Guideline on the regulation of post-approval changes to a registered Biotherapeutic products in Egypt

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1. Introduction

Post-approval changes (PACs) to the registered information of authorized biotherapeutic products are introduced routinely worldwide to maintain routine production, improve product quality, efficiency, and consistency of manufacture, respond to changes in regulatory requirements, and also to update product's labeling information and address administrative changes.

The product marketing authorization holder (MAH) remains responsible for the quality, safety, and efficacy of a product throughout its life-cycle. MAH is required to make changes to the details of the product in order to accommodate technical and scientific progress, improve or introduce additional safeguards for the product.

Egyptian Drug Authority (EDA) adapted WHO guidelines "Annex 3: Guidelines on procedures and data requirements for changes to approved biotherapeutic products", "Annex 4: Guidelines on procedures and data requirements for changes to approved vaccines", and "Annex 3: WHO guidelines on variations to a prequalified product" in addition to European Medicines Agency (EMA): Guidelines on the details of the various categories of variations (2013/C 223/01) and their updates for regulating PAC of imported or locally manufactured products.

This document should be read in conjunction with regulatory guide for mechanisms, procedures, and rules for implementing the decree of the Egyptian Drug Authority's president No. 343/2021 & Guideline for Lot Release of Biological Products (Code No.: EDREX.GL.Bioinn.003), as well as EU and WHO variation guidelines.

2. Scope

This document is intended to provide guidance for the MAH on the regulations and evaluation of PAC in terms of reporting categories, general procedure, required documents, timelines, and reliance mechanism.

3. Abbreviations

API	Active Pharmaceutical Ingredient
CPP	Certificate of Pharmaceutical Product
CTD	Common Technical Document
DS	Drug Substance
EDA	Egyptian Drug Authority
EMA	European Medicine Agency
FDA	Food and Drug Administration
FPP	Finished Pharmaceutical Product
GMP	Good Manufacturing Practice
ICH	International Council for Harmonization
IPI	International product Information
MAH	Marketing Authorization Holder
PACs	Post-Approval Changes
PBRER	Periodic Benefit-Risk Evaluation Report
PIL	Product/prescribing Information Leaflet
PSUR	Periodic Safety Update Report
PV	Pharmacovigilance
RRA	Reference Regulatory Agency
SmPC	Summary of Product Characteristics
WHO	World Health Organization

4. Definitions

- **Biotherapeutic Products:** They are products that contain one or more active ingredients produced or extracted from biological origin. For instance, they may include human vaccines, antisera, blood products and plasma derivatives, biotechnology-manufacturedproducts, and the like, as well as any products or materials that may be created according to scientific developments and/or international standards and references.
- **Biosimilar products:** A biotherapeutic product that is shown to be highly similar in terms of its quality, safety, and efficacy to an already licensed reference product.
- **Dosage form:** The dosage form is the physical manifestation of a product that contains the active ingredient(s) and/or excipient(s) that are intended to be delivered to the patient; it may refer to the form of presentation or the form of administration.
- **Marketing authorization holder:** Any person or legal entity that has received MA or licensure to manufacture and/or distribute a medicine. It also refers to a person or legal entity allowed to apply for a change to the MA or license.
- **Imported Biotherapeutic Products:** they are biotherapeutic products that are either fully manufactured overseas or manufactured overseas and undergo secondary packaging in factories within the Arab Republic of Egypt.
- **Local Biotherapeutic Products:** They are biotherapeutic products manufactured in factories inside the Arab Republic of Egypt or the products imported as bulk to be manufactured or primary filled in the Arab Republic of Egypt.
- **Reference Countries:** An updatable list of countries approved by the technical committee for drug control (published on EDA web site).

- **Post-approval change/Variation:** A change in the quality, safety, and efficacy or in the administrative information of a product that is present in its latest version at the authority, it is categorised according to its potential impacts on the quality, safety, and/or efficacy of the product into: quality changes, labelling changes, and administrative changes.
- **Reliance:** The act whereby the RRA in one jurisdiction may consider and give significant weight to i.e., totally or partially rely upon the evaluation performed by another RRA or trusted institution in reaching its own decision. The relying authority remains independent, responsible, and accountable regarding the decisions taken, even when it relies on the decisions and information of others.
- **Strength:** The strength represents the amount of active substance in the pharmaceutical form, which can be defined per unit dose or as a concentration. The concentration can be stated per unit of mass (250mg/g) or per unit of volume (2mg/ml) or in percentage (5%).

  - For single-dose preparations, total use, the strength is defined as the amount of active substance per unit dose.

  - For single-dose preparations, partial use, the strength is defined as the concentration expressed as the amount of active substance per ml, per puff, per drop, per kg, per m2, in percentage as appropriate.

  - For multi-dose preparations, the strength is defined as the concentration expressed as the amount of active substance per ml, per puff, per drop, per kg, per m^2, as appropriate.

5. Main topic

5.1. Reporting categories of Post-Approval Changes

Post-approval changes (PAC) are categorized according to their potential impacts on the quality, safety, and/or efficacy of the product into: quality changes, labelling changes, and administrative changes.

5.1.1. Reporting categories for Quality changes:

Quality changes are changes that affect the manufacturing or control strategy of the product which impact the quality of that product, and they are categorized into major, moderate, minor, and quality changes with no impact.

- **Major quality changes:** Changes that have **significant potential impact** on the quality, safety, or efficacy of the biotherapeutic product.
- **Moderate quality changes:** Changes that have a **moderate potential impact** on the quality, safety, or efficacy of the biotherapeutic product.
  The major and moderate quality changes should be reviewed and approved by the authority prior to implementation.
- **Minor quality changes:** Changes that have a **minimal potential impact** on the quality, safety, or efficacy of the biotherapeutic product. They should be notified to EDA within established timelines following implementation in accordance with the timeline mentioned in Section 5.2.2 of this guideline.
- **Quality changes with no impact:** Changes that have **no impact** on product quality, safety, or efficacy. They should be notified to EDA annually through email or annotated during the submission of other higher category change if they are related to it or implemented in the updated CTD submitted.

5.1.2. Reporting categories for Labelling Changes:

Labelling changes are changes that affect the safety and/or efficacy of the product. They include prescribing information (or package insert) for healthcare providers or patients, the outer label (which is a carton), and the inner label (which is a container label).

They are categorized into: Safety and efficacy changes; product labelling information changes and administrative product labelling information changes.

- **Safety and efficacy changes (i.e. scientific data):** changes that have an impact on the clinical use of the biotherapeutic product in relation to safety, efficacy, dosage, and administration.
- **Product labelling information changes (i.e. safety data):** changes to the labelling items that have the potential to improve the management of risk to the population for which use of the product is currently approved.
- **Administrative product labelling information changes:** Changes that are not expected to affect the safe and efficacious use of the product & they also include editorial updates.

5.1.3. Reporting categories for Administrative changes:

Administrative changes are those with no impact on the quality, safety, or efficacy of the product. They are related to the administrative as well as the legal information of the biotherapeutic product. (i.e. MAH change, name and address of manufacturing facility, etc.). For administrative changes not included in the WHO, **refer to Annex 1**.

General consideration:

- Certain changes in dosage form, route of administration, and/or presentation as per "Categorization of Type of Application as New Product or Variation for Parenteral Biotherapeutic Preparations" may necessitate the filing of a new application for marketing authorization and cannot be evaluated as post-approval changes **(refer to Annex 2).**
- Upon categorization of the PAC, In case of not fulfilling the conditions outlined for a given change, the change is automatically considered to be the next higher level of change; for example, if any conditions recommended for a moderate quality change are not fulfilled, the change is considered to be a major quality change.
- In case the supporting data for a given change are not provided, are different, or are not considered applicable, then adequate scientific justification should be provided.
- It is important to note that EDA has the right to request additional information to clarify or define conditions not specifically described in adopted international guidelines, for adequate assessment of the quality, safety, and efficacy.
- If there is a PAC that is not included in this guideline or if the MAH has any inquiry regarding PAC documentation or classification, the EDA may be consulted for the correct classification and documentation through the submission of scientific advice requests.
- A biosimilar product is considered to be independent from the reference product and has its own life-cycle however, when new safety information on the reference product is added, the biosimilar product should follow the changes made for the reference product unless it can be demonstrated that the new information on the reference product is not relevant to the biosimilar.

5.2. PAC Handling procedures

5.2.1 General procedure

There are 4 phases for handling a PAC starting with the submission phase, passing through the validation, and scientific review phases, and finally the decision phase as follows:

Submission Phase

- MAH requests an appointment for submission of the PAC through an email sent to bioreg.variation@edaegypt.gov.eg with the variation application form.

The MAH should receive an appointment within **3 WDs** in order to submit the file.

- On the predefined appointment, the MAH submits the variation package on the electronic portal.
- For imported products, parallel submission can be applied, allowing the MAH to submit the PAC without providing the regulatory authority's approval from the country of origin however, MAHs are encouraged to share any raised questions and provide any documents submitted to the authority of the country of origin to EDA, taking into consideration that the final decision will not be issued until the receipt of the approval of the authority in the country of origin.

Validation Phase

- In this phase, the submitted documents are validated within **5 WDs** to identify other required documents before proceeding to the scientific review phase.
- At the end of this phase, the MAH receives a validation report that includes information about the outcome of this phase, the required documents, and the evaluation timeline.
- The MAH is granted a period of 30 WDs to fulfill any required documents requested during the validation period in order to receive the file and proceed to the next phase.

Scientific Review Phase

- The potential effect of the PAC on the quality, safety, and efficacy of the product is evaluated through the provided documents and as per the specified time frames.
- Whenever complementary documents or scientific justification are required during the scientific review phase, the MAH is granted a 20 WDs grace period to fulfil them.

Note:

- Local biotherapeutic products follow the same procedures **except for major quality changes, where the MAH receives** a preliminary approval letter after the validation phase that includes the required documents that should be fulfilled before proceeding to the scientific review phase.

- Submission of PAC that involves addition of a manufacturing facility for either DS or FPP for a local product or product imported from a non-reference country (with no valid GMP from reference countries) will require inspection of the proposed facility by the central administration of inspection on pharmaceutical institution as part of the evaluation for this PAC before the final decision for this change.

Decision Phase

It is considered the final phase in handling PAC, where one of the following outcomes is expected:

a- If EDA determines that the information submitted supports the quality, safety, and efficacy of the post-changed product, the EDA will issue a written approval letter.

Note: A written conditional approval letter may be issued in certain cases, for example: re-analysis or the requirement of specific documentation that doesn't hinder approval. Upon fulfilment of the condition, the MAH shall receive a notification email that the condition is fulfilled.

b- If EDA determines that the information submitted fails to support the quality, safety, or efficacy of the product manufactured with the change, a written disapproval letter will be issued to MAH.

5.2.1.1 Documentation

Two types of documents are required for PAC evaluation:

– **Administrative documents:**

- Covering letter on the MAH head letter dated, signed, and stamped with a clear and detailed scope, declaring that all data in the file is true, accurate, and identical to the submitted soft copy.
- Variation application form for each variation file, describing the variation submitted with a clear and detailed scope aligned with the covering letter.
- Variation service consideration fee.
- For imported products only, approval on the variation from the country of origin of the product or other relevant documents (CPP).

– **Technical supportive documents:**

- The technical document will vary according to the type and reporting category of the proposed PAC, and is determined as per the adapted guidelines (EMA & WHO).
- Other EDA-specific requirements for specific cases are mentioned in **Annex 1**.

5.2.2 Submission of minor changes:

Changes in this category may be implemented by the marketing authorization holder without prior review by the EDA.

For imported products: Grouped or single minor variations should be notified to EDA within 6 months from the approval by the authority in the country of origin.

For local products: Minor variations should be notified within 30 calendar days of implementation.

Required documents: MAH should notify EDA by submitting the following documents on the electronic portal:

- Covering letter that includes a short overview of the nature of the changes and declares that all data in the file is true and accurate on MAH's head letter, dated, signed, and stamped.
- Variation application form for each variation.
- Variation service consideration fee.
- Supportive documentation for all the submitted variations.
- For imported products only, submitted annual report to RRA with its acknowledgment/ RRA approval.

MAH shall receive an acknowledgement of receipt via e-mail within **30 calendar days** following receipt of the notification.

Note: If the classification of a change is incorrect, the conditions for minor variation are not met, or the supporting data are not considered acceptable then EDA may request additional supporting data, or the MAH may be requested to resubmit the PAC with the correct classification (i.e., major or moderate quality change).

5.2.3 Timelines

Administrative Changes	
Reporting category	**Review timeline**
Administrative change	10 WD
Quality Changes	
Major quality changes	60 WD
Moderate quality changes	40 WD
Minor/annual report	N.A
Labelling update Change	
Safety and efficacy changes	40 WD
Product labelling information changes	30 WD
Administrative product labeling update	10 WD
Pack updates	10 WD

These timelines are calculated from the date of receiving the variation file excluding the time granted for the MAH to fulfil any complementary documents.

5.2.4 Implementation of PAC

- The anticipated date for the implementation of the change should be indicated in the submission of the PAC (if applicable).
- Labelling changes that include safety and efficacy changes or product labelling information changes should be implemented within 6 months of the EDA approval date.
- Outer/inner packs update could be implemented within 12 months of the EDA approval date.

5.2.5 Reliance in PAC

- Reliance pathway brings benefits to patients, industry, and government by facilitating and accelerating access to quality-assured, effective, and safe medicinal products while saving resources and reducing duplication of regulatory efforts.

- In this context, reliance for post-approval changes is applied on products approved from reference countries.

- To ensure continuous harmonization between the reference country dossier and the EDA dossier, PACs approved by the reference authority better to be submitted regularly to EDA.

Reliance is applicable on:

- Quality changes.
- Product labelling information changes

5.2.5.1 Handling procedure

- ***Submission Phase***

MAH request an appointment for submission of PAC by sending an email to bioreg.variation@edaegypt.gov.eg with the variation application form.

The MAH shall receive an appointment within 3 WDs in order to upload the file.

On the predefined appointment, the MAH submits the variation package on the electronic portal.

- ***Verification Phase***

In this phase, the submitted documentation is checked versus the reliance checklist to verify that the mandatory documents are fulfilled.

The MAH shall receive an e-mail within 5 WDs showing the submission status. *Noting that the absence of any of these documents hinders the acceptance of the submission*

Whenever complementary documents are required during the verification phase, the MAH is granted a 20 WDs grace period to fulfil them.

- ***Decision Phase***

This is the final phase in the process of handling PAC, where the MAH will be informed of the final outcome, either approval, conditional approval, or disapproval. **Refer to Section 5.2.1. Decision Phase.**

5.2.5.2 Documentation

1- Cover letter from the MAH signed and stamped requesting submission through the reliance pathway, describing PAC and declaring the sameness of the dossier in EDA and RRA, in addition to a Commitment letter from the MAH to report to EDA any rejection or amendment of the RRA decision upon implementation of PAC.
2- Variation application form .
3- RRA PAC approval or CPP (if applicable).
4- Complete unredacted assessment report with annexes and/or list of questions and answers from RRA.
5- RRA variation application form, or equivalent with annexes, if needed.
6- RRA variation data package, including the impacted/updated CTD section, in addition to all supplementary documents needed to support the change.

Note: The submitted documents should be the same as those submitted to the reference regulatory authority; however, some potential differences could exist. These differences should be justified for evaluation on a case-by-case basis.

5.2.5.3 Timeline

Administrative Changes	
Reporting category	**Timeline**
Quality Changes	
Major quality changes	15 WD
Moderate quality changes	10 WD
Labelling update Change	
Product labelling information changes	10 WD

These timelines are calculated from the date of receiving the variation file excluding the time granted for the MAH to fulfil any complementary document.

5.3. Retesting for variation

Certain major quality changes require re-analysis after the implementation of the change on the first upcoming batch on which the change is implemented in accordance with lot release administration policy.

Such cases include the following:

1. Change in the description or composition of the product.
2. Addition or replacement of a manufacturing facility for the drug product.
3. Addition or replacement of a manufacturing facility for the drug substance.
4. Major change in the manufacturing process of the drug product.
5. Major change in the manufacturing process of the drug substance directly or indirectly affects the drug product.
6. Change in the drug product primary container closure system.
7. Replacement / addition of a supplier/manufacture of diluent/excipient.
8. Change in the supplier for the plasma-derived excipient.

For the above-mentioned scopes of variation, the MAH shall receive a conditional approval at the end of the process. After re-analysis and issuance of the conformity of the testing certificate, the MAH will receive a notification via e-mail that the condition is fulfilled.

5.4. Grouping of variations

Multiple related changes may be submitted in the same dossier however, the following should be considered.

General grouping conditions:

- Changes should be consequential and/or related, i.e., meaningful to be reviewed simultaneously.
- The same change affects multiple FPPs, e.g., addition of a new API manufacturing site for multiple FPPs.
- Quality, non-clinical, and clinical changes cannot be grouped unless exceptionally justified.
- Quality variations of the active substance cannot be grouped with finished product variations unless justified.

Note:

- For the submission that includes multiple changes, the marketing authorization holder should: indicate the association between grouped variations, specify the supportive data for each change, and consider and submit the conditions and documentation for each change.

- In case many changes are filed within the same submission, or if major issues are identified with a change and extensive time would be required to review them, EDA may ask the marketing authorization holder to divide the changes into separate submissions and to resubmit the file.

- An application involving two or more types of variations will be categorized as the highest category, e.g., a variation grouping both a minor change and a major change will be classified as a major change and follow the review timeline of the major changes.

6. References

- EDA Chairman Decree (343/2021)
- EMEA Guidelines on the details of the various categories of variations (2013/C 223/01).
- Guideline for Lot Release of Biological Products in Egypt 2022 (EDREX.GL.Bioinn.003)
- WHO Annex 3 guidelines on procedures and data requirements for changes to approved biotherapeutic products.
- WHO Annex 4: guidelines on procedures and data requirements for changes to approved vaccines" and "guidance on variation to a prequalified vaccine", for regulating PAC on imported or locally manufactured products.

7. Annexes

Annex 1: Documents for post-approval changes not covered in the WHO guidelines

Annex 2: Categorization of Type of Application as New Product or Variation for Parenteral Biotherapeutic Preparations

Annex 1: Documents for post-approval changes not covered in the WHO guidelines:

I-Administrative Changes

Scope	**1. Changes related to the Market Authorization Holder / License Holder:** a. Change in the MAH/License holder b. Change in the MAH/License holder name and/or update in the current address c. Update in the MAH/License holder address without change in the physical location	
Product type	**Imported Biotherapeutic Products**	**Local Biotherapeutic Products**
Documentation	**In addition to the administrative documentation the following should be submitted:**	
	a. Change in MAH / License Holder. **b. Change in Name and / or update in the current Address.** • Reference regulatory authority approval/ or Updated Original CPP** **c. Change in the MAH/License holder without change in the physical location** • Reference regulatory authority approval or any equivalent official document from the concerned agency • Declaration letter from the MAH confirming that the physical location remain unchanged.	**a. Change in MAH / License Holder** • Signed and stamped Legal agreement between the involved parties **b. Change in Name and /or update in the current Address.** • Commercial register record **c. Change in the MAH/License holder address without change in the physical location** • Company commercial record or any relevant official document
Scope	**2. Changes related to the MAH in Egypt (i.e. applicant)** *(which could be a company or a scientific office):* a. Change in the MAH in Egypt b. Change in the MAH in Egypt name and/or update in the current address	
Product type	**Imported Biotherapeutic Products**	**Local Biotherapeutic Products**

Documentation	**In addition to the administrative documentation the following should be submitted:**	
	a. Change in the MAH in Egypt 1. Original Legalized authorization letter from the current MAH stating the name and responsibilities of the new MAH in Egypt 2. Termination letter from the current MAH for the previous MAH in Egypt 3. Arabic Translation for all the submitted documents from an accredited translation center (if requested). **b. Change in the MAH in Egypt name and/or update in the current address** • Copy of the updated scientific office license is required *(if the MAH in Egypt is a scientific office).* • Copy of Tax Card and Commercial Register (*if* the MAH in Egypt is a company).	1. Original letter with the name and the duties of the proposed MAH in Egypt in Arabic language. 2. Termination letter for the previous MAH in Egypt in Arabic language. 3.Original, Signed and stamped Legal agreement between the involved parties
Scope	**3. Change in the manufacturing facility name and/or update in the current address** a. Change in the manufacturing facility name b. Update in the manufacturing facility address without change in the physical location c. Change in the manufacturing facility name with Update in the manufacturing facility address without change in the physical location	
Product type	**Imported Biotherapeutic Products**	**Local Biotherapeutic Products**
Documentation	**In addition to the administrative documentation the following should be submitted:**	
	a. Change in the manufacturing facility name 1. Reference regulatory authority approval/ or Updated Original CPP**	1. MAH declaration state that the physical location of the facility, as well as personnel, equipment, manufacturing process, specification, test methods, in- process control remain the same.

	2. Updated Valid GMP from Reference drug authority 3. Updated valid Manufacturing license for proposed facility **b. Change in the MAH/License holder without change in the physical location** 1. Reference regulatory authority approval or any equivalent official document from the concerned agency 2. Declaration letter from the MAH confirming that the physical location of the facility, as well as personnel, equipment, manufacturing process, specification, test methods, in- process control remain the same 3. Updated Valid GMP from Reference drug authority 4. Updated valid Manufacturing license for proposed facility. **c. Change in the manufacturing facility name with Update in the manufacturing facility address without change in the physical location** *Refer to documentation in both a and b*	2. Manufacturing license for proposed facility. 3. Valid GMP
Scope	**4. Change in the Product Name** a. Change in the trade name b. Change in the API name	
Product type	**Imported Biotherapeutic Products**	**Local Biotherapeutic Products**
Documentation	**In addition to the administrative documentation the following should be submitted:**	

	a. Change in the trade name Updated Original CPP** **b. Change in the API name** • Updated Original CPP** • Reference for the updated name (i.e updated pharmacopeia for pharmacopeia API name update)	**a. Change in the trade name** Justification for the name change **b. Change in the API name** Reference for the updated name (i.e updated pharmacopeia for pharmacopeia API name update)

II- Labeling update changes

Proposed Labels could be:

- Similar to the one marketed in the Country-of-origin pack
- Standard Export Pack which is a unified pack for exportation to different countries.
- Shared Pack marketed in specific region e.g.: Golf, Levant countries.
- Country Specific Pack: which is a customized pack intended to be marketed in Egypt

Scope	**1. Insert update (PIL /IPI or SMPC) include:** **a. Safety and efficacy changes** **b. Product labelling information changes** **c. Administrative/editorial data update**
Product type	**Imported or Local Biotherapeutic Products**
Documentation	**In addition to the administrative documentation the following should be submitted:**
	General requirements: 1. Declaration letter from the MAH* with the proposed insert attached. 2. **2** copies from proposed insert on A4 paper, numbered & without header or footer. 3. **1** copy from current approved insert. 4. Tracking of changes between the proposed and current insert. 5. Reference to the proposed insert. ***In addition to the general requirements the following should be submitted for:***

	Safety and efficacy changes • Folder contains current, proposed insert, highlighted tracking, colored scan copy of yellow PV receipt and most updated **PSUR** or **PBRER** and its proof of submission. • Module 2 & Module 5 • Main and summary report templates. **Product labelling information changes** • Folder contains current, proposed SmPC and PIL, highlighted tracking, colored scan copy of yellow PV receipt and most updated **PSUR** or **PBRER** and/or its proof of submission**.** For insert updates of Local products and country specific inserts of imported products, Pharmacovigilance reporting information should be included *Refer to General Administration for Pharmaceutical Vigilance for local PV reporting information*	
Scope	**Pack Update** 1. **Editorial changes:** Design, Color, Pack Accessories, No. of Units/Pack, Data 2. **Update Consequential to other (quality and or non-quality changes):** Change of MAH, Change in Name and / or Address of MAH, Addition of manufacturing site for FPP, Change in Name and / or Address of manufacturing site for FPP……etc**.**	
Product type	**Imported Biotherapeutic Products**	**Local Biotherapeutic Products**
Documentation	**In addition to the administrative documentation the following should be submitted:**	
	1. Declaration letter from the MAH* with the proposed packs attached. 2. **7** copies of colored artwork for proposed pack (outer pack &inner label) 3. **1** copy from the current approved pack. 4. Tracking of changes between the proposed and current packs	

Note: *may require legalization

**original legalized CPP may be required in case electronic CPP is not available

Annex 2: Categorization of Type of Application as New Product or Variation for Parenteral Biotherapeutic Preparations

Type of change:

1- Strength

- The concept of strength and the concept of concentration are inherently linked. The strength represents the amount of active substances in the pharmaceutical form, which can be defined per unit dose or as a concentration. The concentration can be stated per unit of mass or per unit of volume or in percentage.
- For single-dose preparations, total use, the strength is defined as the amount of active substance per unit dose
- For single-dose preparations, partial use, the strength is defined as the concentration expressed as the amount of active substance per ml, per actuation, per drop, per kg, per m 2, or in percentage as appropriate.
- A change from multi-dose to single-dose or vice-versa always results in submission of a new application (for both addition and replacement).
- A change or addition of a dosage form results in submission of a new application.
- A different strength results in submission of a new application as mentioned below.

Examples	Strength	Type of submission
Liquid ready-to-use – Single-dose, total use (Solution for injection - pre-filled syringe)		
From 100 mg/1 ml To 200 mg/1 ml	100mg 200 mg	New
From 100 mg/1 ml To 200 mg/2 ml	100 mg 200 mg	New
From 100 mg/1 ml To 100 mg/0.5 ml **i.e. If the Strength is changed, it is considered as a new file**	100 mg 100 mg	Variation

Liquid ready-to-use – Multi-dose or Single-dose, partial use (Solution for injection - vial) From 500 mg/50 ml To 1000 mg/50 ml From 500 mg/10 ml To 1000 mg/20 ml **i.e. If the concentration is changed, it is considered as a new file**	 10 mg/ml 20 mg/ml 50 mg/ml 50 mg/ml	 New Variation
Powder for reconstitution – Single-dose, total use (Powder for solution for injection) From 100 mg (to 2 ml) To 200 mg (to 2 ml) From 250 IU (to 5 ml) To 500 IU (to 5 ml) From 100 mg (to 2 ml) To 200 mg (to 4 ml) From 3 g (to 5 ml) To 3g (to 10 ml) **i.e. If the Strength is changed, it is considered as a new file**	 100 mg 200 mg 250 IU 500 IU 100 mg 200 mg 3 g 3 g	 New New New Variation
Powder for reconstitution – Multi-dose or Single-dose, partial use (Powder for concentrate for infusion) From 500 mg (to 50 ml) To 1000 mg (to 50 ml) From 200 IU (to 100 ml) To 600 IU (to 200 ml)	 10 mg/ml 20 mg/ml 20 IU/ml 30 IU/ml	 New New

From 500 mg (to 50 ml) To 1000 mg (to 100ml **i.e. If the concentration after reconstitution is changed, it is considered as new file**	10 mg/ml 10 mg/ml	Variation
Concentrate for solution (Concentrate for solution for infusion) From 1 g/10 ml To 2 g/10 ml From 1 g/10 ml To 2 g/20 ml **i.e. If the concentration before dilution is changed, it is considered as a new file**	**BEFORE DILUTION** 100 mg/ml 200 mg/ml 100 mg/ml 100 mg/ml	 New Variation
Parenteral – Change in container only **Solution for injection** A) From vial to pre-filled syringe (same concentration) B) From vial to ampoule (same concentration) **Solution for injection** A) From vial to cartridge (same concentration) B) From cartridge to cartridge in disposable pen (same conc. &cartridge) **Powder + Solvent** solvent from vial to pre-filled syringe (same concentration)		 Variation Variation Variation Variation Variation

2- Presentation

- The presentation includes the size of the container (fill volume / Fill weight) and/or the pack size (number of tablets, number of sachets, number of ampoules, etc. per outer packaging).
- Change in container, pack-size, fill-volume or fill-weight, which does not involve a change in strength and/or composition, is submitted as variation.

3- Route of administration

Replacement	**Presentation**	**Type of submission**
e.g. From SC To IM a) No change in the composition and/or specifications of the finished product	IM (one product)	Variation
b) change in the composition and/or specifications of the finished product	IM (one product)	New
Addition of a different presentation e.g. From SC To SC and IM	IM and SC (two products)	New
Addition to the same presentation e.g. From SC To SC/IM c) No change in the composition and/or specifications of the finished product	SC/IM (one product)	Variation
d) change in the composition and/or specifications of the finished product	SC/IM (one product)	New