GUIDELINE ON

Administrative requirements for variation submission of Biological Products

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1 Introduction

The regulation of changes to approved products is the **key** to ensuring that post change products are of **consistent** quality, safety and efficacy.

In addition to WHO Guidelines on procedures and data requirements for changes to approved biotherapeutic products/vaccines for assessment of post approval changes submitted to Biologics variations unit other documents are required for file assessment.

This guideline provides Guidance on required administrative documents for variation file submission to assist the applicant in preparing variation file submissions in addition to other requirements for variation scopes not mentioned in the WHO guidelines

2 Scope

The guideline primarily addresses the required Administrative documents for every variation file submission, labelling updates and other variation scopes documents not covered by "**WHO Guidelines on procedures and data requirements for changes to approved biotherapeutic products/vaccines"** and also provide a timeframe for issuing final decision regarding the submitted variation file

3 Definitions

- **Biological Products:** Preparations made of substances extracted from or produced by living sources, whether they are genetically-modified microorganisms or liquids and tissues extracted from various human or animal sources.

- **Variation:** Amendment to the contents of the documentation on which the original decision on the marketing authorization was based

- **Major quality changes:** changes to the product composition, manufacturing process, quality controls, facilities or equipment that have significant potential to have an impact on the quality, safety or efficacy of the biological products.
- **Moderate quality changes:** change to the product composition, manufacturing process, quality controls, facilities or equipment that have a moderate potential to have an impact on the quality, safety or efficacy of the biological products.
- **Minor quality changes:** change to the product composition, manufacturing process, quality controls, facilities or equipment that have a minimal potential to have an impact on the quality, safety or efficacy of the biological product

- **Non reportable quality changes:** changes that have no impact on product quality, safety or efficacy may be implemented by the marketing authorization holder without prior review by the EDA
- **Administrative changes:** Changes that are not expected to affect the safe and efficacious use of biotherapeutic product E.g Any editorial Changes, approved major changes that will be reflected on insert/pack (addition of the name of manufacturing site, shelf-life, storage condition).
- **Product labelling information changes:** change related to the clinical use of a product or to product labelling information on the safe and effective use of a biological product .The product labelling information includes prescribing information(or package insert) for health-care providers or patients, outer label (that is, carton) and inner label (that is, container label).
- **Marketing authorization holder:** any person or legal entity that has received a marketing authorization or licence to manufacture and/or distribute a medicine. It also refers to a person or legal entity allowed to apply for a change to the marketing authorization or licence.
- **Applicant:** a legal entity authorized from Market authorization holder to be responsible for distribution, dissemination of medical and scientific information, regulatory support and supply for the products. **N.B** In case of Local products applicant is Marketing Authorization Holder.

4 Procedures

- The following documents should be included with each application, where applicable, for any Type of variation:

1. Covering letter with cleared & detailed scope on applicant head letter dated, signed, stamped.
2. Registration license (copy)
3. Variation Application form for each variation describing the variation submitted with cleared & detailed scope as in covering letter.
4. Approval on the variation from the Health authority in the country of origin (Legalized), or other relevant documents (CPP, ……). For imported products.
5. A declaration on applicant head letter that all data in the file is true, accurate and identical to the submitted soft copy.
6. Payment receipt.

➢ Requirements for Some Variations Not Mentioned in WHO Guidelines:

Imported Biological Products	Local Biological Products
Requirements for Insert update Either Smpc or PIL or IPI	
1. Original Legalized Declaration Letter from Market Authorization Holder or License Holder **attached with Proposed SMPC or PIL or IPI** State that "This insert version no… is most updated one and marketed in country of origin." 2. The Scientific data related to the scope of variation Submitted (if needed). 3. Most updated **PSUR** or **PBRER** (if needed). 4. **2** copies from proposed insert. 5. **1** copy from current approved insert. 6. Tracking between the proposed and current inserts.	1. Covering letter with cleared & detailed scope on applicant head letter dated, signed, stamped. 2. The Scientific data related to the scope of variation Submitted. 3. **2** copies from proposed insert. 4. **1** copy from current approved insert. 5. Tracking between the proposed and current inserts.
Requirements for pack update: • Design • colour • No. of units/pack**.**	
1. Original Legalized Declaration Letter from Market Authorization Holder or Licenses Holder attached with new pack State that "This pack is most updated one and marketed in country of origin." 2. **14** copies from colored art work of proposed pack (outer pack &inner Pack) 3. **1** copy from the current approved pack. *If there is no current approved pack the company will submit the marketed original pack.	1. Covering letter with cleared & detailed scope on applicant head letter dated, signed, stamped. 2. **14** copies from colored art work of proposed pack (outer pack &inner Pack) 3. **1** copy from the current approved pack. *If there is no current pproved pack the company will submit the marketed original pack.
Requirements for Market Authorization Holder / License Holder Change: • The variation Change In MAH / License Holder. • The variation either Change in Name or Address.	
1. Original Legalized CPP mentioned in it the new market authorization holder.	1. Covering letter with cleared & detailed scope on applicant head letter dated, signed, stamped by the registration general manager**.**
Requirements for Applicant Change:	
1. Original Legalized authorization letter mentioned the name and the duties of the proposed applicant. 2. Termination letter for the previous applicant. 3. Translation into Arabic for all submitted documents.	1. Original authorization letter mentioned the name and the duties of the proposed applicant. 2. Termination letter for the previous applicant. 3. Translation into Arabic for all submitted documents.

Requirements for Manufacturing Facility Change: ˇ If the variation either Change in Name or Address	
1. Original Legalized CPP mentioned in it The Name and address of the proposed facility. 2. Copy Legalized of Valid GMP form Health authority for proposed facility. 3. Copy Legalized of valid Manufacturing license for proposed facility.	1. Covering letter with cleared & detailed scope on applicant head letter dated, signed, stamped by the registration general manager**.** 2. Manufacturing license for proposed facility.
Requirements for Product Name Change:	
1. Original Legalized CPP mentioned in it the New Product Name.	1. Covering letter with cleared & detailed scope on applicant head letter dated, signed, stamped by the registration general manager**.**
Requirements for Annual Strain	
1. WHO Recommendation 2. EMA Recommendation 3. Original Legalized Composition 4. 1 copy of current Insert 5. 7 copies of pack 6. Stability Studies for the previous approved strains 7. Original Signed Stability commitment Letter for the proposed strain. 8. Batch Analysis 9. All data support the update 10. Tracking insert	

➢ Time Frame for Issuing Notifications/ Approvals:

- **In case of Minor / Non – reportable Variations:**

BRS issues notification letters within 1 week from receiving a complete variation file.

- **In case of Administrative Changes/ Pack update & Insert Editorial Changes:**

BRS issues the final approvals/ disapprovals within 1 week from receiving a complete variation file.

- **In case of Moderate/ Major Variations/ Scientific & Safety Insert Update:**

BRS issues the final approvals/ disapprovals within 1 week from receiving the last reply from internal and/or external evaluation parties.

5 References:

1.1 EDA Chairman decree 343/2021 Rules for registration of biological medicinal products
1.2 EDA Chairman Decree no.38/2022 regarding amendment of article no.4 of EDA Chairman Decree no.343/2021
1.3 Regulatory guide for mechanisms, procedures and rules for implementing the EDA chairman Decree no. 343/2021
1.4 Guidelines for Categorization of Type of Application as New Product or Variation for Parenteral Biological Preparations. (GL-RBP-03)
1.5 Technical committee Resolution on 16-7-2019 for WHO Guidelines and General Administrative Requirement (Annex 3 & 4).
1.6 Technical decision for identifying the variations to be displayed on the technical committee (3/3/2011)
1.7 Technical committee Resolution on 15-07-2021 concerning analysis of registered biological product after implementation of variations for local and imported products
1.8 Technical committee Resolution (31/12/2009) for the list of reference countries
1.9 EDA Chairman decree 59/2020 for Service Consideration Update
1.10 EDA Chairman decree 61/2021 for Service consideration update
1.11 EDA Chairman decree 310/2021 for Service consideration update

6 Annexes

- Annex 1 Check List for the documents required for Assessment/ Evaluation of variation file
- Annex 2 Application for variation to a marketing authorization for biological medicinal products for human use