Arab Republic of Egypt
Egyptian Drug Authority
CA of Biological and Innovative products and clinical studies.
GA of Biological products
Registration Directorate

جمهورية مصر العربية
هيئة الدواء المصرية
الادارة المركزية للمستحضرات الحيوية والمبتكرة والدراسات الاكلينيكية
الإدارة العامة للمستحضرات الحيوية
إدارة التسجيل

Guidance to Applicants Submitting Marketing Authorization File for Biological Products

Second Edition

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I. Introduction :

This is one in a series of guidance documents that provide recommendations for applicants preparing a Common Technical Document for the Registration of Biological products intended to be placed in the Egyptian Market as a step towards the Good Submission Practice of applications & to ensure complete awareness of our regulatory requirements that saves time consumed in the process of Marketing Authorization & Registration of Biological Products

This guidance document is intended to describe how to organize new Biological application to be used together with the CTD guidance as per International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines on the CTD that are adopted by the National Regulatory Authority In Egypt for years in the Scope of Biological Products for Human Use.

This guidance document presents general considerations for the overall organization of the marketing application & is released in parallel with the application of the automated submission by applicants in order to enhance the Marketing Authorization & Registration Function.

II. Background:

To market a biological product in Egypt, you must provide adequate information to the Egyptian Drug Authority demonstrating that the product is safe and effective for the conditions prescribed, recommended, or suggested in the proposed labeling for the product.

The regulations under the ministerial decree 297 /2009 & 820/2016 describe the information required for the Application of Biological Products

An application organized as described in this guidance will fulfill the regulatory requirements

III. Proper Concept Of Reliance

The ministerial Decree 820/2016 allows registration during one month in case of EMA & FDA approved products , two months in case of EMA or FDA approved products & in six months for CTD files submission

To achieve the proper concept of Reliance on other Competent Regulatory Authorities, A complete File **Identical to the one submitted to The Country of Origin Regulatory Authority** should be submitted to the Egyptian Drug Authority

IV . Contents of file submitted for evaluation:

A. Hard File Contents :

-Kindly pay attention to all the sub-items that describe in full details the documents that should be included

-The fees that should be paid for registration through ministerial decree 820/2016 is as follows :

1) 250,000 for Local Products
2) 350,000 for Imported

Products The fees are distributed as follows :

1) 20,000 for Request Inquiry Approval
2) 25,000 for Pricing
3) The rest of fees are divided into 2 parts (part 1 : during submission of hard file & part 2 : before receiving of MA certificate)
   - Note that there are separate fees that should be paid in Lab evaluation directorate for registration through 820/2016 ministerial decree

-Appendix 1 containing the checklist of hard file content together with other MA file contents attached to the guidance

- The checklist contains items of five parts to be evaluated each by the specified evaluation department. Items that should be included in the hard file are to be evaluated by the reception section Of the Biological Registration Directorate

-Hard file contains both parts ; Part one : administrative data (certificates required according to our legal provisions) & Part two : data about product active & inactive ingredients , packaging & labeling materials

B- Inspection File Contents:

-In Registration through ministerial decree 297/2009 (either normal or fast track procedures) , the inspection file is submitted to the reception section for verification then transferred to Biological Inspection Directorate for evaluation while in Registration through 820/2016 , the inspection file is directly received by the Biological Inspection Directorate

-Detailed Checklist is attached to the guidance

C- Stability Documents :

- Both drug substance & drug product stability studies are evaluated by Stability department during product registration either through 297 /2009 or 820/2016 ministerial decrees

- The stability documents are transferred to stability department for evaluation while in Registration through 820/2016 , the stability department directly receives them .

a) - Summary sheet (Hard copy and soft copy on e-mail) (E-mail: stabilityimported@eda.mohealth.gov.eg)
(E-mail: stab.imported@eda.mohealth.gov.eg)

b) Transfer letter from the biological department.
c) Valid CPP includes trade name, dosage form, active ingredients & composition and stating the license holder, manufacturers of the finished product.
d) SmPC (Must be in English. If not, official translation is required)
- If SmPC isn't available, then Patient Information Leaflet (PIL) from Mother Company is required.

e) <u>Requirements for the drug substance:</u>

1. Manufacturer(s) section from CTD "3.2.S.2.1"
2. Specification section from CTD "3.2.S.4.1"
3. "C.O.A" or Batch Analysis section from CTD "3.2.S.4.4"
4. Justification of Specification section from CTD "3.2.S.4.5"
5. Container Closure System section from CTD "3.2.S.6"
6. Stability data "3.2.S.7.3 ":
   i. Stability Summary and Conclusion from CTD section "3.2.S.7.1"
   ii. Post-approval Stability Protocol and Stability Commitment from CTD section "3.2.S.7.2"
   iii. <u>Stability studies:</u>

-Stability studies and its protocol of 3 primary batches (pilot or production scale) carried out in the intended drug substance container-closure system, containing manufacturing site, manufacturing date and tested parameters that include: Appearance and description, Identity, Purity and impurities, Potency, etc….)

- <u>N.B:</u>

- If the stability studies are performed on batches manufactured in a manufacturing site that differs from the site that will be registered in Egypt, then a justification is required.
-In case of presence of more than one concentrations or volumes for the finished product, stability study must be done on 3 batches for the higher and 3 batches for the lower concentration or volume in case of new registration but in case of re-registration so one batch for the higher and one batch for the lower concentration or volume.
-In case of more than one manufacturer, all stability studies must be submitted from each manufacturer.
-Pilot scale batches can be provided with a commitment from the mother company to place the first three production scale batches into the long-term stability program after approval and submitting the study once completed mentioning the date of submission in

the commitment.

-The stability protocol used for studies on commitment batches should be the same as that for the pilot batches, unless otherwise scientifically justified.

f) <u>Requirements for the drug product:</u>

1. <u>Composition:</u>

i. Composition from the C.T.D section "3.2.P.1" which is similar to Composition in C.P.P.
⇨ If the composition isn't present in C.P.P, so legalized composition is required.

ii. Signed & stamped composition on company papers mentioning trade name, dosage form, strength and includes a table that contain (ingredients with their grades, function of each ingredient, quantity & reference).

2. The responsibilities of the manufacturers from CTD section "3.2.P.3.1" that clarify the manufacturers, Packagers (primary & secondary), batch release, and stability testing site, and if any of them is not present in this section then a signed and stamped declaration letter is required from Mother Company.
3. If shelf life and storage conditions aren't present in SmPC or in case of storage conditions in SmPC is "it doesn't require any specialized conditions", then a declaration letter for the required storage conditions with exact temperature is required from Mother Company signed, stamped and legalized.
-In case of (EMEA or FDA) approved products: If the storage conditions in SmPC are "it doesn't require any specialized conditions", then a declaration letter for the required storage conditions and exact temperature, signed and stamped from Mother Company is required.
4. In case of storage temperature at (25 °C), a commitment from the applicant to store the product in warehouses and pharmacies at temperature not exceeding (25 °C) is required.
5. Pack layout (marketed in reference country) and proposed pack for Egypt.
6. Container closure system from the C.T.D section "3.2.P.7" including full Pack description in details (number of units per pack, primary pack description in terms of material, color, volume; secondary pack)
7. Release and shelf life specifications from CTD section "3.2.P.5.1"
8. Batch analysis section from CTD "3.2.P.5.4"
9. Justification of specification section from CTD "3.2.P.5.6"
10. Signed and Stamped certificate of analysis "C.O.A" of recently manufactured finished product (through the past 10 years), containing manufacturing & expiry dates (corresponds to the required shelf life) and tested parameters that include but not specific to: Appearance and description, Identity, Purity and impurities, Potency, sterility testing or alternatives, etc….)
⇨ If the product is powder: the color of powder before & after reconstitution should be mentioned in the COA or CTD or SmPC or signed & stamped declaration.

11. Stability data:

i. Stability Summary and Conclusion from CTD section "3.2.P.8.1"
ii. Post-approval Stability Protocol and Stability Commitment from CTD section "3.2.P.8.2".

Stability studies:

⇨ Long-term stability study and its protocol of 3 primary batches (pilot or production scale) carried out in the intended drug product container-closure system, containing manufacturing site, manufacturing & expiry dates (corresponds to the required shelf life of the product & manufactured through the past 10 years) and tested parameters that include: Appearance and description, Identity, Purity and impurities, Potency, sterility testing or alternatives, etc….). The stability data should support the conclusions regarding the recommended storage and shipping conditions and the shelf-life/storage period for the drug product.

⇨ Accelerated stability study and its protocol of 3 primary batches (pilot or production scale) carried out in the intended drug product container-closure system, containing manufacturing site, manufacturing & expiry dates (corresponds to the required shelf life of the product & manufactured through the past 10 years) and tested parameters that include: Appearance and description, Identity, Purity and impurities, Potency, sterility testing or alternatives, etc….).

⇨ In-use :(after opening / after dilution / after reconstitution) stability study on at least two pilot scale batches containing manufacturing site, manufacturing & expiry dates (corresponds to the required shelf life).

⇨ Photo-stablity study.

- **N.B:**

-The stability studies must be performed on the exact composition as that in the submitted CPP.

-If the stability studies are performed on batches manufactured in a manufacturing site that differs from the site that will be registered in Egypt, then a justification is required.

- In case of the finished product has more than one strength, container type or size , stability study must be done on 3 batches (in case of new registration) or one batch (in case of renewal) for each individual strength, container type or size, unless bracketing is applied.

-In case of more than one manufacturer, all stability studies must be submitted from each manufacturer (except photo-stability study).

- If the scale of batches (production / pilot) is not stated in the CTD, scanned copy of signed and stamped declaration is needed to clarify the scale of the submitted batches.

-Pilot scale batches can be provided with a commitment from the mother company to place the first three production scale batches into the long-term stability program after approval and submitting the study once completed mentioning the date of submission in the commitment.

-The stability protocol used for studies on commitment batches should be the same as that for the pilot batches, unless otherwise scientifically justified.

g) CD containing module 3 and soft copies of all documents submitted in the file.
h) All CTD documents submitted as hard copy must be stamped by the applicant.

D- Pharmaco-vigellence File Contents :

- To ensure complete awareness with the work flow and required documents , The Egyptian Pharmaceutical Vigilance Center (EPVC) has published many explanatory notes in this guidance with attached detailed checklist

- **Action letter**

The applicant should submit a copy of the Box Approval letter. (In case of 820, it is checked through 820 system)

- **Risk Management Plan**

According to the Guideline on Good Pharmacovigilance Practices (GVP) for Arab Countries a risk management plan (RMP) document should be submitted in all registration files as a general rule for all medicinal products.

The content and requirement for risk management plan (RMP) are described in the Guidelines on GVP- for Arab countries (most updated version).

Generally RMP document should be submitted as searchable PDF file (text) on a CD.

- **Risk Management Plan (RMP)/ Justification for not submitting Risk Management Plan**
- All applicants should submit a risk management plan (RMP) document which describes activities and interventions designed to identify, characterize, prevent or minimize risks relating to medicinal products including the assessment of the effectiveness of those activities and interventions.
- This is not applicable for companies having EU RMP (See subsection 1.5.2.2).
- The submission of a risk management plan may not be required if a suitable justification has been provided by the applicant for non-submission of the RMP with adequate scientific references. An acceptable justification should contain the following:

a) Clear statement that the innovator has no RMP, with an evidence from reference countries (if applicable)
b) Table reflecting the updated summary of safety concerns of the product

c) Table reflecting the proposed routine risk minimization activities, and how such routine activities will be sufficient to manage the product safety concerns**.**
Nevertheless, in cases where a change in the relationship between the benefits and the risks of a medicinal product is suspected, EPVC may request that a RMP to be submitted for that medicinal product.

- **European Risk Management Plan (EU RMP)/ Justification for not submitting European Risk Management Plan**
- An EU RMP (including its annexes) is applicable for Multinational companies having EU RMP in place. Thus, for simplification, EU RMP and its Egyptian display should be submitted (See subsection 1.5.2.3).
- For any reason if the multinational company has no EU RMP required for the product in Europe, a statement from applicant Headquarter justifying the non-submission EU RMP can be acceptable (e.g. not required by EU authorities, the RMP not approved yet in EU…. etc). In addition, if the application is for generic product the justification should include adequate scientific references (See subsection 1.5.2.1).
- **National Display of the Risk Management Plan**

The National Display of RMP document is required for any MAH/Applicants having EU RMP to be applied in Egypt (whether innovators, generics or importers), submitted together with most updated version EU RMP.

1.5.3 Pharmacovigilance system

The marketing authorization holder for Medicinal products must operate a Pharmacovigilance system to fulfil the tasks, responsibilities, monitor the safety of authorized medicinal products and detect any change to their risk-benefit balance.
Details on the structure of the system and the content of the PSMF/PSSF are described in the Guidelines on GVP- for Arab countries (most updated version).
Generally Pharmacovigilance system documents should be submitted as searchable PDF file (text) on a CD.

- **Summary of PSMF**
- The applicant should submit summary of PSMF in all registration files whether PSMF is approved or not.
- It should include the following:
  a) proof that the applicant has at his disposal a QPPV and that he resides in the Arab Country concerned
  b) The contact details of the QPPV;
  c) A statement signed by the applicant to the effect that the applicant has the necessary means to Fulfill on the national level the Pharmacovigilance tasks and responsibilities listed in this GVP Modules;

d) Reference to the location where the PSMF for the medicinal product is kept.

- **Summary of PSSF**
- The applicant should submit summary of PSSF in all registration files whether PSSF is approved or not.
- PSSF is applicable for Multinational applicants.
- It should include the following:
  a) proof that the applicant has at his disposal a LSR and that he resides in Egypt;
  b) the contact details of the LSR;
  c) a statement signed by the applicant to the effect that the applicant has the necessary means to fulfill on the national level the pharmacovigilance tasks and responsibilities listed in this GVP modules;
  d) a reference to the location where the national PSSF for the medicinal product is kept.
- **Pharmacovigilance System Master File (PSMF(/Copy of EPVC approval letter**
- The full PSMF is requested to be submitted in the marketing authorization applications on some situations kindly refer to the Guideline on GVP "*II.C.2. Accessibility/ submission of the pharmacovigilance system master file "*.
- In case the PSMF is previously approved by EPVC, Copy of EPVC approval letter for PSMF should be submitted.
- **Pharmacovigilance sub system File (PSSF) or Copy of EPVC approval letter.**
  (In case of Agency): Pharmacovigilance System Master File (PSMF) or Copy of EPVC approval letter
- Pharmacovigilance sub System File is requested to be submitted in the marketing authorization applications on some situations kindly refer to the Guideline on GVP "II.C.3.5. Submission of multinational MAH's PSMF and national PSSF"
- PSSF is applicable if the applicant is affiliate of a Multinational applicant in order to illustrate key elements of PV infrastructure in Egypt and highlight role of LSR in Egypt in integration with the global pharmacovigilance system of the company.
- In case the PSSF is previously approved by EPVC, Copy of EPVC approval letter for PSSF should be submitted.
- PSSF is not applicable if the applicant is agent, instead PSMF of agent should be submitted.
- Copy of EPVC approval letter for PSMF of agent should be submitted in case the PSMF of agent is previously approved by EPVC
- **Periodic benefit-risk evaluation report (PBRER) / Justification**
- Periodic safety update reports (PSURs) are Pharmacovigilance documents intended to provide an evaluation of the risk-benefit balance of a medicinal product for submission by marketing authorization holders at defined time points during the post-authorization phase.

- PBRER is required only from multinational companies where concerned products are already registered and there are post marketing data.
- where there is no PBRER released yet a statement/justification from applicant Headquarter for non- submission PBRER can be acceptable

▪ **Submission Requirements for different MAH types:**

1. **For Local/National companies:**

a) Pharmacovigilance System Master File (PSMF) / Copy of EPVC approval letter of PSMF.
b) Summary of Pharmacovigilance system.
c) Risk management plan.

2. **For agents:**

a) Pharmacovigilance System Master File of the global MAH (including annexes and SOPs) /Copy of EPVC approval letter of global PSMF and summary.
b) Pharmacovigilance System Master File of the agent (including annexes and SOPs) / Copy of EPVC approval letter of agent PSMF and summary.
c) European Risk Management Plan (EU RMP) or Justification from the Global Company for not submitting European Risk Management Plan.
d) National Display of the Risk Management Plan.
e) Periodic benefit-risk evaluation report (PBRER) / Justification

3. **For Multi-national companies:**

a) Pharmacovigilance System Master File of the global MAH (including annexes and SOPs)/ Copy of EPVC approval letter of PSMF and summary.
b) The National Pharmacovigilance Sub-System File (PSSF) (including annexes and SOPs)/ Copy of EPVC approval letter of PSSF and summary.
c) European Risk Management Plan (EU RMP) or Justification from Head Quarter for not submitting European Risk Management Plan.
d) National Display of the Risk Management Plan.
e) Periodic benefit-risk evaluation report (PBRER) / Justification

- Detailed Checklist is attached to the guidance

E- Scientific file contents:

The scientific department receives 2 major kinds of files:

Applicant submits documents for scientific department for new files (normal and fast track), re-registration files, or exemption requests from marketing in reference countries.

1. Documents for scientific committee submission

- Submitted files may follow either minister decree 297/2009 or 820/2016 according to attached checklists

2. Documents for Insert approval

- In case of submission according to minister decree 297/2009 follow documents submitted in attached checklist
    - In case of submission according to minister decree 820/2016, no documents for insert approval are submitted (submitted already in the scientific file)

The main difference in requirements between submission according to minister decree 820/2016 and 297/2009 is:

- Submission of copies for scientific committee members in minister decree 820/2016 with the scientific file (for acceleration of process).
- Filling product information sheet (template 1) and scientific summary appeal (template 2) in minister decree 820/2016 (Both are attached)
- Submission of declarations required for insert approval.

F- Lab evaluation directorate and Clinical studies file :

- As per the new work instruction of Registration through ministerial decree 820/2016 , lab evaluation directorate and clinical studies file is transferred after issuing the box approval & lab evaluation directorate and clinical studies requirements should be fulfilled during submission of Registration file in order to receive the whole file by other evaluation departments .
- To facilitate Registration procedure through the specified timeline , Awareness with Lab evaluation directorate and Clinical Studies full requirements is ensured in this guidance as the requirements are listed in the guideline