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An Overview of Variation of API (DMF) in Regulated Markets (USFDA, Canada, EU and EDQM (CEP)

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ABSTRACT

The purpose of this article is to present a concise overview of the variation of Active pharmaceutical ingredient (API) for Generic Drugs in various regulatory authorities such as USFDA, TPD, EU, and EDQM as per ICH-CTD. A regulatory process, by which a person/ organization/ sponsor/ innovator once gets authorization to launch drugs in the market, changes to be filed to maintain Product Life Cycle Management (PLCM) is known as the Variation process. The variation process will be done by submitting technical information to the authority i.e., an amendment to Drug Master File. A Drug Master File or DMF variation is a reference source that provides drug evaluator's product life cycle management information about the specific process and components used in the manufacturing, control, processing, and packaging of drugs meant for Human /Animal use.

INTRODUCTION

Product Life Cycle Management (PLCM) is the complete cycle for the medicinal products which contains changes. Changes may be in the manufacturing, processing, controlling, container closure, stability, or the administrative changes which is part of continual improvement. Many reasons for making changes to medicinal products once the initial submission is done and regulatory approval is obtained. For each change, it is necessary to find out the acceptability of the proposed changes, to prove that the specified change does not hurt the quality of the product.

Some of the changes which are having adverse effect or impact on quality may be rejected by the authority to implement. Changes for medicinal products are differently classified and from authority to authority, it changes. Changes done in the companies are tracked by one of power full system i.e., change control.

These change controls are evaluated and implemented by the Regulatory Affairs team will do a technical assessment to know the impact on the quality and stability of the medicinal products with relevant regulatory guidance. (2)

Role of Variations in API:

Variations i.e. changes in API made will have a direct impact or indirect impact on the finished product which will be consumed by humans/animals. Important are explained below;

1. Major changes in chemistry (route of synthesis) will impact on stability if API stability impact finished product expiry to be revised.

2. Changes in starting material used in API will have a direct impact on the finished product.

3. Change in polymorph, particle size or any other changes in control in API will have a direct impact on the finished product.

US Drug Master Variations:

Types of Variations in the US:

1. Major Changes [Prior approval supplement (PAS)]

2. Moderate changes [Supplement - Changes Being Effected]

- Supplement - Changes Being Effected in ‘30’ days (CBE-30)
- Supplement - Changes Being Effected in ‘0’ days (CBE-0)

3. Minor changes (Annual report) (3)

1. Major Changes [Prior approval supplement (PAS)]

The major change is a change that has a substantial potential to hurt the identity, strength, quality, purity, or potency of drugs as these factors may relate to the safety or effectiveness of the drugs. A major change requires the submission of an amendment and approval by the FDA before the distribution of the drugs made using the change. This type of amendment is called and should be clearly labeled as the Prior Approval Supplement (PAS). (4)

An applicant may ask FDA to expedite its review of a prior approval supplement for public health reasons (e.g., drugs shortage) or if a delay in making the change described in it would impose an extraordinary hardship on the applicant. This type of amendment is called, and should be clearly labeled, a Prior Approval Supplement (PAS) - Expedited Review Requested. (3)

Product affected by these changes cannot be distributed until approval which should take up to four months, assuming there are no technical issues. (4)

2. Moderate changes [Supplement - Changes Being Effected]

Moderate change is a change that has a moderate potential to hurt the identity, strength, quality, purity, or potency of the drug as these factors may relate to the safety or effectiveness of the drug. (3)

There are two types of moderate change.

- **Supplement - Changes Being Effected in ‘30’ days (CBE-30)**

Requires the submission of an amendment to FDA at least 30 days before the distribution of the drug made using the change. This type of supplement is called, and should be clearly labeled, an amendment - Changes Being Effected in 30 Days. The drug made using a moderate change cannot be distributed if the FDA informs the applicant within 30 days of receipt of the amendment that a prior approval supplement is required. (3)

However, if the submission of the amendment is rejected, a recall may also be required.

- **Supplement - Changes Being Effected in '0' days (CBE-0)**

Changes classified as CBE-0 are minor changes to the drug which can be implemented from when the FDA receives the supplemental application. No impact on the drug and can be distributed. CBE-0 changes are considered approved six months after receipt if there are no technical issues raised by the FDA. However, if the change is not approved then distribution must cease and a product recall may be required.

3. Minor Changes (Annual Report)

Changes that can be submitted in an annual report are minor and have minimal potential to affect the quality, safety, or efficacy of the drugs. The affected drugs can be distributed at any time after the change has been internally approved and before the details are reported in the Annual Report. At the end of a reporting period, any changes that have been implemented in the previous year are included together in a single notification to the agency. (5)

Variation Fee for US (6)

No Variation fees are applicable for the USFDA.

CANADA Variation:

Below is the Canada classification of quality changes made for drugs that have received a Notice of Compliance (NOC). (7)

1. Level I - Supplements (major quality changes)
2. Level II - Notifiable Changes (moderate-quality changes)
3. Level III - Annual Notification (minor quality changes)
4. Level IV Changes - a record of changes

1. Level I - Supplements (major quality changes)

Changes that have a substantial potential to hurt the identity, strength, quality, purity, or potency of drugs as these factors may relate to the safety or effectiveness of the drugs.

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 chemical synthesis with new starting material). 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 drugs.

The changes included in this reporting category shall be filed, along with the recommended supporting data, to Health Canada as an amendment to a Drug Master File. The change may not be implemented by the sponsor until a NOC has been issued.

2. Level II - Notifiable Changes (moderate-quality changes)

Changes that have a moderate potential to hurt the identity, strength, quality, purity, or potency of the drugs as these factors may relate to the safety or effectiveness of the drug product.

Note: All Level II - Notifiable Changes referred to in this document do not apply to Human Pharmaceuticals.

The changes included in this reporting category should be filed, along with the recommended supporting data, to Health Canada as a Notifiable Change. All Level II changes should not be implemented by the sponsor until a No Objection Letter (NOL) has been issued.

3. Level III - Annual Notification (minor quality changes)

Changes that have minimal potential to hurt the identity, strength, quality, purity, or potency of the drugs as these factors may relate to the safety or effectiveness of the drugs.

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. All Level III changes should be submitted using the Post-Notice of Compliance Changes: Notices of Change (Level III).

Form supporting data for the Level III changes recommended in as per the guidance document should not be submitted; however, the data should be available to Health Canada within thirty (30) calendar days, if requested at any time.

4. Level IV Changes - a record of changes

Level IV (Quality only) changes are changes to a new drug that is not Level I, Level II or Level III and are not expected to hurt the identity, strength, quality, purity, or potency of the drugs as these factors may relate to the safety or effectiveness of the drugs. The changes included in this reporting category may be implemented by the sponsor without prior review by Health Canada. The changes should be retained as part of the drugs record by either the sponsor or the manufacturer and comply with Good Manufacturing Practices (GMP) requirements.

Canada variation fee –Type-I (API) (8)

Type of Submission	Fee in CDN*
DMF Update	$541 Cdn

* DMF fee will be increased by approximately 5% in April.

EU Active substance master file (ASMF) or EDMF Variation

European legislation that defines variation types, a guideline lays out a harmonized list of anticipated variations with classification. A defined list of variations for European MAs has existed since the implementation of the Mutual Recognition Procedure (MRP) in 1998. However, the legislation governing European variation procedures was not fully adopted at the national level by many EU member states at that time. Legislation has periodically been updated and in the most recent update, in August 2013, implementation was made mandatory at the national level and the variation process has been completely harmonized across the EU. (9) (10) and (11)

The classification codes are as follows: (9) (11) and (12)

1. Type IA for notification of minor changes
2. Type IB for minor changes
3. Type II for major changes
4. Line extensions.

ASMF holders shall not modify the contents of ASMF without informing each applicant/MA holder and Authority.

1. Type IA

Changes that fall under this category are classified in two:

- IA_{AN} = Notify change(s) within 12 months ('Annual Report')
- IA_{IN} = Required for the continuous supervision of product (MA to be noted 2-6 months)

Changes are commonly referred to as "**do and tell**" variations because the applicant is required to implement the change and then notify the agency of the details. This level of variation is reserved for administrative changes that are anticipated to have no impact on the safety or efficacy of a drug substance.

Variations that can be submitted as Type IA_{IN} must be must notify the agency within 14 days of implementation. So, this variation will be called Immediate Notification (IN).

Variations that can be submitted as Type IA_{AN} must be implemented and then the required submission made within one year of the implementation date. So, this variation will be called Annual Notification (AN).

Multiples of these variations for a single drug substance can be made at the same time, as long as all of them fall within the required submission deadline. (9) and (10)

2. Type IB

Changes are commonly referred to as "**Minor**" variations that require an assessment of supporting data and are anticipated to potentially have an impact on drug safety or efficacy.

These are also referred to as "**tell and do**" variations. The applicant submits, including all required supporting data, and wait for agency approval before implementing the changes. The process follows a defined assessment period of 30 days, but with agency questions, it can often take up to 90 days. (9) and (10)

3. Type II

This classification is reserved for major variations that are expected to affect the safety and efficacy of drugs and require a careful assessment before the applicant can implement the change. They require considerable supporting documentation and must be assessed and signed off by an appropriately qualified expert in their respective field before being submitted.

The process follows a defined assessment period of 60 days default timetable; 30 days for urgent variations and 90 days for changes / new indication. Implement the changes after 30 days of decision from authority. (9) and (10)

4. Line Extensions (Sponsor / Finished product manufacturer)

Some of the changes which affect the fundamentals of the terms of the authorization cannot be granted via a variation and are submitted as an "**extension application**":

Example like changes to the active substance(s); changes to strength, pharmaceutical form, and route of administration. The process follows a defined assessment period of 210 days as like initial submission. (9) and (10)

Changes not requiring any prior approval	**Changes requiring any prior approval**		
Minor Type IA	**Minor Type IB**	**Major Type II**	**Line extension**

Variation Fee for EU Active substance master file (ASMF) or EDMF Variation

Depends on the route of application and most of the cases the MA holder will pay fees including finished product variations.

European Directorate for the Quality of Medicines & HealthCare (EDQM) REVISIONS

Certificate of Suitability to the monographs of the European Pharmacopoeia (CEP)

CEP is the certificate given by EDQM for complying with European Pharmacopoeia (Ph.Eur.)

EDQM Classified changes and named variations as revisions and details are as below; (12)

The changes are classified in different categories;

1. Annual notification (AN) / immediate notification (IN)
2. Minor (MIN) and
3. Major (MAJ)

The above classification is made depending on the potential impact of the change on the quality of the final substance. These categories are based on those (IA-IAIN/IB/II) of the European Commission Regulation (EC) as discussed above concerning the examination of variations to the terms of marketing authorizations for medicinal products for human use and veterinary medicinal products. (13)

Any change not classified as a notification or a major change should be classified as a minor change, except in the following two cases where a new CEP application should be submitted:

- Addition of a new route of synthesis and/or a new manufacturing site where the specification of the final substance is different from the one already approved and
- Transfer to a new holder, where the transfer does not occur because of a merger or because the company is sold, and where the manufacturer does not take out the CEP in their name. (13)

EDQM guidance "**Guideline on requirements for revision/renewal of certificates of suitability to the European Pharmacopoeia monographs**" clearly specifies the type of changes with example considering conditions, specific documentation, and type of change. (13)

Updates of CEP applications following Ph. Eur. monograph revisions or any other regulatory requirements are treated separately and generally initiated by the EDQM. (13)

EDQM Fee applicable for Revisions; (14)

Revisions of Certificates		
Reference	**Item**	**Fee**
CEP 009	Notification	1000 €
CEP 005	Minor revision	1500 €
CEP 019	Grouped revisions (affecting several dossiers)	2000 €
CEP 006	Transfer of Holders	1500 €
CEP 020	Major revision (may include minor changes and notifications)	2000 €
CEP 004	Renewal	1500 €

DMF Variations	**USFDA**	**CANADA**	**EU**	**EDQM**
Health Authority	U.S Food and Drug Administration	Health Canada / Santé Canada	EUROPEAN MEDICINES AGENCY SCIENCE MEDICINES HEALTH	edqm European Directorate for the Quality of Medicines & HealthCare / Direction européenne de la qualité du médicament & soins de santé
For API	US DMF	DMF	ASMF / EDMF	CEP
Fee for variation	NIL	541 CDN $	Depends on the route of application / paid by the MA holder	Based on the type of variation (1000 € - 2000 €)
Fee type	Onetime fee	Applicable to Major and moderate-quality changes	Depends on EU countries requirements / MA holder	Fee depends on MAJOR changes / Minor changes and Notifications.
Types of Changes	1. Major Changes (PAS) 2. Moderate changes * CBE-30 * (CBE-0) 3. Minor changes (AR)	1. Level I - (Major) 2. Level II - (Moderate) 3. Level III - (Minor) 4. Level IV - (Record of changes)	1. Type IA (Notify Minor) * IA_{AN} * IA_{IN} 2. Type IB (Minor) 3. Type II (Major) 4. Line extensions	1. Annual notification (AN) / immediate notification (IN) 2. Minor (MIN) 3. Major (MAJ)

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