done in following cases:

1. Within the organization and
2. Outside the organization.

Depending on this, the type of variation changes. It is given as stated in Tables 1-3:

API Source Change in the United States of America

Variations in the USA are called as scale up and post approval changes (SUPAC).[8] USA has provided guidance "Post approval changes to drug substances: Guidance for industry." It provides guidance on approved NDAs, ANDAs, ANADAs, DMFs, and VAMFs.

Classification[9]

It depends on potential to have an adverse effect on identity, strength, quality, purity, or potency of the drug products.

1. Major changes: Significant effect on quality, safety, and efficacy of the drug. It requires prior approval supplement (PAS) from FDA before implementation. For example, change in manufacturing site of drug substance
2. Moderate changes: Moderate effect on quality, safety, and efficacy of the drug
   - Change being effected-30 (CBE 30): Applicant notifies FDA at least 30 days in advance before the drug product is manufactured after change being implemented. For example, change in testing facilities of drug substance
   - CBE 0: Applicant notifies about the change to FDA at the time of distribution of drug. For example, change in analytical procedure used for testing components and final intermediates.
3. Minor changes
   - Minimum or no effect on quality, safety, and efficacy of the drug
   - Changes to be submitted in annual report
   - For example, change in labeling site.

Approval procedure[7]

Minor changes are reported in annual report along with summary data. For moderate and major changes, cGMP requirements are applicable (21 Code of Federal Regulation Part 210, 211). Audit inspections are carried out to check cGMP compliance. Once the review of the application with supplementary documents completed, final decision for approval or rejection is given by authority [Figure 5]. The required documents for various types of change [Table 4] and approval timelines for variation is given in Table 5.

EU and USA requirements for change in API source are summarized as below [Tables 6 and 7]:

a. Non-CEP to Non-CEP:
   - GMP certificate is not mandatory in both the countries for API source change, but in case of Europe, GMP compliance is mandatory for production of API.

b. CEP to CEP

Type of variation	EU	USA
Change within the organization	IA_{IN}	CBE-30
Change outside the organization	II	PAS

   - Presence of CEP itself suggests API source complies with cGMP and it complies with the quality described in the relevant monograph of the European pharmacopoeia. Hence, there is no need to submit other documents except CEP certificate.

c. CEP to Non-CEP:

Type of variation	EU	USA
Change within the organization	II	PAS
Change outside the organization	II	PAS

Documents	EU	USA
Drug Master File	✓	↻

CONCLUSION

Post approval API source change is an important factor to consider for manufacturing of medicinal product. As EU and USA classified post approval source change in similar manner, the major change observed was GMP compliance in the EU regulations for API production, change in approval procedure for variation, timeline, and fees for approval. The most of the pharmaceutical industries are changing API source to achieve superior quality products. This made pharmaceutical industries to divert toward API source containing CEP certificate to achieve safety, efficacy, and quality product.

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