GUIDELINE ON

Content File of Biological Products for Registration & Re-registration file

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1 Introduction

This guideline intended to describe how to organize file content of biological product according to EDA Chairman decree 343/2021 together with the CTD guidance as per ICH guidelines Whether new registration file or re-registration file.
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 EDA Chairman decree 343/2021 describe the information required for the Application of Biological Products.
According to EDA Chairman decree 343/2021, the re-registration file will be every 5 years from first date of registration by submitting a request from the company at the last year of product license validation.

2 Scope

The guideline primarily addresses the information required to be submitted in registration or Re-registration applications for biological products submitted through 343/2021 decree

3 Definitions

- **Biological products**: Medicinal products made of substances extracted from or produced by living sources whether they are genetically modified living organisms or liquids and tissues extracted from various human or animal sources.
- **Biosimilar**: A similar biological medicinal product having the same active substance, dosage form, concentration and route of administration of a reference biological product and has proven through a comparability program that its quality, safety and efficacy are highly similar to a reference product when prescribed in a claimed indication.
- **Reference Biological product**: A Product developed and registered on basis of complete dossier with full quality, preclinical and clinical data and used by the manufacturer for comparability studies versus a product supposed to be a biosimilar.
- **Pharmacovigilance**: The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug related problems.
- **Reference Countries**: An updatable list of countries approved by the Technical committee for drug control.

4 Procedures

SECTION ONE:

This section will provide information about registration file contents for biological products submitted through new registration.

- Contents of file submitted for evaluation of new file submission according to EDA chairman decree 343/2021

A. Module 1:

-Contains the administrative data that required to be submitted to comply local Egyptian Drug Authority rules and regulations (for example: inquiry approval, CPP, pack layouts and manufacturing license,….etc.)

- The checklist contains items of Six parts to be evaluated each by the specified evaluation department. Items that should be included in the hard file are to be evaluated by different EDA interested parties including reception unit, stability unit, technical assessment unit, scientific unit, inspection unit and Pharmacovigilance unit

- In Registration through the EDA Chairman decree 343/2021 (either normal or fast track procedures), each file will be directly received by its concerned unit in EDA.

- The main contents are as the following:

- Covering letter on applicant head letter signed and stamped

- Copy of Inquiry approval

- Copy of pricing certificate

- C.D. containing all content of the 5 files (core, inspection, quality, stability, scientific & PV)

- Copy of all approvals or Exemptions related to the Product (technical committee, scientific committee, inspection reports, …)

- Application form for registration of biological medicinal products Signed & Stamped by the Applicant

- Composition Certificate

- CPP issued by Competent Authorities in Country of Origin

- GMP & Manufacturing License

- TSE/BSE free declaration

- Certificate of suitability

- List of the countries where the product is registered & marketed

- pack layouts

- Official declaration stating the relationship between Manufacturer, Importer and Distributor or Copy of Agency or distribution contract

- In case of imported bulk naked vial that manufactured abroad and packed locally, the following is required:

1 - Copy of packaging contract between the importing company & local manufacturing

2 - Original Authorization letter from the abroad mother company to the importing for product registration and packaging with a local licensed packaging site (Should be notarized from the chamber of commerce or its equivalent in the country of origin and Authenticated from the Egyptian embassy abroad & submit original for review).

3 - Letter of Acknowledgment of full responsibility for storing the raw materials and for all stages of manufacturing and for the product's conformity with the technical specifications until the completion of distribution (in case of imported bulk and will be further manufacturing steps locally).

- Submitting a pledge acknowledging his commitment to the provisions of the Intellectual Property Protection Law No. 82 of 2002

- Submit the updated scientific office license, importer register for all importers, Updated Storage License for all Storage sites, updated Tax card & Commercial register

- CD contain CTD modules and all previously mentioned data

-Annex 1 containing the checklist of hard file content is attached to the guideline

B- Stability Documents:

I- Requirements of Stability file for Imported Biological Products

- Summary sheet ((Word) + signed & stamped pdf)

- Inquiry Approval.

- Valid legalized C.P.P that includes:

• Trade name, dosage form, active ingredients & composition

• Stating the license holder, manufacturers of the finished product.

- SmPC (Must be in English. If not, official translation is required)

• If SmPC is not attached to the CPP, then a declaration letter from global is required to confirm that this the most updated version marketed in the country of origin, with commitment to submit the legalized SmPC within 6 months from the date of commitment.

N.B.: (If the CPP is from EMA or FDA, no legalization is needed).

• If SmPC isn't available, then Patient Information Leaflet (PIL) from Mother Company is required.

• 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. N.B.: (If the CPP is from EMA or FDA, no legalization is needed).

• If temperature storage is at (25 °C), a commitment from the applicant to store the product in warehouses and pharmacies at temperature not exceeding (25 °C) is required.

- Signed & stamped declaration from global with the stability testing site for the submitted stability studies, mentioning the batch numbers.

- 7. Composition:

• Composition from the C.T.D section "3.2.P.1"
• It should be similar to Composition in C.P.P.
• If the composition isn't present in C.P.P, so legalized composition is required.
• Signed & stamped composition on company papers
• Mentioning trade name, dosage form, strength
• It should include a table that contain:
(Function, reference to standard & grades (if applicable) of each ingredient)

- If the responsibilities of the manufacturers from CTD section "3.2.P.3.1" does not clarify the manufacturers, Packagers (primary & secondary), batch releaser & stability testing site, than a signed & stamped declaration letter is required from Mother Company.

- Commitment from the applicant that all the data are authentic & accurate.

- Pack layout (marketed in country of origin).

- Full Module 3 (For the drug substance & the drug product).

- Comparability stability study (in case of biosimilar product): **3.2. R**

II- Requirements for Inspection and Stability file of Local Biological Products:

- Summary sheet (Word) + signed & stamped pdf.

- Inquiry approval.

- Certificate of responsibility stamped from the site at which the stability study was performed (signed by Q.C. analyst, Q.C. Head & Q.A Head).

• In case of performing the stability study in place rather than the manufacturer, attach the following:

- Contract between the applicant and the place at which the stability study was performed

(Authenticated by the legal counsel of EDA)

- Copy of the license of the place at which the stability study was performed.

For finished product:

- Composition

- Description of Manufacturing Process and Process Controls (name, dosage form)

- Certificate of analysis ''C.O. A" of 3 batches of finished product (and solvent, if applicable)

- Declaration with the shelf-life & storage conditions of the product

- Pack description

- Sampling record

- Reference product insert marketed in Egypt

- Sample

- Finished product specification

- Justification of specification

- Method of analysis. (detailed procedures)

- Validation of analytical procedure of active ingredient assay and related substances along with HPLC chromatograms for each parameter (in case of HPLC analysis).

- Stability Data

- Additional studies in case of biosimilar product: Side-by-side accelerated and stress studies carried out using a representative number of batches, comparing the biosimilar product to the reference product are mandatory to determine the similarity of the products by showing comparable degradation profiles. Any differences concerning the stability profile of the biosimilar product when compared to the reference product should be justified.

For Drug substance:
- Valid importation Permit
- A commitment letter from the applicant
- A declaration letter from the drug substance manufacturer
- Full S-Part from Module 3
- A commitment from the applicant that the submitted S-Part is authentic & accurate
- C.O.A of recently manufactured drug substance
- Stability data

Please refer to all requirements in details that attached at Annex 2

C- Quality file contents:
- Copy of inquiry approval

- Copy of application form for biological products

- Summary protocol (for blood products & vaccines)

- Detailed SOPs of analytical procedures of the finished product

- Complete CTD

- Certificate of Analysis for Drug substance & Finished product & solvent (if solvent present)

- Any EDA approval or exemption for the concerned product as supporting documents (example: technical committee approvals, Scientific approvals, inspection approvals for non-reference country manufacturing sites,……)

- Annex 1 containing the checklist of quality file content is attached to this guideline

D- Scientific file contents:

I- Administrative Part

- Covering Letter

- List of countries where the product is being registered and marketed

- Copy of CPP in addition to SmPC

- inner leaflet

- Copy of Reference (BNF 61,Vidal,Swiss Compendium, Rote liste)

- Composition certificate signed and stamped

- Approved price

II-Plasma Master File (if plasma derived product)

- Cover Letter contain all registered and under registration products in Egypt.

- Health authority approval on plasma master file

- Certificate of plasma release from national regulatory released same year of PMF submission.

- Soft copy of Plasma Master File

- PMF approval from health authority & viral inactivation, certificate of release from Health Authority, certificate of analysis (plasma derived product as active or excipient)

III- Package leaflet

In Case of imported reference country

- Innovator:

1. Insert marketed in Country of Origin (ENGLISH)

2. Insert marketed in Country of Origin (ARABIC), translated from a Certified translation office, except (Vaccines- Immunosuppressant- IV infusion products- Hospital use only - Immunological products- Contrast agents except iodinated one)

3. Covering Letter

4. SmPC "summary of product characteristics" and/or CCDS "company core data sheet"

5. CPP attached insert

6. Declaration from the mother company that the submitted insert is the most updated & marketed in COO

- Biosimilar product:

1- Cover letter for requesting insert submission & approval

2- Insert marketed in Country of Origin (ENGLISH) (Numbered)

3- Insert marketed in Country of Origin (ARABIC), translated from a Certified translation office, except (Vaccines- Immunosuppressant- IV infusion products- Hospital use only - Immunological products- Contrast agents except iodinated one)

4- innovator product insert

5- Commitment from the mother company that the submitted insert is the most updated one & marketed in COO

6- declaration from the applicant states the COO that relay for the product indication

7- CPP with attached insert

In case of imported product from non-reference country

- Standalone product:

1- Cover letter for requesting insert submission & approval

2- Insert marketed in Country of Origin (ENGLISH) (Numbered)

3- Insert marketed in Country of Origin (ARABIC), translated from a Certified translation office, except (Vaccines- Immunosuppressant- IV infusion products- Hospital use only - Immunological products- Contrast agents except iodinated one)

4- CPP with attached insert

5- Reference model insert

6- Scientific reference (Trials & Literature)

7- Commitment from the mother company that the submitted insert is the most updated one & marketed in COO

- Biosimilar Product

1- Cover letter for requesting insert submission & approval

2- Insert marketed in Country of Origin (ENGLISH)

3- Insert marketed in Country of Origin (ARABIC), translated from a Certified translation office, except (Vaccines- Immunosuppressant- IV infusion products- Hospital use only - Immunological products- Contrast agents except iodinated one)

4- CPP with attached insert

5- Commitment from the mother company that the submitted insert is the most updated one & marketed in COO

6- Declaration from the applicant states the reference country that relay for the product indication

7- Innovator product insert

NOTE:

- Comparative table between reference insert and Proposed insert (in case of insert is different from CPP Insert Or biosimilar (non-reference country)

- Comparative table between current & proposed insert and scientific reference for every part in the insert (For local products)

In case of local products:

- Standalone product:

1. cover letter for requesting insert submission & approval

2. proposed Insert (ENGLISH)

3. proposed Insert (ARABIC), translated from a Certified translation

office, except (Vaccines- Immunosuppressant- IV infusion products- Hospital use only - Immunological products- Contrast agents except iodinated one)

4. Reference model insert

5. Scientific reference (Trials & Literature)

- Biosimilar Product

1. Cover letter for requesting insert submission & approval

2. Proposed Insert (ENGLISH) (Numbered)

3. proposed Insert (ARABIC), translated from a Certified translation office, except (Vaccines- Immunosuppressant- IV infusion products- Hospital use only - Immunological products- Contrast agents except iodinated one)

4. Innovator product insert

5. Declaration from the applicant states the reference country that relay for the product indication

6. Scientific References (clinical studies or literature)

IV- Albumin used as stabilizer Requirements

- EMA Approval if the plasma master file has an approval from EMA

- Certificate of batch release of health authority for this albumin used as a stabilizer.

- Declaration from the MAH declares the trade name of the albumin used as a stabilizer.

- GENERAL INFORMATION (SUMMARY)

1- Plasma-Derived Products' List
2- Overall Safety Strategy
3- General Logistics

- TECHNICAL INFORMATION ON STARTING MATERIALS

1- PLASMA ORIGIN

2- Information on centers or establishments in which blood/ plasma collection is carried out

3- Information on centers or establishments in which testing of donations and plasma pools is carried out

4 -Selection/exclusion criteria for blood/plasma donors

5- System in place which enables the path taken by each donation to be traced from the blood/plasma collection establishment through to finished products and vice versa

- Plasma Quality and Safety

1- Compliance with European Pharmacopoeia Monographs.

2 Testing of blood/plasma donations and pools for infectious agents, including information on test methods and, in the case of plasma pools, validation data on the tests used.

- Technical characteristics of bags for blood and plasma collection, including information on anticoagulant solutions used.

- Annex 1 containing the checklist of scientific file content is attached to the guideline.

E- Inspection File Contents:

- List of each site where the product (Drug Substance and Drug Product), if authorized, is or would be manufactured.

- Updated Site Master File including;

• Relevant Premises & utilities information about each site.

• Current status of the manufacturing site(s) with respect to current good manufacturing practice (cGMP) requirements.

• Legible color printouts of water treatment and air-handling systems, including pipeline and instrumentation drawings in A3 or A2 format.

- List of all the products and dosage forms manufactured on- the same site especially same production lines.

- Process Validations reports for DS & DP manufacturing.

- Latest full inspection report(s) for inspection performed by a stringent regulatory authority in the past three years and their outcomes.

- Last Annual product review.

- One completed batch manufacturing and packaging record.

- Cold chain Storage & transportation procedures.

- List of any recalls in the past three years related to products with quality defects (if found).

- Any warning letter or equivalent regulatory action (production-line specific) (if found).

- Annex 1 containing the checklist of inspection file content is attached this guideline.

F- Pharmacovigilance File Contents:

- For Imported Products:

- Delegation letter

- Updated Cover letter (on the company paper of the PV representative/agent/scientific office) clarifying the Date of the submission (not exceeding 2 days before the submission)/ Directed to the Manager of General Administration of Pharmaceutical Vigilance/ Name of the product /Name of the Active substance/ context of submission/ Name of the MAH/ Content of the submission/ Actual signature of the QPPV or LSR “signature by QPPV or LSR (not print screen)”- “Accepted Digital/Electronic signature”/company stamp.

- Confirmation e-mail by PSMF reception portal (as an evidence of submission of the PSMF of the company to EPVC) OR Latest released valid PSMF assessment report “for all concerned parties”.

- Updated version of Summary of PSMF(s)/PSSF.

- In case of submission by PV representative or agent, the PV rep./agent should submit an authorized and authenticated (by all concerned parties) PV agreement between the MAH & the service provider covering all the PV activities.

- The latest Periodic Safety Update Report (PSUR) in PSUR format “as per GVP for Arab Countries V.2.0” covering at least the last 3 years OR separate PSURs covering at least the last 3 years.

- The most updated "EU/Global/Core-Risk Management Plan (RMP)"of the product.

- The Egyptian display of EU-RMP

- for local products:

- Delegation letter

- Updated Cover letter (on the company paper of the PV representative/agent/scientific office) clarifying the Date of the submission (not exceeding 2 days before the submission)/ Directed to the Manager of General Administration of Pharmaceutical Vigilance/ Name of the product /Name of the Active substance/ context of submission/ Name of the MAH/ Content of the submission/ Actual signature of the QPPV “signature by QPPV (not print screen)”/company stamp.

- Confirmation e-mail by PSMF reception portal (as an evidence of submission of the PSMF of the company to EPVC) or Latest released valid PSMF assessment report “for all concerned parties”.

- Updated version of Summary of PSMF(s)/PSSF.

- In case of submission by PV representative, the PV rep should submit an authorized and authenticated (by all concerned parties) PV agreement between the MAH & the service provider covering all the PV activities.

- Egyptian-Risk Management Plan (RMP)"of the product..
- The latest Periodic Safety Update Report (PSUR) in PBRER format of the imported ready to fill final bulk covering at least the last 3 years.

SECTION TWO:

This section will provide information about Re-registration file contents for biological products submitted through Re-registration process.

- Contents of file submitted for evaluation of Re-registration file submission according to EDA chairman decree 343/2021

A. Module 1 Contents:

- In Re-registration through the EDA Chairman decree 343/2021, each file will be directly received by its concerned unit in EDA

-Contains the administrative data that required to be submitted to comply local Egyptian Drug Authority

rules and regulations (for example: inquiry approval, CPP, pack layouts and manufacturing license,….etc.)

- The checklist contains items of four parts to be evaluated each by the specified evaluation department. Items that should be included in the re-registration file are to be evaluated by different EDA interested parties including reception unit, technical assessment unit, inspection unit, and pharmacovigilance unit.

- The main contents are as the following:

- Covering letter

- Copy of the updated pricing certificate

- Copy of Authorization letter for the person responsible for communication

- Original List OF variations from the MA holder

- Application form for Re-registration of biological medicinal products

- Composition Certificate

- CPP issued by Competent Authorities in Country of Origin

- GMP & Manufacturing license

- pack layouts

- Official declaration stating the relationship between Manufacturer, Importer and Distributor or Copy of Agency or distribution contract

- In case of imported bulk naked vial that manufactured abroad and packed locally, the following is required:

1 - Copy of packaging contract between the importing company & local manufacturing

2 - Original Authorization letter from the abroad mother company to the importing for product registration and packaging with a local licensed packaging site (Should be notarized from the chamber of commerce or its equivalent in the country of origin and Authenticated from the Egyptian embassy abroad & submit original for review).

3 - Letter of Acknowledgment of full responsibility for storing the raw materials and for all stages of manufacturing and for the product's conformity with the technical specifications until the completion of distribution (in case of imported bulk and will be further manufacturing steps locally).

- Submitting a pledge acknowledging his commitment to the provisions of the Intellectual Property

Protection Law No. 82 of 2002

- Submit the updated scientific office license, importer register for all importers, Updated Storage License for all Storage sites, updated Tax card & Commercial register

- CD containing the updated module 3 & the previously mentioned data.

- Annex 4 containing the checklist of hard file content is attached this guideline.

B. Inspection File Contents:

- List of each site where the product (Drug Substance and Drug Product), if authorized, is or would be manufactured.

- Updated Site Master File including;

• Relevant Premises & utilities information about each site.

• Current status of the manufacturing site(s) with respect to current good manufacturing practice (cGMP) requirements.

• Legible color printouts of water treatment and air-handling systems, including pipeline and instrumentation drawings in A3 or A2 format.

- List of all the products and dosage forms manufactured on- the same site especially same production lines.

- Process Validations reports for DS & DP manufacturing.

- Latest full inspection report(s) for inspection performed by a stringent regulatory authority in the past three years and their outcomes.

- Last Annual product review.

- One completed batch manufacturing and packaging record.

- Cold chain Storage & transportation procedures.

- List of any recalls in the past three years related to products with quality defects (if found).

- Any warning letter or equivalent regulatory action (production-line specific) (if found).

- Annex 4 containing the checklist of inspection file content is attached this guideline.

C. Pharmacovigilance file contents

- For Imported Products

- Delegation letter.

- Previous license of the product/s

- Updated Cover letter (on the company paper of the PV representative/agent/scientific office) clarifying the Date of the submission (not exceeding 2 days before the submission)/ Directed to the Manager of General Administration of Pharmaceutical Vigilance/ Name of the product /Name of the Active substance/ context of submission/ Name of the MAH/ Content of the submission/ Actual signature of the QPPV or LSR “signature by QPPV or LSR (not print screen)”- “Accepted Digital/Electronic signature”/company stamp.

- Confirmation e-mail by PSMF reception portal (as an evidence of submission of the PSMF of the company to EPVC) or Latest released valid PSMF assessment report “for all concerned parties”.

- Updated version of Summary of PSMF(s)/PSSF.

- In case of submission by PV representative or agent, the PV rep./agent should submit an authorized and authenticated (by all concerned parties) PV agreement between the MAH & the service provider covering all the PV activities.

- The Addendum to clinical overview (ACO): covering the period since the initial marketing authorization or since the last renewal until 90 days prior to renewal submission.

- The most updated "EU/Global/Core-Risk Management Plan (RMP)"of the product.

- The Egyptian display of EU-RMP.

- For Local Products:

- Delegation letter

- Previous license of the product/s

- Updated Cover letter (on the company paper of the PV representative/agent/scientific office) clarifying the Date of the submission (not exceeding 2 days before the submission)/ Directed to the Manager of General Administration of Pharmaceutical

Vigilance/ Name of the product /Name of the Active substance/ context of submission/ Name of the MAH/ Content of the submission/ Actual signature of the QPPV "signature by QPPV (not print screen)"/company stamp.

- Confirmation e-mail by PSMF reception portal (as an evidence of submission of the PSMF of the company to EPVC) or Latest released valid PSMF assessment report "all concerned parties".

- Updated version of Summary of PSMF(s)/PSSF.

- In case of submission by PV representative, the PV rep should submit an authorized and authenticated (by all concerned parties) PV agreement between the MAH & the service provider covering all the PV activities.

- The Addendum to clinical overview (ACO): covering the period since the initial marketing authorization or since the last renewal until 90 days prior to renewal submission.

- Egyptian-Risk Management Plan (RMP) of the product.

D. Quality file content

- Copy of application form for biological products

- List of Variation

- Summary protocol (for blood products & vaccines)

- Complete updated Module 3

- Certificate of Analysis for Drug substance & Finished product & solvent (if solvent present)

- Annex 4 containing the checklist of inspection file content is attached this guideline.

SECTION THREE:

This section will provide information about pack submission requirements for biological products submitted through new registration or re-registration pathway.

I- General considerations

1- All biological products are required by Egyptian Pharmacy law (127/1955) to be accompanied by outer and inner labelling texts and a package leaflet setting out comprehensive information which is accessible to and understandable by those who receive it, so that they can use their medicine safely and

appropriately.
2- EDA Chairman decree (343/2021) article 9 mentions the following obligations about package labelling:

For outer pack:
- the site address of manufacturer
- the name license holder
- the manufacturing date and expiry date
- the batch number
- the barcode
- the product license number
- the product price

For inner label:
- the site address of manufacturer
- the manufacturing date and expiry date
- the batch number

3- For any changes undertaken for registered products regarding packs & inserts, the applicant should submit application for variation Unit of registration administration for review and assess to regarding the variation undertaken

II- Information That Should Be Submitted in the Biological Product (whether new or re-registration pathway) pack and insert submission:

1- Local Product:

- **Product Trade Name**, the company write the trade name typically as in Inquiry Approval, biological application forms, insert and stability approval. The generic name shall be printed in letters that are at least half as large as the letters comprising the trade name

- **Active ingredients or generic name**, the company should mention their quantities or strengths identical to the approved insert, the product composition certificate submitted with the core file and stability approval.

- **The Pharmaceutical Dosage Form** (e.g.: PFS, Vial, PFP, ….), identical to Inquiry Approval, biological application forms, insert and stability approval.

- **Full List Composition of all inactive ingredients**, identical to the product composition certificate submitted with the core file, insert and stability approval.

- **Route of administration (e.g.: IV, IM. SC, infusion…)**, as mentioned in product insert and approved from scientific committee.

- English speaking pack in addition to Arabic language

- **Warning for all drugs** "Keep out of reach of children" must be mentioned / & **In case of presence of some ingredients** (for exp.: Aspartame. Sunset yellow, Benzalkonium chloride, Benzyl alcohol and others) they should be mentioned.

- If the dosage form or the product is related **to special population** (infant, Children, adults), it should be mentioned on the pack.

- **Number of Units of the dosage form** present in the container or box. If the product contains a lyophilized part and Water for injection part, should mention each unit with its number of units.

- **Different concentration** should have **different printing color** for easier identification and avoid medication error.

- **Manufacturer of the finished product:** full site address should be mentioned and identical to r inquiry approval, manufacturing license and biological product application.

NOTE:

a- the manufacturer is named on the label; the name shall be qualified by one of the following phrases: "**Manufactured by _____** " or "**Manufacturer of finished product is _____** ".

b- the packager is different from the manufacturer of finished product and named on the label; the name shall be qualified by the following phrase: "**Packaged by _____** ".

b- If the Toll manufacturer is named on the label, the name shall be qualified by the following phrase: "**Manufactured by _____ for _____".**

- Solvent manufacturing site (if needed): full site address should be mentioned and identical to inquiry approval, manufacturing license and biological product application.

- **Product License Holder**: full company address should be mentioned and identical to request inquiry approval, manufacturing license and biological product application.

- Batch number

- Manufacturing date

- Expiry date

- Name and number of accessories (if available) (e.g. needles, tubes, swabs, ….)

- Storage conditions

- It is recommended to contain the following information (if needed)

a- Precautions about shaking, freezing, handling.

b- Single use or multiple usage.

c- Storage temperature.

d- After reconstitution state.

e- After opening state.

f- Preparation for use, i.e., shaking, dilution, adjustment of temperature or other manipulation or process.

g- special storage precautions

h- specific precautions relating to the disposal of unused medicinal

- **Quantity of dose delivered** may be mentioned, including usual quantities for each of the uses for which it is intended and usual quantities for persons of different ages.

- **the barcode** (complying the ministerial decree 29/2016 for track and trace inside Egypt)

- the product license number: identical to the number mentioned in the EDA product license

- the product price: identical to the pricing certificate

- the company logo (if needed)

- refer to the insert for any further information that is critical to the patient.

- Pack description in case of Multi packs which are composed of several single packs of the same strength of a medicinal product.

2 - Imported Product:

- **Product Trade Name**, the company write the trade name typically as in CPP, Inquiry Approval,

biological application forms, insert and stability approval. The generic name shall be printed in letters that are at least half as large as the letters comprising the trade name

- **Active ingredients or generic name**, the company should mention their quantities or strengths identical to the approved insert, the product composition certificate submitted with the core file, CPP and stability approval.

- **The Pharmaceutical Dosage Form** (e.g.: PFS, Vial, PFP, ….), identical to Inquiry Approval, biological application forms, insert, CPP and stability approval.

- **Full List Composition of all inactive ingredients**, identical to the product composition certificate submitted with the core file, insert, CPP and stability approval.

- **Route of administration (e.g.: IV, IM. SC, infusion…)**, as mentioned in CPP, product insert and approved from scientific committee.

- Multilingual or English-speaking pack in addition to Arabic language (if available)

- **Warning for all drugs** "Keep out of reach of children" must be mentioned / & **In case of presence of some ingredients** (for exp.: Aspartame. Sunset yellow, Benzalkonium chloride, Benzyl alcohol and others) they should be mentioned.

- If the dosage form or the product is related **to special population** (infant, Children, adults), it should be mentioned on the pack.

- **Number of Units of the dosage form** present in the container or box. If the product contains a lyophilized part and Water for injection part, should mention each unit with its number of units.

- **Different concentration** should have **different printing color** for easier identification and avoid medication error.

- **Manufacturer of the finished product:** full site address should be mentioned and identical to request inquiry approval, manufacturing license, CPP and biological product application.

- Solvent manufacturing site (if needed): full site address should be mentioned and identical to request inquiry approval, manufacturing license, CPP and biological product application.

NOTE:

*** - if the pack is country specific pack:**

a- the manufacturer is named on the label; the name shall be qualified by one of the following phrases: **"Manufactured by _____ "** or **"Manufacturer of finished product is _____ "**.

b - If the batch releaser is identified on the label, the name shall be qualified by the phrase **"Batch Releaser site is _____".**

c- the packager is named on the label; the name shall be qualified by one of the following phrases: **"Packaged by _____ "**.

*** - if the pack is country of origin pack, international or shared pack:**

a- the company will stamp the manufacturing site by inkjet on outer pack (according to technical committee 9/7/2020) in case of not mentioning the manufacturer of finished product

- **Product License Holder**: full company address should be mentioned and identical to request inquiry approval, manufacturing license, CPP and biological product application.

- **the importer:** full company address should be mentioned and identical to biological product application and importer register

- Batch number

- Manufacturing date

- Expiry date

- Name and number of accessories (if available) (e.g. needles, tubes, swabs, ….)

- Storage conditions

It is recommended to contain the following information (if needed)

a- Precautions about shaking, freezing, handling.

b- Single use or multiple usage.

c- Storage temperature.

d- After reconstitution state.

e- After opening state.

f- Preparation for use, i.e., shaking, dilution, adjustment of temperature or other manipulation or

process.

g- special storage precautions

h- specific precautions relating to the disposal of unused medicinal

- **Quantity of dose delivered** may be mentioned, including usual quantities for each of the uses for which it is intended and usual quantities for persons of different ages.

- **The barcode** (complying the ministerial decree 29/2016 for track and trace inside Egypt)

- The product license number: identical to the number mentioned in the EDA product license

- The product price: identical to the pricing certificate

- The company logo (if needed)

- **Refer to the insert** for any further information that is critical to the patient.

III-Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors to promote safe administration and use of the product:

A. Poor Design of Product Container Labels and Carton Labeling Can Obscure Critical Safety Information

Poor label design can contribute to medication errors by making it difficult for healthcare professionals and/or patients to readily locate and understand critical safety information. Examples from reports of medication errors include:

• Key information, such as the product name, strength, and dosage form expressed in a confusing manner; or is not properly located and displayed.

• Key information does not appear in the same field of vision (i.e., the information is not readable without having to turn or rotate the container).

• Container labels and carton labeling look similar across multiple strengths of the same product or across multiple products within a company's product line.

• Container labels and carton labeling look similar among multiple products from different manufacturers.

• Container labels and carton labeling are visually cluttered by extraneous text or distracting graphics.

B- Error-prone abbreviations or symbols

Text is difficult to read because of font size or style, insufficient color contrast, or other design elements.

• Overlapping text is printed on both sides of a clear, transparent, or translucent container label such as those that might be found on syringes, ampules, vials or intravenous bags

- Critical Product Information Should Appear on the pack layout

- Trade name
- generic name
- Product strength
- Route(s) of administration
- Warnings (if any) or cautionary statements (if any)

The information listed above should be the most prominent information on the pack layout. Other information on the pack layout such as the net quantity statement, manufacturer name, and logo should not compete in size and prominence with the important information listed above. Information such as the product strength equivalency statement, “each vial contains” statement, and manufacturer name and logo is best placed on the side or back of pack layout to maximize the prominence of the important information listed above.

C. Labels should be Legible, Readable, and Easy to Understand

EDA recommends that the text on the container label and carton labeling should be (1) generally oriented in the same direction; (2) placed in the same field of vision (i.e., readable without having to turn or rotate the container); and (3) surrounded by adequate white space to improve readability and avoid crowding. Important factors to consider include the following:

- Contrast of Text and Background Color

The color contrast between the text and the container label background color should be chosen to afford adequate legibility of the text. Companies should avoid color combinations that do not afford maximum legibility of text (e.g., pale yellow text on white container label background)

- Information Crowding and Visual Clutter

When labels are crowded, text size generally decreased, and important information may be difficult to read. Lines or blocks of text should be separated by sufficient white space to avoid crowding or clutter.

EDA recommend placing less important information on a side or back panel of the container label and carton labeling. Apart from required information about a product's manufacturer, distributor or packer, information about business partnerships should not appear on the label or labeling .

- The graphic design should not compete with, interrupt, or distort important information.

Images of dosage form can help pharmacists or Doctors confirm they are dispensing the correct medication when comparing the product to be dispensed against the product contained in the commercial container closure system. the image better to be appeared at the bottom of the label and should not compete in size or prominence with the proprietary and/or nonproprietary name and strength information. Images should represent the actual dosage form.

D .Dangerous Abbreviations, Acronyms, and Symbols

Certain abbreviations, acronyms, and symbols are dangerous and should not be used because they are frequently misinterpreted and can lead to mistakes that result in patient harm. For example, the abbreviation µg for microgram should not be used because it has been mistaken as mg, meaning milligram. The abbreviation mcg is an appropriate abbreviation for microgram.

The abbreviation IU for international unit also should not be used because it has been confused for the intravenous route of administration.

Mistakes can also result from the use of abbreviations, symbols, and dose designations whose meaning is non-standardized and/or unfamiliar to the healthcare professional or other target reader. For these reasons, sponsors should avoid using error-prone abbreviations or symbols for product names, doses, and strength designations on container labels and carton labeling.

E. Avoid Look-alike Container Labels and Carton Labeling

Look-alike container labels and carton labeling have frequently contributed to product selection errors and administration of the wrong drug, wrong strength and/or wrong dose. Companies should create a container label and carton labeling design that is sufficiently distinct from that of their other products and the products of other manufacturers so that the end user is able to correctly identify, select, dispense, and administer the appropriate medication, strength, and dose.

EDA recommends the usage of Color Differentiation, Color differentiation is an effective tool that can (1) differentiate products within a manufacturer's product line; (2) differentiate strengths within a manufacturer's product line; and (3) highlight certain aspects of the label, such as important warning statements.

IV-Pack submission for review and approval:

A- the biological Reception Unit is responsible for pack review and approval for new registration products or Renewal licenses:

B- biological registration specialist receives the following from applicant:

- in case of new products:

1- Seven layouts of proposed outer pack and inner label for each concentration from each manufacturing site (if more than one site)

2- Pricing certificate

3- If the trade name is a registered trade name, the company will submit the approval certificate

4- Request inquiry approval

6- Official declaration (from scientific office or from manufacturer) stating the type of the submitted pack (COO pack, country-specific pack, international pack …..ect) with differences in a tabulated form.

7- Administrative data include (Composition certificate, importer register, contracts, CPP, GMPs, Manufacturing Licenses, tax card and commercial register).

8- site abroad inspection approval for non-reference & non-WHO prequalified.

- in case of re-registration products:

1- Seven layouts of proposed outer pack and inner label for each concentration from each manufacturing site (if more than one site).

2- Official declaration (from scientific office or from manufacturer) stating the type of the submitted pack (COO pack, country-specific pack, international pack …..ect) with differences in a tabulated form.

3- If there is updated pack approved previously from variation unit, the company will submit the variation approval and declaration that the pack is the most updated one and this will be attached with renewal license.

4-the most updated original pack that marketed in Egypt

5- If the trade name is a registered trade name, the company will submit the approval certificate

6- Official declaration (from scientific office or from manufacturer) stating the type of the submitted pack

(COO pack, country-specific pack, international pack …..ect) with differences in a tabulated form.

7- Administrative data include (Composition certificate, the updated pricing certificate, importer register, contracts, CPP, GMPs, Manufacturing Licenses, tax card and commercial register).

8- site abroad inspection approval for non-reference & non-WHO prequalified.

C- the biological reception specialist starts to assess and approve the pack after Inspection file approval, Stability file approval, scientific file approval and insert approval.

D- Biological Reception Specialist performs a detailed review on the packs and layouts according to packs requirements and ensures the consistency of the data on the outer and inner labels with the data in the stability decision, approved insert and the CPP for imported products.

E- If comments are present, BRS sends an email with listing the required documents.

F- Once documents are completed, concerned BRS approves the submitted layouts by signing and stamping the layouts and writing the obligations that should be stated on outer and inner labels.

SECTION FOUR

This section will provide information about insert submission requirements for biological products submitted through new registration or Re-registration.

Submission requirements

I – Imported Products:

A- If the product is the reference product (Innovator):

1. A cover letter from the company directed to the GA of Registration requesting the approval of the insert

2. Proposed insert (A4 layout, Numbered, clear version)

3. Currently marketed & most updated version of the leaflet at the country of origin

4. An Arabic translated version of the currently marketed & most updated version of the leaflet at the country of origin, provided that it has been translated by an accredited translation office. (An English version only is needed in case of (Vaccines- Immunosuppressant- IV infusion products- Hospital use only - Immunological products- Contrast agents except iodinated one)

5. SmPC "summary of product characteristics" and/or CCDS "company core data sheet"

6. CPP attached with the proposed insert (if applicable)

7. Declaration from license holder that the proposed insert is the most updated one and the currently marketed in the country of origin

8. Currently approved insert in case of re-registration or variation.

- If the product is a bio similar:

1. A cover letter from the company directed to the GA of Registration requesting the approval of the insert

2. Proposed insert (A4 layout, Numbered, clear version)

3. Currently marketed & most updated version of the leaflet at the country of origin

4. An Arabic translated version of the currently marketed & most updated version of the leaflet at the country of origin, provided that it has been translated by an accredited translation office. (An English version only is needed in case of (Vaccines- immunosuppressant- IV infusion products- Hospital use only - Immunological products- Contrast agents except iodinated one)

5. SmPC "summary of product characteristics" and/or CCDS "company core data sheet"

6. CPP attached with the proposed insert (if applicable)

7. Declaration from license holder that the proposed insert is the most updated one and the currently marketed in the country of origin

8. Currently approved insert in case of re-registration or variation.

9. insert of reference product (innovator)

10. A statement from the license holder stating the name of the reference country in which the indications for use have been relied

B- Products imported from non-reference country:

- If the product does not have a reference product (Standalone):

1. A cover letter from the company directed to the GA of Registration requesting the approval of the insert

2. Proposed insert (A4 layout, Numbered, clear version)

3. Currently marketed & most updated version of the leaflet at the country of origin

4. An Arabic translated version of the currently marketed & most updated version of the leaflet at the country of origin, provided that it has been translated by an accredited translation office. (An English version only is needed in case of (Vaccines- immunosuppressant- IV infusion products- Hospital use only - Immunological products- Contrast agents except iodinated one)

5. SmPC "summary of product characteristics" and/or CCDS "company core data sheet"

6. CPP attached with the proposed insert (if applicable)

7. Declaration from license holder that the insert is the most updated one and marketed in the country of origin

8. The scientific reference for all the scientific data mentioned in the insert (through the studies carried out by the company and literatures.

9. Comparative table between reference insert and Proposed insert (in case of insert is different from CPP Insert or bio similar).

- If the product is a bio similar:

1. A cover letter from the company directed to the GA of Registration requesting the approval of the insert

2. Proposed insert (A4 layout, Numbered, clear version)

3. Currently marketed & most updated version of the leaflet at the country of origin

4. An Arabic translated version of the currently marketed & most updated version of the leaflet at the country of origin, provided that it has been translated by an accredited translation office. (An English version only is needed in case of (Vaccines- immunosuppressant- IV infusion products- Hospital use only - Immunological products- Contrast agents except iodinated one)

5. SmPC "summary of product characteristics" and/or CCDS "company core data sheet"

6. CPP attached with the proposed insert (if applicable)

7. Declaration from license holder that the proposed insert is the most updated one and the currently marketed in the country of origin

8. Currently approved insert in case of re-registration or variation.

9. insert of reference product (innovator)

10. A statement from the license holder stating the name of the reference country in which the indications for use have been relied

11. Comparative table between reference insert and Proposed insert (in case of insert is different from CPP Insert or bio similar).

II- Local products:

- If the product Standalone:

1. A cover letter from the company directed to the GA of Registration requesting the approval of the insert

2. Proposed insert (A4 layout, Numbered, clear version)

3. An Arabic translated version of the currently marketed & most updated version of the leaflet at the country of origin, provided that it has been translated by an accredited translation office. (An English version only is needed in case of (Vaccines- immunosuppressant- IV infusion products- Hospital use only - Immunological products- Contrast agents except iodinated one)

4. insert of reference product which the proposed insert has been relied

5. Reference model insert

6. The scientific reference for all the scientific data mentioned in the insert (through the studies carried out by the company and literatures

7. current approved insert from EDA if present

8. Comparative table between current & proposed insert and scientific reference for every part in the insert.

- If the product is a bio similar:

1. A cover letter from the company directed to the GA of Registration requesting the approval of the insert

2. Proposed insert (A4 layout, Numbered, clear version)

3. An Arabic translated version of the currently marketed & most updated version of the leaflet at the country of origin, provided that it has been translated by an accredited translation office. (An English version only is needed in case of (Vaccines- immunosuppressant- IV infusion products- Hospital use only -

Immunological products- Contrast agents except iodinated one)

4. insert of reference product which the proposed insert has been relied

5. Reference model insert

6. The scientific reference for all the scientific data mentioned in the insert (through the studies carried out by the company and literatures

7. current approved insert from EDA if present

8. Comparative table between current & proposed insert and scientific reference for every part in the insert.

9. A statement from the license holder stating the name of the reference country in which the indications for use have been relied.

5 References:

- Egyptian pharmacy law (127/1955)
- Egyptian Drug Authority establishing decree (151/2019)
- Prime minister decree at (777/2020)
- EDA Chairman Decree (343/2021)
- Ministerial decree 250/2015
- Determination of service consideration decree (640/2012)
- EDA chairman decree 59/2020 for service considerations update
- EDA chairman decree 61/2021 for service considerations update
- EDA Chairman Decree no. 38/2022 regarding amendment of article no. 4 of EDA Chairman Decree no. 343/2021.
- Regulatory guide for mechanisms, procedures and rules for implementing the EDA Chairman Decree no. 343/2021.

6 Annexes

- Annex 1 Checklist for new products Registration file submission
- Annex 2 Requirements for stability file
- Annex 3 Checklist for PV file
- Annex 4 Checklist for Re-registration file submission

Annex I

Check list for documents of new biological products registration file

Date of Submission	
Product Name	
Applicant Name	
Applicant Representative	
Biological Registration Specialist	

Prepare 6 separate files as follows		Check	Notes
File I: Core Registration file			
First: Administrative data			
1	**Company profile submitted & updated**		
2	**Index**		
3	**Covering letter on applicant head letter signed and stamped by the registration general manager for file submission for registration**		
4	**Copy of Inquiry approval**		
5	**Copy of pricing certificate (NA in registration through 820)**		
6	**C.D. containing all content of the 5 files (core, inspection, quality, stability, scientific & PV)**		
7	**A certification that all data in the file is true and accurate and updated and identical to the CD**		
8	**Copy of all approvals or Exemptions related to the Product (technical committee, scientific committee, inspection reports, …)**		
8	**Copy of Authorization letter for the person responsible for communication on behalf of applicant during the procedure and this letter should be certified as truly signed**		
9	**Payment receipt (according to last update of fees decree)**		

10	**Application form for registration of biological medicinal products Signed & Stamped by the Applicant (each paper)**		
11	**Composition Certificate**		
	Original		
	Authenticated & Notarized (if not attached to CPP) * for imported products		
	On license holder letter head		
	Signed & Stamped by the license holder		
	Trade name of the product is specified		
	Dosage form of the product is specified		
	Active ingredient (s) with its (their) quantity (ies) per unit dose is (are) specified		
	inactive ingredient (s) with its (their) quantity (ies) per unit dose is (are) specified		
	Specifications of Active & inactive ingredients are mentioned (e.g. in house specification , USP ,EU ,JP ,British pharmacopeia)		
	The overage should be mentioned		
	Identical to CPP & CTD		
	API name is specified (the INN, scientific, pharmacopoeia, common name accompanied by its salt or hydrate form (if any))		
12	**<u>For Imported products:</u> CPP issued by Competent Authorities in Country of Origin**		
	Original		
	Authenticated from Embassy		
	Valid		
	The Arab Republic of Egypt is mentioned as Importing Country		
	Number of product license is specified		
	Date of issue is specified		
	Dosage form (s) and Strength (s) are specified.		
	License Holder (address, city, country) is specified		
	Role of License Holder is specified		
	Manufacturer of solvent should be mentioned (if different from manufacturer of the finished product)		
	Product marketed in the COO		
	Manufacturing sites involved in the manufacturing of the product should be mentioned with its role (Finished product, Primary Packager, Secondary Packager, Batch releaser, Solvent manufacturer)		
	Good Manufacturing Practice (GMP) of the manufacturer is specified		
	Pack Presentation and pack size(s) of the Product is (are) specified (could be as an attachment)		

	Active Ingredient(s) by its salt or hydrate form (if any) with its (their) quantity (ies) per unit dose is (are) specified		
	Inactive Ingredient(s) with its (their) quantity (ies) per unit dose is (are) specified (could be as an attachment)		
	Shelf-life of the Product is specified (could be as an attachment)		
	Storage Conditions of the Product is specified (could be as an attachment)		
	SPC or package insert of the product (could be as an attachment)		
	If the Name of the product may change in Egypt, copy of CPP from any reference country with the name targeted to be in Egypt should be submitted (technical committee decision on 22/5/2014).		
13	**GMP of all the manufacturers involved in the production process** **(Manufacturer of active substance, Manufacturer of finished, Manufacturer of solvent, primary packager, Secondary packager and Batch Releaser)**		
	Authenticated (From Embassy) original or true copy (authentication on the certificate)		
	Valid		
	The name of plant by its address should be specified		
	The date of the last inspection should be specified		
	The invalidation date should be mentioned		
	The production lines are specified		
14	**Copy of Manufacturing license for <u>All manufacturing sites</u>**		
	Valid		
	Authenticated (From Embassy) original or true copy (authentication on the certificate)		
	The name of plant by its address should be specified		
	The invalidation date should be mentioned		
	The production lines are specified		
	Issued from the health authority of the specified country		
15	**TSE/BSE free declaration for products contain animal-derived materials used at any stage in the manufacturing**		
	Original letter from the company mentioning that Product is TSE free and mentioning Countries of origin of source materials		
16	**Certificate of suitability (applicable in case the presence of animal materials susceptible to transmit TSE)** **if Not applicable: Supplier official declaration(s) stating the safety of the substances used in the product manufacturing**		
17	**<u>In cases of imported bulk products and packing in local manufacturing site:</u>** the packaging contract between the foreign manufacturing company and the local packaging site should submitted		

18	**<u>In case of Toll manufacturing:</u> the manufacturing contract specifying the intended product should be submitted should be certified as truly signed**		
19	**<u>For Imported products:</u> List of the countries where the product is registered & marketed including trade name in each country & marketing status:** Should be notarized from the chamber of commerce or its equivalent in the country of origin and certified from the Egyptian embassy abroad		
20	**Outer label of the Product (1 original pack and 7 layouts)**		
	Trade Name is typed in the same way and style (identical to the CPP, approved insert or SPC & stability approval)		
	The Pharmaceutical dosage Form (identical to the CPP)		
	Composition of all inactive ingredients (as mentioned on the pack of the COO)		
	Active ingredients or generic name with their quantities or strengths are mentioned on the Outer pack (identical to the CPP, approved insert or SPC & stability approval)		
	Manufacturer of the finished product & solvent (if needed) with their address		
	Route of administration (e.g.: IV, IM. SC, infusion…)		
	Concentration (with equivalence).		
	If the dosage form or the product is related to special population (infant, Children, adults), it should be mentioned on the pack		
	Different concentration should have different printing color for easier identification		
	Number of Units of the dosage form present in the container or inquiry approval (as pricing approval)		
	Batch number is mentioned on the Outer pack		
	Manufacturing date is mentioned on the Outer pack		
	Expiry date is mentioned on the Outer pack		
	Storage conditions are mentioned on the Outer pack (as stability approval)		
	Warning for all drugs "Keep out of reach of children" must be mentioned / & In case of presence of some ingredients (for exp.: Aspartame. Sunset yellow, Benzalkonium chloride, Benzyl alcohol and others) they should be mentioned		
	English speaking pack (in addition to Arabic language in case of local products)		
21	**Inner Label of the product (1 original label and 7 layouts)**		
	The manufacturer and / or the license holder by their logo should be specified		
	The trade name		
	Generic Name with strength		
	Batch number is specified		
	Manufacturing date is specified		
	Expire date is specified		

22	**Official declaration (from scientific office or from manufacturer) stating the type of the submitted pack (COO pack , country-specific pack , international pack …..etc.) with differences**		
23	**Official declaration stating the relationship between Manufacturer, Importer and Distributor that Should be notarized from the chamber of commerce or its equivalent in the country of origin and Authenticated from the Egyptian embassy abroad**		
24	**Copy of Agency or distribution contract that Should be notarized from the chamber of commerce or its equivalent in the country of origin and Authenticated from the Egyptian embassy abroad & submit original for review**		
25	**<u>In case of imported bulk naked vial</u> that manufactured abroad and packed locally, the following is required:** **- Copy of packaging contract between the importing company & local manufacturing** **- Original Authorization letter from the abroad mother company to the importing for product registration and packaging with a local licensed packaging site (Should be notarized from the chamber of commerce or its equivalent in the country of origin and Authenticated from the Egyptian embassy abroad & submit original for review)**		
26	**Letter of Acknowledgment of full responsibility for storing the raw materials and for all stages of manufacturing and for the product's conformity with the technical specifications until the completion of distribution**		
27	**Submitting a pledge acknowledging his commitment to the provisions of the Intellectual Property Protection Law No. 82 of 2002**		
28	**Submit the updated scientific office license, importer register for all importers, Updated Storage License for all Storage sites, updated Tax card & Commercial register**		
29	**Product insert**		

Second: Ingredients & packaging materials			
A) Active ingredients:			
30	**Specifications of the active ingredients and the relevant tests.**		
31	**Certificate of Analysis (one COA for each manufacturing site)**		
	Original		
	Signed by the Company or the concerned center or laboratory that held the analysis		
	Stamped by the Company or the concerned center or laboratory that held the analysis		
	Product name, strength and form are specified		
	Manufacturing date is specified		
	Expiry date is specified		
	Batch number is specified		
B) Excipients:			
32	**Specifications of the inactive ingredients and the relevant tests.**		
33	**Certificate of Analysis**		
	Signed by the Company or the concerned center or laboratory that held the analysis		
	Stamped by the Company or the concerned center or laboratory that held the analysis		
	Product name, strength and form are specified		
	Manufacturing date is specified		
	Expiry date is specified		
	Batch number is specified		
34	**Supplier name & origin**		
35	**If the blood derivatives as excipients the company submit:** - plasma source certificate - HIV-1, HIV-2, HBsAG, HCV freedom certificate for the plasma **<u>If the blood derivative manufacturer is not approved in Egypt</u> a commitment letter that the supplier for blood derivate will inform the applicant with any information related to safety and efficacy of the product**		
C) Finished product			
36	**Specifications of the finished product and the relevant tests**		
37	**Certificate of Analysis of finished products for each manufacturing site (if present)**		
	Original & valid while submission		

	Signed by the Company or the concerned center or laboratory that held the analysis (**Authenticated and Notarized**)		
	Stamped by the Company or the concerned center or laboratory that held the analysis		
	Product name, strength and form are specified		
	Manufacturing date is specified		
	Expiry date is specified		
	Batch number is specified		
38	**COA of solvent for each manufacturing site (if present) Authenticated and Notarized)**		
39	**CD containing Complete & updated CTD**		
40	**If the materials entering in the product formulation are from blood derivatives, the following will be presented:**		
	Plasma Master file that contain information of plasma source starting from collection passing all production process & in-process control & Viral safety		
	Official certificates declaring plasma source (legalized in case of blood products active substance)		
	HV-1,HV-2,HBsAG,HCV freedom legalized certificate for the plasma		
	Copy of Certificate of release from Health authority (Drug substance only)		
File II: Inspection file			
1	**Site master file (for Manufacturer of active substance, Manufacturer of finished, Manufacturer of solvent, primary & secondary packager and batch releaser) including:**		
	•Covering letter from the License holder declaring that the submitted SMF is the most updated and approved signed, stamped and Authorized •Relevant Premises & utilities information about each site. •Current status of the manufacturing site(s) with respect to current good manufacturing practice (cGMP) requirements. •Legible color printouts of water treatment and air-handling systems, including pipeline and instrumentation drawings in A3 or A2 format. •List of all the products and dosage forms manufactured on- the same site especially same production lines.		
2	**GMP of all the manufacturers involved in the production process & Manufacturing license indicating production lines** **(Active substance, Manufacturer of finished, Manufacturer of solvent, primary packager)**		

3	- Latest full inspection report(s) for inspection performed by a stringent regulatory authority in the past three years and their outcomes. -Last Annual product review. -One completed batch manufacturing and packaging record. -List of any recalls in the past three years related to products with quality defects (if found). -Any warning letter or equivalent regulatory action (production-line specific) (if found).		
4	CPP of the product		
5	Manufacturing process for Active substance and Finished product (and solvent, if present)		
6	Manufacturing process validation for Active substance and Finished product (and solvent, if present)		
7	Cold chain Storage & transportation procedures.		
8	Copy of inquiry & List of each site where the product (Drug Substance and Drug Product), if authorized, is or would be manufactured.		
9	Copy of application form for biological products		
File III: Quality file			
1	Copy of inquiry approval		
2	Copy of application form for biological products		
3	Summary protocol (for blood products & vaccines)		
4	Detailed SOPs of analytical procedures of the finished product		
5	Complete CTD		
6	Certificate of Analysis for Drug substance & Finished product & solvent (if solvent present)		
7	Any EDA approval or exemption for the concerned product as supporting documents (example: technical committee approvals, Scientific approvals, inspection approvals for non-reference country manufacturing sites,……)		

File IV : Stability Dossier Documents			
A. Requirements of Stability file for Imported Biological Products			
1	**Administrative documents**		
2	**Cover letter clarifying the purpose of submission**		
3	**Summary sheet (Word + signed & stamped PDF)**		
4	**Updated inquiry approval**		
5	**Valid legalized C.P.P that includes:** - Trade name, dosage form, active ingredients & composition - Stating the license holder, manufacturers of the finished product.		
6	**SmPC (Must be in English. If not, official translation is required)** *- If SmPC is not attached to the CPP, then a declaration letter from global is required to confirm that this the most updated version marketed in the country of origin, with commitment to submit the legalized SmPC within 6 months from the date of commitment.* *N.B.: (If the CPP is from EMA or FDA, no legalization is needed).* *- If SmPC isn't available, then Patient Information Leaflet (PIL) from Mother Company is required.* *- 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. N.B.: (If the CPP is from EMA or FDA, no legalization is needed).* *- If temperature storage is at (25 °C), a commitment from the applicant to store the product in warehouses and pharmacies at temperature not exceeding (25 °C) is required.*		
7	**Signed & stamped declaration from global with the stability testing site for the submitted stability studies, mentioning the batch numbers.**		
8	**Composition:** • Composition from the C.T.D section "3.2.P.1" - It should be similar to Composition in C.P.P. - If the composition isn't present in C.P.P, so legalized composition is required. - Signed & stamped composition on company papers - Mentioning trade name, dosage form, strength - It should include a table that contain:		

	(Function, reference to standard & grades (if applicable) of each ingredient)		
9	**If the responsibilities of the manufacturers from CTD section "3.2.P.3.1" does not clarify the manufacturers, Packagers (primary & secondary), batch releaser & stability testing site, than a signed & stamped declaration letter is required from Mother Company**.		
10	**Commitment from the applicant that all the data are authentic & accurate(تعهد صحة البيانات).**		
11	**Pack layout (marketed in country of origin).**		
12	**Full Module 3 (For the drug substance & the drug product).**		
B. Requirements for the drug substance			
13	**Certificate of analysis (C.O.A) of recently manufactured drug substance (5-10 years):** - Clarifying the manufacturer name & address, - With manufacturing & expiry dates (corresponds to the required shelf life) and tested parameters following the same specifications as in section "3.2.S.4.1".		
14	**Stability studies:** - Stability studies (Long-term & accelerated) & its protocol of 3 (pilot or production scale) batches carried out in the intended drug substance container-closure system, containing manufacturing site, manufacturing date and tested parameters that follows the same specifications as in section "3.2.S.4.1".		
15	N.B: - If the drug substance has more than one manufacturer, 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 and batch numbers (in case of on-going stability on production batches). - The stability protocol used for studies on production scale batches should be the same as that for the pilot batches, unless otherwise scientifically justified. - For imported products from non-reference countries only: Assay chromatograms should be submitted for each time point (in case of HPLC analysis) or (last time interval by HPLC in case of any other method of analysis) for all batches included in all stability studies.		
C. Requirements for the drug product:			

16	Certificate of analysis "C.O. A" of recently manufactured **finished product** (5-10 years): - Signed and Stamped - Clarifying the manufacturer and primary packager. - With manufacturing & expiry dates (corresponds to the required shelf life) and tested parameters that follows specifications as in CTD section "3.2.P.5.1". - If the product is powder: the color of powder before & after reconstitution should be mentioned in the COA and specifications, unless otherwise scientifically justified.		
17	Certificate of analysis "C.O. A" of recently manufactured **solvent** (5-10 years), if applicable.		
18	Stability studies: - **Long-term stability** study & its protocol of 3 (pilot or production scale) batches - **Accelerated stability** study & its protocol of 3 (pilot or production scale) batches - **In-use** :(after reconstitution / after dilution) stability study on at least two pilot scale batches (The age of one batch is at the beginning of shelf-life and the age of the other near the end of shelf-life) - Stability of solvent: long-term and accelerated & its protocol of 3 (pilot or production scale) batches (If applicable). - **Photo-stability study** on at least one pilot scale batch. - **For Biosimilar products**: Side-by-side accelerated and stress studies carried out using a representative number of batches, comparing the biosimilar product to the reference product are mandatory to determine the similarity of the products by showing comparable degradation profiles. Any differences concerning the stability profile of the biosimilar product when compared to the reference product should be justified.		
19	N.B: **- The stability studies must be performed as follows:** - *On the exact composition as that in the submitted CPP.* - *Carried out in the intended commercial drug product container-closure system* - *Contain name of the manufacturing site & primary packager* - *Contain manufacturing date (within 5- 10 years)* - *Contain tested parameters that follow specifications as in CTD section "3.2.P.5.1".*		

	- If 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. - If FP has more than one manufacturer/ primary packager, all stability studies must be submitted from each manufacturer/ primary packager. - Stability studies should include samples maintained in the inverted or horizontal position (i.e., in contact with the closure), as well as in the upright position. (worst scenario) - If the scale of batches (production / pilot) is not stated in the CTD, then a 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 and batch numbers (in case of on-going stability on production batches). - The stability protocol used for studies on production scale batches should be the same as that for the pilot batches, unless otherwise scientifically justified. - For imported products from non-reference countries only: Assay chromatograms should be submitted for each time point (in case of HPLC analysis) or (last time interval by HPLC in case of any other method of analysis) for all batches included in all stability studies.		
D. Requirements for Inspection and Stability file of Local Biological Products			
20	**- Inspection Requirements:** 1. Cover letter clarifying the purpose of submission. 2. Summary sheet (signed & stamped pdf). 3. Certificate of responsibility stamped from the site at which the stability study was performed (signed by Q.C. analyst, Q.C. Head & Q.A Head). - In case of performing the stability study in place rather than the manufacturer, attach the following: - Contract between the applicant and the place at which the stability study was performed (Authenticated by the legal counsel of EDA) - Copy of the license of the place at which the stability study was performed. 4. Finished product specification: - Tested parameters: Appearance and description, Identity, Purity and		

	impurities, Potency, Sterility test or alternatives, etc…. - Mentioning method of analysis and reference for each method. - Justification of specification 5. Method of analysis. (detailed procedures) 6. Validation of analytical procedure of active ingredient assay and related substances along with HPLC chromatograms for each parameter (in case of HPLC analysis) 7. Stability Studies: a) Stability Summary and Conclusion - Summarizing the following details for each study (Long-term, accelerated, In-use, after reconstitution, after dilution, photo-stability or solvent): - Storage conditions (temperature & relative humidity) and duration of the study. - Details of tested batches (Manufacturing date, manufacturer & primary packager of finished product, pack details, batch scale (pilot or production)) - Study protocol in tabular format (Tested attributes as per specifications and the frequency of testing for each test) - Summary of test results and justification for any out-of-specification results. - Conclusion for shelf-life and storage conditions. b) Post-approval Stability Protocol and Stability Commitment. - In case of issuing stability approval for pilot scale batches: a commitment 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 production scale batches should be the same as that for the pilot batches, unless otherwise scientifically justified. c) Stability Data Tables and assay chromatograms for each time point (in case of HPLC analysis) or (last time interval by HPLC in case of any other method of analysis) for all batches included in all stability studies: - Each table should include the study type (long-term, accelerated, In-use, after reconstitution, after dilution, photo-stability), trade name & strength, batch number and pack size. - The shelf-life will be based on the stability data submitted (12 months data = shelf-life of 12 months, 18 months data = shelf-life of 18 months….etc.). • **N.B:** - 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		

	manufacturer 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 production scale batches should be the same as that for the pilot batches, unless otherwise scientifically justified. **- Required number of batches for each study:** 1- **Long-term and accelerated studies** on 3 (pilot or production) batches. 2- **In-use** :(after opening / after reconstitution / after dilution) stability study on at least two pilot scale batches. (The age of one batch is at the beginning of shelf-life and the age of the other near the end of shelf-life). 3- **Photo-stability study** on at least one pilot scale batch. 4- **Long-term stability study** of solvent on 3 (pilot or production) batches. - The stability studies must be performed on the exact composition as that attached to transfer letter - In case of the finished product has more than one strength, container type or size, stability study must be done on 3 batches 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). - **Additional studies in case of biosimilar product**: Side-by-side accelerated and stress studies carried out using a representative number of batches, comparing the biosimilar product to the reference product are mandatory to determine the similarity of the products by showing comparable degradation profiles. Any differences concerning the stability profile of the biosimilar product when compared to the reference product should be justified.		
File V : Scientific File Documents			
A- Administrative Part			
1	Covering Letter to Biological Manager (signed and stamped on company Letter head)		
2	List of countries where the product is being registered and marketed indicating the registration number & date in each country		
3	Copy of CPP in addition to SmPC		
4	Product Insert		
5	inner leaflet		
6	Copy of Reference (BNF 61,Vidal,Swiss Compendium, Rote liste)		

7	Composition signed and stamped		
8	Approved price (*or suggested price & pricing receipt (signed and stamped on company Letter head) in case of 820 products, exemption & fast track)*		
9	if plasma derived product (plasma master file &viral inactivation)		
11	CD containing Module 2 , Module 4 and Module 5 and contents of all the scientific dossier		
12	Inquiry Approval		
B-Plasma Master File			
13	Cover Letter (signed and stamped with all registered and under registration products in Egypt)		
14	Health authority approval on plasma master file		
15	Certificate of plasma release from national regulatory released same year of PMF submission.		
16	Proof of Payment		
17	Soft copy of Plasma Master File		
18	PMF approval from health authority & viral inactivation, certificate of release from Health Authority, certificate of analysis (plasma derived product as active or excipient)		
C- Package leaflet			
19	**In Case of imported reference country** **- Innovator:** 1. Insert marketed in Country of Origin (ENGLISH) (Numbered) 2. Insert marketed in Country of Origin (ARABIC), translated from a Certified translation office, except (Vaccines- Immunosuppressant- IV infusion products- Hospital use only - Immunological products- Contrast agents except iodinated one) 3. Covering Letter to Biological Manager (signed and stamped on company Letter head 4. SmPC "summary of product characteristics" and/or CCDS "company core data sheet" 5. CPP attached insert 6. Declaration from the mother company that the submitted insert is the most updated & marketed in COO **- Biosimilar product:** 1- cover letter for requesting insert submission & approval 2- Insert marketed in Country of Origin (ENGLISH) (Numbered)		

	3- Insert marketed in Country of Origin (ARABIC), translated from a Certified translation office, except (Vaccines- Immunosuppressant- IV infusion products- Hospital use only - Immunological products- Contrast agents except iodinated one) 4- innovator product insert 5- Commitment from the mother company that the submitted insert is the most updated one & marketed in COO 6- declaration from the applicant states the COO that relay for the product indication 7- CPP with attached insert		
20	**In case of imported product from non-reference country - Standalone product:** 1- cover letter for requesting insert submission & approval 2- Insert marketed in Country of Origin (ENGLISH) (Numbered) 3- Insert marketed in Country of Origin (ARABIC), translated from a Certified translation office, except (Vaccines- Immunosuppressant- IV infusion products- Hospital use only - Immunological products- Contrast agents except iodinated one) 4- CPP with attached insert 5- Reference model insert نموذج النشرة المرجعي التى قامت الشركة بكتابة نشرتها بناءاً عليه 6- Scientific reference (Trials & Literature) : المرجع العلمي لكافة البيانات العلمية المذكورة بالنشرة من خلال الدراسات التى قامت بها الشركة و/او الliterature) 7- Commitment from the mother company that the submitted insert is the most updated one & marketed in COO **- Biosimilar Product** 1- cover letter for requesting insert submission & approval 2- Insert marketed in Country of Origin (ENGLISH) (Numbered) 3- Insert marketed in Country of Origin (ARABIC), translated from a Certified translation office, except (Vaccines- Immunosuppressant- IV infusion products- Hospital use only - Immunological products- Contrast agents except iodinated one) 4- CPP with attached insert 5- Commitment from the mother company that the submitted insert is the most updated one & marketed in COO 6- declaration from the applicant states the reference country that relay for the product indication		

	7- innovator product insert		
21	Comparative table between reference insert and Proposed insert (in case of insert is different from CPP Insert Or biosimilar (non-reference country)		
22	Comparative table between current & proposed insert and scientific reference for every part in the insert (For local products)		
23	SmPC or SmPC like information Clean PDF copy to be published on EDA website After approval		
24	CD containing all the contents of the dossier		
25	**In case of local products:** **- Standalone product:** 1. cover letter for requesting insert submission & approval 2. proposed Insert (ENGLISH) (Numbered) 3. proposed Insert (ARABIC), translated from a Certified translation office, except (Vaccines- Immunosuppressant- IV infusion products- Hospital use only - Immunological products- Contrast agents except iodinated one) 4. Reference model insert 5. Scientific reference (Trials & Literature) **- Biosimilar Product** 1. cover letter for requesting insert submission & approval 2. proposed Insert (ENGLISH) (Numbered) 3. proposed Insert (ARABIC), translated from a Certified translation office, except (Vaccines- Immunosuppressant- IV infusion products- Hospital use only - Immunological products- Contrast agents except iodinated one) 4. innovator product insert 5. declaration from the applicant states the reference country that relay for the product indication 6. Scientific References (clinical studies or literature)		
D- Albumin used as stabilizer Requirements			
26	EMA Approval if the plasma master file has an approval from EMA		
27	Certificate of batch release of health authority for this albumin used as a stabilizer.		
28	Declaration from the MAH declares the trade name of the albumin used as a stabilizer.		
29	GENERAL INFORMATION (SUMMARY) 1- Plasma-Derived Products' List		

	2- Overall Safety Strategy 3- General Logistics		
30	**TECHNICAL INFORMATION ON STARTING MATERIALS** 1- PLASMA ORIGIN 2- Information on centers or establishments in which blood/ plasma collection is carried out, including inspection and approval, and epidemiological data on blood transmissible infections 3- Information on centers or establishments in which testing of donations and plasma pools is carried out, including inspection and approval status 4 -Selection/exclusion criteria for blood/plasma donors 5- System in place which enables the path taken by each donation to be traced from the blood/plasma collection establishment through to finished products and vice versa		
31	**Plasma Quality and Safety** 1 Compliance with European Pharmacopoeia Monographs. 2 Testing of blood/plasma donations and pools for infectious agents, including information on test methods and, in the case of plasma pools, validation data on the tests used .		
32	Technical characteristics of bags for blood and plasma collection, including information on anticoagulant solutions used.		
File VI- PV requirements			
33	Covering Letter to EPVC Manager (signed and stamped on company Letter head)		
34	The latest periodic safety update report (PSUR) in PBRER format covering at least the last 3 years OR separate PSURs covering at least the last 3 years or addendum to clinical overview (Most updated)		
35	**<u>Imported products:</u>** Soft copy searchable text PDF: 1. Delegation letter "التفويض خطاب" 2. Updated Cover letter (on the company paper of the PV representative/agent/scientific office) clarifying the Date of the submission (not exceeding 2 days before the submission)/ Directed to the Manager of General Administration of Pharmaceutical Vigilance/ Name of the product /Name of the Active substance/ context of submission/ Name of the MAH/ Content of the submission/ Actual signature of the QPPV or LSR “signature by QPPV or LSR (not print screen)”- “Accepted Digital/Electronic signature”/company stamp		

	3. صورة ضوئية من أصل ايصال سداد + "pink receipt" صورة ضوئية من أصل ايصال سداد "yellow receipt" لكل **(Application number)** مقابل الخدمات المقدمة من الادارة المركزية للرعاية الصيدلية مختوما بختم اليقظة بقيمة 1000 جنيه مصري" لا تشمل ضريبة القيمة المضافة "عن طلب تقييم التقرير /التقارير المجمعة الدورية لمأمونية المستحضر (PSUR) طبقا لقرار السيد الاستاذ الدكتور رئيس الهيئة رقم 99 / 2022 4. صورة ضوئية من أصل ايصال سداد + "pink receipt" صورة ضوئية من أصل ايصال سداد "yellow receipt" لكل **(Application number)** مقابل الخدمات المقدمة من الادارة المركزية للرعاية الصيدلية مختوم ا بختم اليقظة بقيمة 1000 جنيه مصري" لا تشمل ضريبة القيمة المضافة "عن طلب تقييم خطة إدارة المخاطر (RMP)طبقا لقرار السيد الاستاذ الدكتور رئيس الهيئة رقم2021 / 6 (موضحا بالايصال اسم المستحضر/المادة الفعالة/التركيز – الشكل الصيدلي/اطار التقديم / اسم الشركة صاحبة المستحضر) 5. Confirmation e-mail by PSMF reception portal (as an evidence of submission of the PSMF of the company to EPVC) **OR** Latest released valid PSMF assessment report "for all concerned parties" 6. Updated version of Summary of PSMF(s)/PSSF 7. In case of submission by PV representative or agent, the PV rep./agent should submit an authorized and authenticated (by all concerned parties) PV agreement between the MAH & the service provider covering all the PV activities 8. The latest Periodic Safety Update Report (PSUR) in PSUR format "as per GVP for Arab Countries V.2.0" covering at least the last 3 years OR separate PSURs covering at least the last 3 years. 9. The most updated "EU/Global/Core-Risk Management Plan (RMP)"of the product. 10. The Egyptian display of EU-RMP		
36	**<u>Local Product:</u>** Soft copy searchable text PDF: 1. Delegation letter تفويض خطاب 2. Updated Cover letter (on the company paper of the PV representative/agent/scientific office) clarifying the Date of the submission (not exceeding 2 days before the submission)/ Directed to the Manager of General Administration of Pharmaceutical Vigilance/ Name of the product /Name of the Active substance/ context of submission/ Name of the MAH/ Content of the submission/ Actual		

	signature of the QPPV “signature by QPPV (not print screen)”/company stamp 3. صورة ضوئية من أصل ايصال سداد + "pink receipt“ صورة ضوئية من أصل ايصال سداد ”yellow receipt“ لكل **(Application number)** مقابل الخدمات المقدمة من الادارة المركزية للرعاية الصيدلية مختوم ا بختم اليقظة بقيمة 500 جنيه مصري" لا تشمل ضريبة القيمة المضافة "عن طلب تقييم خطة إدارة المخاطر (RMP)طبقا لقرار السيد الاستاذ الدكتور رئيس الهيئة رقم2021 / 6 (موضحا بالايصال اسم المستحضر/المادة الفعالة/التركيز – الشكل الصيدلي/اطار التقديم / اسم الشركة صاحبة المستحضر) 4. Confirmation e-mail by PSMF reception portal (as an evidence of submission of the PSMF of the company to EPVC) or Latest released valid PSMF assessment report “for all concerned parties” 5. Updated version of Summary of PSMF(s)/PSSF 6. In case of submission by PV representative, the PV rep should submit an authorized and authenticated (by all concerned parties) PV agreement between the MAH & the service provider covering all the PV activities 7. Egyptian-Risk Management Plan (RMP)"of the product. 8. The latest Periodic Safety Update Report (PSUR) in PBRER format of the imported ready to fill final bulk covering at least the last 3 years** ** يتعين على الشركة تقديم صورة ضوئية من أصل ايصال لكل ”yellow receipt“ سداد ايصال أصل من ضوئية صورة +"pink receipt“ سداد **(Application number)** مقابل الخدمات المقدمة من جنيه 0010 بقيمة اليقظة بختم ا مختوم الصيدلية للرعاية المركزية الادارة التقارير /التقرير تقييم طلب عن "المضافة القيمة ضريبة تشمل لا" مصري الاستاذ السيد لقرار طبقا (PSUR) المستحضر لمأمونية الدورية المجمعة / 99 رقم الهيئة رئيس الدكتور		

Annex II

Requirements of Stability file for Imported Biological Products

1. Administrative documents

1. Cover letter clarifying the purpose of submission.
2. Summary sheet ((Word) + signed & stamped pdf.)
3. Box Approval (in case of 343 or 820).
4. Valid legalized C.P.P that includes:
   - Trade name, dosage form, active ingredients & composition
   - Stating the license holder, manufacturers of the finished product.
5. SmPC (Must be in English. If not, official translation is required)
   - If SmPC is not attached to the CPP, then a declaration letter from global is required to confirm that this

the most updated version marketed in the country of origin, with commitment to submit the legalized SmPC within 6 months from the date of commitment.

N.B.: (If the CPP is from EMA or FDA, no legalization is needed).

   - If SmPC isn't available, then Patient Information Leaflet (PIL) from Mother Company is required.
   - 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.

N.B.: (If the CPP is from EMA or FDA, no legalization is needed).

   - If temperature storage is at (25 °C), a commitment from the applicant to store the product in warehouses and pharmacies at temperature not exceeding (25 °C) is required.

6. Signed & stamped declaration from global with the stability testing site for the submitted stability studies, mentioning the batch numbers.
7. Composition:

• Composition from the C.T.D section "3.2.P.1"

   - It should be similar to Composition in C.P.P.
   - If the composition isn't present in C.P.P, so legalized composition is required.
   - Signed & stamped composition on company papers
   - Mentioning trade name, dosage form, strength
   - It should include a table that contain:

(Function, reference to standard & grades (if applicable) of each ingredient)

8. If the responsibilities of the manufacturers from CTD section "3.2.P.3.1" does not clarify the

manufacturers, Packagers (primary & secondary), batch releaser & stability testing site, than a signed & stamped declaration letter is required from Mother Company.
9. Commitment from the applicant that all the data are authentic & accurate.(تعهد صحة البيانات)
10. Pack layout (marketed in country of origin).
11. Full Module 3 (For the drug substance & the drug product).

2. Requirements for the drug substance:

1. Certificate of analysis (C.O.A) of recently manufactured drug substance (5-10 years):
- Clarifying the manufacturer name & address,
- With manufacturing & expiry dates (corresponds to the required shelf life) and tested parameters following the same specifications as in section "3.2.S.4.1".

2. Stability studies:
- Stability studies (Long-term & accelerated) & its protocol of 3 (pilot or production scale) batches carried out in the intended drug substance container-closure system, containing manufacturing site, manufacturing date and tested parameters that follows the same specifications as in section "3.2.S.4.1".

N.B:
- If the drug substance has more than one manufacturer, 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 and batch numbers (in case of on-going stability on production batches).
- The stability protocol used for studies on production scale batches should be the same as that for the pilot batches, unless otherwise scientifically justified.
- **For imported products from non-reference countries only:** Assay chromatograms should be submitted for each time point (in case of HPLC analysis) or (last time interval by HPLC in case of any other method of analysis) for all batches included in all stability studies.

3. Requirements for the drug product:

1. Certificate of analysis "C.O. A" of recently manufactured finished product (5-10 years):
- Signed and Stamped
- Clarifying the manufacturer and primary packager.
- With manufacturing & expiry dates (corresponds to the required shelf life) and tested parameters that follows specifications as in CTD section "3.2.P.5.1".
- **If the product is powder:** the color of powder before & after reconstitution should be mentioned in the COA and specifications, unless otherwise scientifically justified.

2. Certificate of analysis "C.O. A" of recently manufactured solvent (5-10 years), if applicable.

3. Stability studies:

- **Long-term stability study** & its protocol of 3 (pilot or production scale) batches
- **Accelerated stability study** & its protocol of 3 (pilot or production scale) batches
- **In-use :**(after reconstitution / after dilution) stability study on at least two pilot scale batches (The age of one batch is at the beginning of shelf-life and the age of the other near the end of shelf life)
- **Stability of solvent**: long-term and accelerated & its protocol of 3 (pilot or production scale) batches (If applicable).
- **Photo-stability study** on at least one pilot scale batch.
- **For Biosimilar products:** Side-by-side accelerated and stress studies carried out using a representative number of batches, comparing the biosimilar product to the reference product are mandatory to determine the similarity of the products by showing comparable degradation profiles.

Any differences concerning the stability profile of the biosimilar product when compared to the reference product should be justified.

N.B:

- The stability studies must be performed as follows:

- On the exact composition as that in the submitted CPP.
- Carried out in the intended commercial drug product container-closure system
- Contain name of the manufacturing site & primary packager
- Contain manufacturing date (within 5- 10 years)
- Contain tested parameters that follow specifications as in CTD section "3.2.P.5.1".

- If 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.
- If FP has more than one manufacturer/ primary packager, all stability studies must be submitted from each manufacturer/ primary packager.
- Stability studies should include samples maintained in the inverted or horizontal position (i.e., in contact with the closure), as well as in the upright position. (worst scenario)
- If the scale of batches (production / pilot) is not stated in the CTD, then a 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 and batch numbers (in case of on-going stability on production batches).
- The stability protocol used for studies on production scale batches should be the same as that

for the pilot batches, unless otherwise scientifically justified.

- **For imported products from non-reference countries only:** Assay chromatograms should be submitted for each time point (in case of HPLC analysis) or (last time interval by HPLC in case of any other method of analysis) for all batches included in all stability studies.

Requirements for Inspection and Stability file of Local Biological Products

A. Administrative documents

1. Cover letter clarifying the purpose of submission.
2. Summary sheet (Word) + signed & stamped pdf.
3. Box Approval (in case of 343 or 820).
4. Certificate of responsibility stamped from the site at which the stability study was performed (signed by Q.C. analyst, Q.C. Head & Q.A Head).

- **In case of** performing the stability study in place rather than the manufacturer, attach the following:

- Contract between the applicant and the place at which the stability study was performed (Authenticated by the legal counsel of EDA)
- Copy of the license of the place at which the stability study was performed.

B. Requirements for finished product:

1. Composition:
   - Stamped and signed on applicant paper
   - Mentioning trade name, dosage form, strength
   - Mentioning function, reference to standard & grades (if applicable) of each ingredient.
2. Description of Manufacturing Process and Process Controls (name, dosage form)
3. Certificate of analysis "C.O. A" of 3 batches of finished product (and solvent, if applicable):
   - Signed and Stamped
   - It should mention trade name, strength, dosage form, pack size & description, the manufacturer & primary packager.
   - With manufacturing & expiry dates (corresponds to the required shelf life) and tested parameters as stated in specifications submitted in the file.
   - **If the product is powder:** the color of powder before & after reconstitution should be mentioned in the COA and specifications.
4. Declaration with the shelf-life & storage conditions of the product:
   - Signed &stamped from the manufacturer and to use the same wording of the proposed conditions as the reference product insert marketed in Egypt.
   - 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 description:

- Signed &stamped from the manufacturer
- Mentioning color, material of each component of primary pack, no. of units per secondary pack & its description.

6. Sampling record (محضر السحب), include the following:
- Batch no. (same as in stability study)
- Batch scale (pilot or production)
- Manufacturing date of batches

7. Reference product insert marketed in Egypt.
8. Sample.
9. Finished product specification:
- Tested parameters: Appearance and description, Identity, Purity and impurities, Potency, Sterility test or alternatives, etc….
- Mentioning method of analysis and reference for each method.
- Justification of specification

10. Method of analysis. (detailed procedures)
11. Validation of analytical procedure of active ingredient assay and related substances along with HPLC chromatograms for each parameter (in case of HPLC analysis)
12. Stability Studies:

a) Stability Summary and Conclusion

⇨ Summarizing the following details for each study (Long-term, accelerated, In-use, after reconstitution, after dilution, photostability or solvent):

- Storage conditions (temperature & relative humidity) and duration of the study.
- Details of tested batches (Manufacturing date, manufacturer & primary packager of finished product, pack details, batch scale (pilot or production))
- Study protocol in tabular format (Tested attributes as per specifications and the frequency of testing for each test)
- Summary of test results and justification for any out-of-specification results.
- Conclusion for shelf-life and storage conditions.

b) Post-approval Stability Protocol and Stability Commitment.

- In case of issuing stability approval for pilot scale batches: a commitment 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 production scale batches should be the same as that for the pilot batches, unless otherwise scientifically justified.

c) Stability Data Tables and assay chromatograms for each time point (in case of HPLC analysis) or (last time interval by HPLC in case of any other method of analysis) for all batches included in

all stability studies:
- Each table should include the study type (long-term, accelerated, In-use, after reconstitution, after dilution, photostability), trade name & strength, batch number and pack size.
- The shelf-life will be based on the stability data submitted (12 months data = shelf-life of 12 months, 18 months data = shelf-life of 18 months….etc.).

• **N.B:**

➢ 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 manufacturer 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 production scale batches should be the same as that for the pilot batches, unless otherwise scientifically justified.

➢ Required number of batches for each study:

1- Long-term and accelerated studies on 3 (pilot or production) batches.
2- In-use :(after opening / after reconstitution / after dilution) stability study on at least two pilot scale batches. (The age of one batch is at the beginning of shelf-life and the age of the other near the end of shelf-life).
3- Photo-stability study on at least one pilot scale batch.
4- Long-term stability study of solvent on 3 (pilot or production) batches.

➢ The stability studies must be performed on the exact composition as that attached to transfer letter

➢ In case of the finished product has more than one strength, container type or size, stability study must be done on 3 batches 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).

➢ **Additional studies in case of biosimilar product:** Side-by-side accelerated and stress studies carried out using a representative number of batches, comparing the biosimilar product to the reference product are mandatory to determine the similarity of the products by showing comparable degradation profiles. Any differences concerning the stability profile of the biosimilar product when compared to the reference product should be justified.

C. Requirements for the drug substance:

- 1موافقة استيرادية سارية

2- A commitment letter from the applicant mentioning:

➢ Drug substance manufacturer name & full address

- Batch number of finished product batches.

3- A declaration letter from the drug substance manufacturer clarifying:

- The stability testing site (name & address) mentioning drug substance batch numbers.

4- Full S-Part from Module 3.

5- A commitment from the applicant that the submitted S-Part is authentic & accurate. (تعهد صحة البيانات)

6- C.O.A of recently manufactured drug substance:

- Clarifying the manufacturer name & address
- With manufacturing & expiry dates (corresponds to the required shelf life) and tested parameters following the same specifications as in section "3.2.S.4.1".

7- Stability Study:

- Stability studies "3.2.S.7.3"and assay chromatograms for each time point (in case of HPLC analysis) or (last time interval by HPLC in case of any other method of analysis) for all batches included in all stability studies (for all batches included in all stability studies):

- Long-term and accelerated stability studies and its protocol of 3 (pilot or production) batches carried out in the intended drug substance container-closure system, containing manufacturing site, manufacturing date and tested parameters that follow the same specifications as in section "3.2.S.4.1", unless otherwise justified.

N.B:

- 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 manufacturer 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 and batch numbers (in case of on-going stability on production batches).
- The stability protocol used for studies on production scale batches should be the same as that for the pilot batches, unless otherwise scientifically justified

Annex III

متطلبات وحدة مأمونية المستحضرات الحيوية في اطار التسجيل واعادة التسجيل

المسار	نوع المستحضر	المتطلبات
تسجيل	مستورد	Soft copy searchable text PDF: 1. Delegation letter "خطاب التفويض" 2. Updated Cover letter (on the company paper of the PV representative/agent/scientific office) clarifying the Date of the submission (not exceeding 2 days before the submission)/ Directed to the Manager of General Administration of Pharmaceutical Vigilance/ Name of the product /Name of the Active substance/ context of submission/ Name of the MAH/ Content of the submission/ Actual signature of the QPPV or LSR "signature by QPPV or LSR (not print screen)"- "Accepted Digital/Electronic signature"/company stamp 3. صورة ضوئية من أصل ايصال سداد "pink receipt" + صورة ضوئية من أصل ايصال سداد "yellow receipt" لكل **(Application number)** مقابل الخدمات المقدمة من الادارة المركزية للرعاية الصيدلية مختوماً بختم اليقظة بقيمة 1000 جنيه مصري "لا تشمل ضريبة القيمة المضافة" عن طلب تقييم التقرير/ التقارير المجمعة الدورية لمأمونية المستحضر (PSUR) طبقاً لقرار السيد الاستاذ الدكتور رئيس الهيئة رقم 2022/99 4. صورة ضوئية من أصل ايصال سداد "pink receipt" + صورة ضوئية من أصل ايصال سداد "yellow receipt" لكل **(Application number)** مقابل الخدمات المقدمة من الادارة المركزية للرعاية الصيدلية مختوماً بختم اليقظة بقيمة 1000 جنيه مصري "لا تشمل ضريبة القيمة المضافة" عن طلب تقييم خطة إدارة المخاطر(RMP) طبقاً لقرار السيد الاستاذ الدكتور رئيس الهيئة رقم 2021/6 (موضحًا بالايصال اسم المستحضر/المادة الفعالة/التركيز - الشكل الصيدلي/اطار التقديم/ اسم الشركة صاحبة المستحضر) 5. Confirmation e-mail by PSMF reception portal (as an evidence of submission of the PSMF of the company to EPVC) **OR** Latest released valid PSMF assessment report "for all concerned parties" 6. Updated version of Summary of PSMF(s)/PSSF 7. In case of submission by PV representative or agent, the PV rep./agent should submit an authorized and authenticated (by all concerned parties) PV agreement

between the MAH & the service provider covering all the PV activities 8. The latest Periodic Safety Update Report (PSUR) in PSUR format "as per GVP for Arab Countries V.2.0" covering at least the last 3 years OR separate PSURs covering at least the last 3 years. 9. The most updated "EU/Global/Core-Risk Management Plan (RMP)"of the product. 10. The Egyptian display of EU-RMP		
Soft copy searchable text PDF: 1. Delegation letter خطاب التفويض 2. Previous license of the product/s 3. Updated Cover letter (on the company paper of the PV representative/agent/scientific office) clarifying the Date of the submission (not exceeding 2 days before the submission)/ Directed to the Manager of General Administration of Pharmaceutical Vigilance/ Name of the product /Name of the Active substance/ context of submission/ Name of the MAH/ Content of the submission/ Actual signature of the QPPV or LSR "signature by QPPV or LSR (not print screen)"- "Accepted Digital/Electronic signature"/company stamp 4. صورة ضوئية من أصل ايصال سداد "pink receipt" + صورة ضوئية من أصل ايصال سداد "yellow receipt" لكل **(File number)** مقابل الخدمات المقدمة من الادارة المركزية للرعاية الصيدلية مختوماً بختم اليقظة بقيمة 1000 جنيه مصري "لا تشمل ضريبة القيمة المضافة" عن طلب تقييم ملحق تحديث المعلومات الإكلينيكية المقدم في إطار إعادة التسجيل (ACO) طبقاً لقرار السيد الاستاذ الدكتور رئيس الهيئة رقم 2022/99، 5. صورة ضوئية من أصل ايصال سداد "pink receipt" + صورة ضوئية من أصل ايصال سداد "yellow receipt" لكل **(File number)** مقابل الخدمات المقدمة من الادارة المركزية للرعاية الصيدلية مختوماً بختم اليقظة بقيمة 1000 جنيه مصري "لا تشمل ضريبة القيمة المضافة" عن طلب تقييم خطة إدارة المخاطر (RMP) طبقاً لقرار السيد الاستاذ الدكتور رئيس الهيئة رقم 2021/6 (موضحًا بالايصال اسم المستحضر/المادة الفعالة/التركيز - الشكل الصيدلي/اطار التقديم/ اسم الشركة صاحبة المستحضر) 6. Confirmation e-mail by PSMF reception portal (as an evidence of submission of the PSMF of the company to		اعادة تسجيل

EPVC) **or** Latest released valid PSMF assessment report "for all concerned parties" 7. Updated version of Summary of PSMF(s)/PSSF 8. In case of submission by PV representative or agent, the PV rep./agent should submit an authorized and authenticated (by all concerned parties) PV agreement between the MAH & the service provider covering all the PV activities 9. The Addendum to clinical overview (ACO): covering the period since the initial marketing authorization or since the last renewal until 90 days prior to renewal submission. 10. The most updated "EU/Global/Core-Risk Management Plan (RMP)"of the product. 11. The Egyptian display of EU-RMP		
Soft copy searchable text PDF: 1. Delegation letter خطاب تفويض 2. Updated Cover letter (on the company paper of the PV representative/agent/scientific office) clarifying the Date of the submission (not exceeding 2 days before the submission)/ Directed to the Manager of General Administration of Pharmaceutical Vigilance/ Name of the product /Name of the Active substance/ context of submission/ Name of the MAH/ Content of the submission/ Actual signature of the QPPV "signature by QPPV (not print screen)"/company stamp 3. صورة ضوئية من أصل ايصال سداد "pink receipt" + صورة ضوئية من أصل ايصال سداد "yellow receipt" لكل **(Application number)** مقابل الخدمات المقدمة من الادارة المركزية للرعاية الصيدلية مختوماً بختم اليقظة بقيمة 500 جنيه مصري "لا تشمل ضريبة القيمة المضافة" عن طلب تقييم خطة إدارة المخاطر(RMP) طبقاً لقرار السيد الاستاذ الدكتور رئيس الهيئة رقم 2021/6 (موضحًا بالايصال اسم المستحضر/المادة الفعالة/التركيز - الشكل الصيدلي/اطار التقديم/ اسم الشركة صاحبة المستحضر) 4. Confirmation e-mail by PSMF reception portal (as an evidence of submission of the PSMF of the company to EPVC) or Latest released valid PSMF assessment report "for all concerned parties" 5. Updated version of Summary of PSMF(s)/PSSF	محلي	تسجيل

6. In case of submission by PV representative, the PV rep should submit an authorized and authenticated (by all concerned parties) PV agreement between the MAH & the service provider covering all the PV activities 7. Egyptian-Risk Management Plan (RMP)"of the product. 8. The latest Periodic Safety Update Report (PSUR) in PBRER format of the imported ready to fill final bulk covering at least the last 3 years** ** وفي هذه الحالة يتعين على الشركة تقديم صورة ضوئية من أصل ايصال yellow"صورة ضوئية من أصل ايصال سداد +"pink receipt"سداد مقابل الخدمات المقدمة من **(Application number)** لكل "receipt الادارة المركزية للرعاية الصيدلية مختوماً بختم اليقظة بقيمة 1000 جنيه مصري "لا تشمل ضريبة القيمة المضافة" عن طلب تقييم التقرير / التقارير طبقاً لقرار السيد الاستاذ (PSUR)المجمعة الدورية لمأمونية المستحضر الدكتور رئيس الهيئة رقم 2022/99		
Soft copy searchable text PDF: 1. Delegation letter خطاب تفويض 2. Previous license of the product/s 3. Updated Cover letter (on the company paper of the PV representative/agent/scientific office) clarifying the Date of the submission (not exceeding 2 days before the submission)/ Directed to the Manager of General Administration of Pharmaceutical Vigilance/ Name of the product /Name of the Active substance/ context of submission/ Name of the MAH/ Content of the submission/ Actual signature of the QPPV "signature by QPPV (not print screen)"/company stamp 4. صورة ضوئية من أصل ايصال سداد "pink receipt" + "yellow receipt" لكل **(File number)** مقابل الخدمات المقدمة من الادارة المركزية للرعاية الصيدلية مختوماً بختم اليقظة بقيمة 1000 جنيه مصري "لا تشمل ضريبة القيمة المضافة" عن طلب تقييم ملحق تحديث المعلومات الإكلينيكية المقدم في إطار إعادة التسجيل (ACO) طبقاً لقرار السيد الاستاذ الدكتور رئيس الهيئة رقم 2022/99، 5. صورة ضوئية من أصل ايصال سداد pink + "yellow receipt" لكل**(File number)** مقابل الخدمات المقدمة من الادارة المركزية للرعاية الصيدلية مختوماً بختم اليقظة بقيمة 500 جنيه مصري "لا تشمل ضريبة القيمة المضافة" عن طلب تقييم خطة إدارة المخاطر (RMP) طبقاً لقرار السيد الاستاذ الدكتور رئيس الهيئة رقم 2021/6		اعادة تسجيل

(موضحًا بالايصال اسم المستحضر/المادة الفعالة/التركيز - الشكل الصيدلي/اطار التقديم/ اسم الشركة صاحبة المستحضر) 6. Confirmation e-mail by PSMF reception portal (as an evidence of submission of the PSMF of the company to EPVC) or Latest released valid PSMF assessment report "all concerned parties" 7. Updated version of Summary of PSMF(s)/PSSF 8. In case of submission by PV representative, the PV rep should submit an authorized and authenticated (by all concerned parties) PV agreement between the MAH & the service provider covering all the PV activities 9. The Addendum to clinical overview (ACO): covering the period since the initial marketing authorization or since the last renewal until 90 days prior to renewal submission. 10. Egyptian-Risk Management Plan (RMP) of the product.		

ملحوظة هامة بالنسبة إلى ايصالات الدفع:

❖ **يتعين على الشركات تقديم الاتي:**

١- **الإيصال الاصفر** (مختوماً بختم الإدارة المركزية الرعاية الصيدلية)
٢- **الايصال الأحمر** (مختوماً بختم الإدارة المركزية الرعاية الصيدلية)

❖ **يتعين على الشركات كتابة التفاصيل الاتية (بخط اليد) على إيصالات الدفع (الأصفر+الأحمر):**

✓ **في حالة ملفات التسجيل/إعادة التسجيل/ التقرير الدوري لتقييم المنافع و المخاطر(RoutinePBRER):**

١. إطار تقديم الملف (context of submission)
٢. الإدارة المقدم إليها الملف (إدارة اليقظة الصيدلية)
٣. اسم المستحضر/المادة الفعالة/التركيز/الشكل الصيدلي
٤. **Application number**: في حالة ملفات **التسجيل**
File number: في حالة ملفات **إعادة التسجيل**

Annex IV

Check list for documents of Re-registration biological products file

Date of Submission	
Product Name	
Applicant Name	
Applicant Representative	
Biological Registration Specialist	

Prepare the following items		Check	Notes
I. Core Registration file			
First: Administrative data			
1	Company profile submitted & updated		
2	Index		
3	Covering letter on applicant head letter signed and stamped by the registration general manager for file submission for Renewal process		
5	Copy of the updated pricing certificate		
6	C.D. containing all content of the 3 files (core, inspection, quality)		
7	A certification that all data in the file is true and accurate and updated and identical to the CD		
8	Copy of all approvals or Exemptions related to the Product (technical committee, scientific committee, inspection reports, …)		
9	Copy of Authorization letter for the person responsible for communication on behalf of applicant during the procedure and this letter should be certified as truly signed		
10	Payment receipt (according to the last update of fees decree)		
11	Original List OF variations from the MA holder		

12	**Application form for Renewal of biological medicinal products Signed & Stamped by the Applicant (each paper)**		
13	**Composition Certificate**		
	Original		
	Authenticated & Notarized **(if not attached to CPP)** * for imported products		
	On license holder letter head		
	Signed & Stamped by the license holder		
	Trade name of the product is specified		
	Dosage form of the product is specified		
	Active ingredient (s) with its (their) quantity (ies) per unit dose is (are) specified		
	inactive ingredient (s) with its (their) quantity (ies) per unit dose is (are) specified		
	Specifications of Active & inactive ingredients are mentioned (e.g. in house specification , USP ,EU ,JP ,British pharmacopeia)		
	The overage should be mentioned		
	Identical to CPP & CTD		
	API name is specified (the INN, scientific, pharmacopoeia, common name accompanied by its salt or hydrate form (if any))		
14	**For Imported products: CPP issued by Competent Authorities in Country of Origin**		
	Original		
	Authenticated from Embassy		
	Valid		
	The Arab Republic of Egypt is mentioned as Importing Country		
	Number of product license is specified		
	Date of issue is specified		
	Dosage form (s) and Strength (s) are specified.		
	License Holder (address, city, country) is specified		
	Role of License Holder is specified		
	Manufacturer of solvent should be mentioned (if different from manufacturer of the finished product)		
	Product marketed in the COO		
	Manufacturing sites involved in the Production of the product should be mentioned with its role (Finished product, Primary Packager, Secondary Packager, Batch releaser, Solvent manufacturer)		
	Good Manufacturing Practice (GMP) of the manufacturer is specified		
	Pack Presentation and pack size(s) of the Product is (are) specified (could be as an attachment)		

	Active Ingredient(s) by its salt or hydrate form (if any) with its (their) quantity (ies) per unit dose is (are) specified		
	Inactive Ingredient(s) with its (their) quantity (ies) per unit dose is (are) specified (could be as an attachment)		
	Shelf-life of the Product is specified (could be as an attachment)		
	Storage Conditions of the Product is specified (could be as an attachment)		
	SPC or package insert of the product (could be as an attachment)		
	If the Name of the product may change in Egypt, copy of CPP from any reference country with the name targeted to be in Egypt should be submitted (technical committee decision on 22/5/2014).		
15	**GMP of all the manufacturers involved in the production process** **(Manufacturer of active substance, Manufacturer of finished, Manufacturer of solvent, primary packager, Secondary packager and Batch Releaser)**		
	Authenticated (From Embassy) original or true copy (authentication on the certificate)		
	Valid		
	The name of plant by its address should be specified		
	The date of the last inspection should be specified		
	The invalidation date should be mentioned		
	The production lines are specified		
16	**Copy of Manufacturing license for all manufacturers**		
	Valid		
	Authenticated (From Embassy) original or true copy (authentication on the certificate)		
	The name of plant by its address should be specified		
	The invalidation date should be mentioned		
	The production lines are specified		
	Issued from the health authority of the specified country		
17	**Outer label of the Product (1 original pack recently marketed in Egyptian market and 7 layouts)**		
18	**Inner Label of the product (1 original label that recently marketed in Egyptian market and 7 layouts)**		
19	**Official declaration (from scientific office or from manufacturer) stating the type of the submitted pack (COO pack , country-specific pack , international pack …..etc.) with differences**		

20	**Official declaration stating the relationship between Manufacturer, Importer and Distributor that Should be notarized from the chamber of commerce or its equivalent in the country of origin and Authenticated from the Egyptian embassy**		
21	**Copy of Agency or distribution contract that Should be notarized from the chamber of commerce or its equivalent in the country of origin and Authenticated from the Egyptian embassy abroad & submit original for review**		
22	**In case of imported bulk naked vial** that manufactured abroad and packed locally, the following is required: - Copy of packaging contract between the importing company & local manufacturing - Original Authorization letter from the abroad mother company to the importing for product registration and packaging with a local licensed packaging site (Should be notarized from the chamber of commerce or its equivalent in the country of origin and Authenticated from the Egyptian embassy abroad & submit original for review)		
23	**Letter of Acknowledgment of full responsibility for storing the raw materials and for all stages of manufacturing and for the product's conformity with the technical specifications until the completion of distribution**		
24	**Submitting a pledge acknowledging his commitment to the provisions of the Intellectual Property Protection Law No. 82 of 2002**		
25	**Submit the updated scientific office license, importer register for all importers, Updated Storage License for all Storage sites, updated Tax card & Commercial register**		
26	**Copy of insert**		
27	**CD containing Complete & updated Module 3**		
28	**A declaration from the license holder mentioning the product name submitted that the submitted Module 3 (version number & date) at the renewal process is the updated and complete**		

29	**A declaration letter from the applicant mentioning that there are no updates in the scientific file at the renewal submission date and all updates are submitted and approved previously (or there is no updates undertaken from the product license issuance till renewal submission)**		
30	**A declaration letter from the applicant mentioning that there are no updates in the stability file at the renewal submission date and all updates are submitted and approved previously (or there is no updates undertaken from the product license issuance till renewal submission)**		
31	**COA for active substance & finished Product (solvent if needed)**		
٣٢	**TSE free certificate from license holder**		
٣٣	**<u>If the materials entering in the product formulation are from blood derivatives, the following will be presented:</u>**		
	Official certificates declaring plasma source (legalized in case of blood products active substance)		
	HV-1, HV-2, HBsAG, HCV freedom legalized certificate for the plasma		
	Copy of Certificate of release from Health authority (Drug substance only)		
File II: Inspection file			
1	**Site master file (for Manufacturer of active substance, Manufacturer of finished, Manufacturer of solvent, primary & secondary packager and batch releaser) including:** • Covering letter from the License holder declaring that the submitted SMF is the most updated and approved signed, stamped and Authorized • Relevant Premises & utilities information about each site. • Current status of the manufacturing site(s) with respect to current good manufacturing practice (cGMP) requirements. • Legible color printouts of water treatment and air-handling systems, including pipeline and instrumentation drawings in A3 or A2 format. • List of all the products and dosage forms manufactured on- the same site especially same production lines.		
2	**GMP of all the manufacturers involved in the production process & Manufacturing license indicating production lines (Active substance, Manufacturer of finished, Manufacturer of solvent, primary packager)**		

3	**- Latest full inspection report(s) for inspection performed by a stringent regulatory authority in the past three years and their outcomes.** **- Last Annual product review.** **- One completed batch manufacturing and packaging record.** **- List of any recalls in the past three years related to products with quality defects (if found).** **- Any warning letter or equivalent regulatory action (production-line specific) (if found).**		
4	**CPP of the product**		
5	**Manufacturing process for Active substance and Finished product (and solvent, if present)**		
6	**Manufacturing validation for Active substance and Finished product (and solvent, if present)**		
7	**Cold chain Storage & transportation procedures.**		
8	**Copy of application form for biological products**		
9	**List of each site where the product (Drug Substance and Drug Product), if authorized, is or would be manufactured.**		
File III: Quality file			
1	**Copy of application form for biological products**		
2	**Summary protocol (for blood products & vaccines)**		
3	**Complete updated CTD**		
4	**Certificate of Analysis for Drug substance & Finished product & solvent (if solvent present)**		
File IV- PV requirements			
٥	**إعادة تسجيل مستحضر حيوي مستورد، المستندات المطلوبة كالتالي:** Soft copy searchable text PDF: 1. Delegation letter التفويض خطاب 2. Previous license of the product/s 3. Updated Cover letter (on the company paper of the PV representative/agent/scientific office) clarifying the Date of the submission (not exceeding 2 days before the submission)/ Directed to the Manager of General Administration of Pharmaceutical Vigilance/ Name of the product /Name of the Active substance/ context of		

	submission/ Name of the MAH/ Content of the submission/ Actual signature of the QPPV or LSR “signature by QPPV or LSR (not print screen)”- “Accepted Digital/Electronic signature”/company stamp . 4صورة ضوئية من أصل ايصال سداد + "pink receipt“ صورة ضوئية من أصل ايصال سداد ”yellow receipt“ لكل **(File number)** مقابل الخدمات المقدمة من الادارة المركزية للرعاية الصيدلية مختوم ا بختم اليقظة بقيمة 1000 جنيه مصري" لا تشمل ضريبة القيمة المضافة "عن طلب تقييم ملحق تحديث المعلومات الإكلينيكية المقدم في إطار إعادة التسجيل(ACO) طبقا لقرار السيد الاستاذ الدكتور رئيس الهيئة رقم / 99 ،2022 . 5صورة ضوئية من أصل ايصال سداد + "pink receipt“ صورة ضوئية من أصل ايصال سداد ”yellow receipt“ لكل **(File number)** مقابل الخدمات المقدمة من الادارة المركزية للرعاية الصيدلية مختوم ا بختم اليقظة بقيمة 1000 جنيه مصري" لا تشمل ضريبة القيمة المضافة "عن طلب تقييم خطة إدارة المخاطر (RMP) طبقا لقرار السيد الاستاذ الدكتور رئيس الهيئة رقم2021 / 6 (موضحا بالايصال اسم المستحضر/المادة الفعالة/التركيز – الشكل الصيدلي/اطار التقديم / اسم الشركة صاحبة المستحضر) 6. Confirmation e-mail by PSMF reception portal (as an evidence of submission of the PSMF of the company to EPVC) **or** Latest released valid PSMF assessment report “for all concerned parties” 7. Updated version of Summary of PSMF(s)/PSSF 8. In case of submission by PV representative or agent, the PV rep./agent should submit an authorized and authenticated (by all concerned parties) PV agreement between the MAH & the service provider covering all the PV activities 9. The Addendum to clinical overview (ACO): covering the period since the initial marketing authorization or since the last renewal until 90 days prior to renewal submission. 10. The most updated "EU/Global/Core-Risk Management Plan (RMP)"of the product. 11. The Egyptian display of EU-RMP		
٦	**<u>بالنسبة لإعادة تسجيل مستحضر حيوي محلي المستندات المطلوبة</u>** Soft copy searchable text PDF: 1. Delegation letter تفويض خطاب 2. Previous license of the product/s 3. Updated Cover letter (on the company paper of the PV representative/agent/scientific office) clarifying the Date of the		

	submission (not exceeding 2 days before the submission)/ Directed to the Manager of General Administration of Pharmaceutical Vigilance/ Name of the product /Name of the Active substance/ context of submission/ Name of the MAH/ Content of the submission/ Actual signature of the QPPV "signature by QPPV (not print screen)"/company stamp 4. صورة ضوئية من أصل ايصال سداد "pink receipt" + "yellow receipt" لكل **(File number)** مقابل الخدمات المقدمة من الادارة المركزية للرعاية الصيدلية مختوم ا بختم اليقظة بقيمة 1000 جنيه مصري "لا تشمل ضريبة القيمة المضافة "عن طلب تقييم ملحق تحديث المعلومات الإكلينيكية المقدم في إطار إعادة التسجيل (ACO) طبقا لقرار السيد الاستاذ الدكتور رئيس الهيئة رقم 99 / 2022 ، 5. صورة ضوئية من أصل ايصال سداد "yellow receipt + pink receipt" لكل **(File number)** مقابل الخدمات المقدمة من الادارة المركزية للرعاية الصيدلية مختوم ا بختم اليقظة بقيمة 500 جنيه مصري" لا تشمل ضريبة القيمة المضافة "عن طلب تقييم خطة إدارة المخاطر(RMP) طبق ا لقرار السيد الاستاذ الدكتور رئيس الهيئة رقم 6 / 2021 (موضحا بالايصال اسم المستحضر/المادة الفعالة/التركيز – الشكل الصيدلي/اطار التقديم /اسم الشركة صاحبة المستحضر) 6. Confirmation e-mail by PSMF reception portal (as an evidence of submission of the PSMF of the company to EPVC) or Latest released valid PSMF assessment report "all concerned parties" 7. Updated version of Summary of PSMF(s)/PSSF 8. In case of submission by PV representative, the PV rep should submit an authorized and authenticated (by all concerned parties) PV agreement between the MAH & the service provider covering all the PV activities 9. The Addendum to clinical overview (ACO): covering the period since the initial marketing authorization or since the last renewal until 90 days prior to renewal submission. 10. Egyptian-Risk Management Plan (RMP) of the product.		