Central Administration of biological and innovative products and clinical studies
General Administration of biological products

Guideline

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

2023

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1. Introduction

-This guideline intended to describe how to organize Biological applications according to EDA Chairman Decree 343/2021 together with the CTD guideline as per ICH guidelines (ICH M4Q (R4) Organization of the Common Technical Document for the Registration of Pharmaceuticals for Human Use) 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 should be submitted **every 5 years** from first date of registration by submitting a request from the MA Holder 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**: Products containing one or more active ingredients produced or derived from a biological source, including but not limited to, Human vaccines, serum, blood and plasma products and derivatives, also products manufactured using biotechnology and the like, as well as, any products or substances that may be created based on science updates and/or international standard and references
- **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

4.1 file contents for biological products submitted through new registration.

- All MAH for biological products must submit updated information for the purpose of registration to EDA according to EDA Chairman decree 343/2021 (either normal or fast track procedures) or second brand.
- Each file will be directly received & evaluated by its concerned unit in EDA to ensure Safety, efficacy and quality of the product in addition to appropriateness of the product information.

- 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 (PV)

-There are 6 files contents submitted for evaluation of new file submission according to EDA chairman decree 343/2021 as a following:

1. Core registration file
2. Inspection file
3. Quality file
4. Stability file
5. Scientific file
6. PV file

For the detailed requirements for each file, please refer to **Annex I**

4.2File contents for biological products submitted through Re-registration process.

- Marketing authorization approval for biological products is valid for 5 years according to EDA Chairman Decree 343/2021.
- The re-registration file must be submitted through a request from the MAH at the last year of product license validation.
- In Re-registration, each file will be directly received & evaluated by its concerned unit in EDA & 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 PV unit.

There are 4 file Contents submitted for evaluation of Re-registration file submission according to EDA chairman decree 343/2021 as a following:

1. Administration file
2. Quality
3. Inspection file
4. PV file

For the detailed requirements for each file, please refer to **Annex II**

4.3 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 of license holder
- The manufacturing date and expiry date
- The batch numbers
- The barcode
- The product license number
- The product prices

For inner label:
- The site address of manufacturer
- The manufacturing date and expiry date
- The batch numbers

3- For any changes undertaken for registered products regarding packs & inserts, the applicant should submit the variations for variation unit of biological registration administration for review and assess to issue a variations approval.

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 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 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……** ".
c- 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, and 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 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 images and 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 are 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)

(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 Re registration Products:

B- Biological registration specialist receives the following from applicant:

In case of new 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- Pricing certificate (not required in case of products comply reliance model)
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.

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 …..etc) 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 …..etc) 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, and 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, Biological registration specialist sends an email with listing the required documents.

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

4.4 Insert submission requirements for biological products submitted through new registration or Re-registration.

The scope of this section is to describe the requirements for the leaflet file documents needed for the submission of the biological products in case of registration of new biological product, re-registration of a biological product.

Submission requirements

I – Imported products:

1. Proposed English Insert marketed in Country of Origin (Numbered)
2. Proposed translated Arabic Insert, translated from a Certified translation office, except (Vaccines- Immunosuppressant- IV infusion products- Hospital use only - Immunological products- Contrast agents except iodinated one)
3. SPC "summary of product characteristics" and/or CCDS "company core data sheet"
4. Declaration from MAH that the submitted insert is the most updated & marketed in COO (insert status)
5. Current insert (In case of Re-reg and variation)
6. Innovator product insert (in case of biosimilar)
7. Reference model insert (in case of non-reference country)

   نموذج النشرة المرجعي التى قامت الشركة بكتابة نشرتها بناءاً عليه
8. Scientific reference (in case of non-reference country)

   المرجع العلمي و / أو Literatures لكافة البيانات العلمية المذكورة بالنشرة من خلال الدراسات التى قامت بها الشركة
9. Tracking (In case of variation and in case of re-registration products) (Colored, numbered)
10. Module 2-5 soft copy (In case of insert update)
11. Comparative table between reference insert & proposed insert (in case of proposed insert is different than reference insert)

II- Local products:

1. Proposed English Insert (Numbered)
2. Proposed translated Arabic Insert, translated from a Certified translation office, except (Vaccines- Immunosuppressant- IV infusion products- Hospital use only - Immunological products- Contrast agents except iodinated one)
3. SPC "summary of product characteristics"
4. Reference model insert

نموذج النشرة المرجعي التى قامت الشركة بكتابة نشرتها بناءاً عليه

5. Scientific reference (Trials & Literature):

المرجع العلمي و / أو Literatures لكافة البيانات العلمية المذكورة بالنشرة من خلال الدراسات التى قامت بها الشركة

6. Declaration from MAH that the submitted insert is the most updated (insert status, mention revision date)
7. Current insert (In case of Re-reg –variation)
8. Innovator product insert (in case of biosimilar)
9. Tracking (In case of variation and in case of re-registration products) (Colored, numbered)
10. Module 2-5 soft copy (In case of insert update)
11. Comparative table between reference insert & proposed insert (in case of proposed insert is different than reference insert)
12. Comparative table between current & proposed insert and scientific reference for every part in the insert

4.5 Patient Information Leaflet (PIL)

- The PIL is intended for the patient/user. If the PIL is well designed and clearly worded, this maximizes the number of people who can use the information

A Separate patient information leaflet should be provided per strength and per pharmaceutical form in cases of different indications for different strengths and/or dosage forms. However, applicants may present patient information leaflets for different strengths in one document during the evaluation process, clearly indicating the strength or presentation to which alternative text elements refer. Where applicants consider to also market a combined package leaflet, a detailed justification for such a combined patient information leaflet should be provided in the application at submission. E.g. (Different strengths have the same indication).

-The items must appear in the patient information leaflet as required by this guidance as a following:

{(Invented) name strength pharmaceutical form}
{Active substance(s)}
The (invented) name of the medicinal product (referred to as X throughout this document) followed by the strength and pharmaceutical form (i.e. as it appears in the SPC) should be stated here in bold. This should be followed by the active substance(s), which may be written on the line below.

<▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side affects you may get. See the end of section 4 for how to report side effects>.

NB: (inverted black triangle should be added if mentioned in the country-of-origin leaflet)

<**Read all of this leaflet carefully before you start <taking> <using> this medicine.**

- Keep this leaflet. You may need to read it again.

- If you have any further questions, ask your < health care provider>

- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.

- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your < health care provider>

In this leaflet:

1. What {product name} is and what it is used for

Pharmacotherapeutic group: The pharmacotherapeutic group or type of activity should be stated here using patient understandable language.

Therapeutic indications: The therapeutic indications should be stated here, using patient understandable language. If appropriate, specify that:

<This medicine is for diagnostic use only.>

2. Before you <take> <use> {product name}

a. Do not <take> <use> {product name}

 <if you are allergic (hypersensitive) to {active substance(s)} or any of the other ingredients of {product name}.>

 <if ...>

b. Take special care with {product name}

 <if you ...>

 <when ...>

 <Before treatment with {product name},>

c. <Taking> <Using> other medicines, herbal or dietary supplements

 Describe the effects of other products on {product name} and vice versa.

<Please tell your <doctor, health care provider> <or> <pharmacist> if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.>

d. <Taking> <Using> {product name} with food and drink

 Interactions not related to medicinal products should be mentioned here. Where relevant, guidance should always be included to clarify if the medicine must be taken with food, during/before meals, or clearly state if food/meals have no influence, etc.

e. Pregnancy and breast-feeding

 Where the information is significantly different, pregnancy and breast-feeding information can be presented under separate headings.

 Include conclusion summary of the information given in the SPC, in addition to the following optional statement:

<Ask your <doctor, health care provider> <or> <pharmacist> for advice before taking any medicine.>

f. Driving and using machines
 <Do not drive <because...>.>
 <Do not use any tools or machines.>
g. Important information about some of the ingredients of {product name}
 if appropriate, details of those excipients knowledge of which is important for the safe and effective use of the medicinal product, including relevant warnings for residues from the manufacturing process.

3. How to <take> <use> {product name}
<Always <take> <use> {product name} exactly as your doctor or health care provider has told you. You should check with your <doctor, health care provider> <or> <pharmacist> if you are not sure.> <The usual dose is...>
You may include the following sub-headings within the headings given below if needed to increase readability:
 Instructions for proper use
 Dosage
 Method and/or route(s) of administration
 Frequency of administration
 Duration of treatment
a. If you <take> <use> more {product name} than you should
 Describe how to recognize if someone has taken an overdose and what to do.
b. If you forget to <take> <use> {product name}
 Make clear to patients what they should do after irregular use of a product; e.g.
<Do not take a double dose to make up for a forgotten <tablet> <dose> <…>.>
c. If you stop <taking> <using> {product name}
 Indicate any effects of interrupting or ending the treatment early, if applicable.
 Indicate withdrawal effects when the treatment ends, when necessary.
 As appropriate, close this section with:
<If you have any further questions on the use of this product, ask your <doctor, health care provider><or><pharmacist>.

4. Possible side effects
 describe the side effects and whenever possible, an estimate of frequency should be provided, expressed in standard category of frequency.
 Begin this section with: "Like all medicines, {product name} can cause side effects, although not everybody gets them".
Describe, if necessary, the actions to be taken. If the patient needs to seek help urgently, the use of the term <immediately> is recommended; for less urgent conditions, <as soon as possible> can be used.
 Close this section with: "If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your <doctor, health care provider> <or> <pharmacist>".

5. How to store {product name}
 Keep out of the reach and sight of children.
 <Do not store above ºC>, <Store in the original <container><carton>>

 Do not use {product name} after the expiry date which is stated on the <label> <carton> <bottle> <...> <after {abbreviation used for expiry date}.> <The expiry date refers to the last day of that month.>
 <Do not use {product name} if you notice {description of the visible signs of deterioration}.>
 <Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.>

6. Contents of the pack and other information

a. What {product name} contains
 the active substance(s) (expressed qualitatively and quantitatively) and the other ingredients (expressed qualitatively) should be identified.
 The active substance(s) is (are)…
 The other ingredient(s) is (are)...

b. What {product name} looks like and contents of the pack
 The pharmaceutical form should be stated.
 It is recommended to include a physical description e.g. shape, color, texture, imprint.
 All pack sizes for this pharmaceutical form and strength should be detailed here; if appropriate indicate that not all pack sizes may be marketed. A cross-reference to other pharmaceutical forms and strengths may be included.

c. Marketing Authorization Holder and Manufacturer
{Name and address}
< {tel}>
< {Fax}>
< {E-mail}>
For any information about this medicinal product, please contact the <local representative of the> Marketing Authorization Holder:
{Name}
< {Address} {City}>
Tel: + {telephone number}
< {E-mail}>
<As appropriate, add additional local representatives to the above table>

d. This leaflet was last approved in {MM/YYYY}; version number { }

e. To report any side effect(s):

• Egypt:

- Egyptian Pharmacovigilance Centre (EPVC):

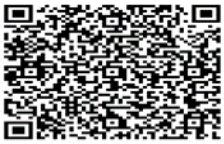
Adress: 21 AbdelAziz Al Saoud St., Manial ElRawda, Giza, Egypt.

e-mail for reporting: pv.followup@edaegypt.gov.eg

Website for reporting: www.edaegypt.gov.eg

Hotline: 15301

Sean QR code:



This patient information leaflet is approved by the Egyptian Drug Authority.
The following statements issued by the Council of Arab Health Ministers should be printed in the PIL.

This is a Medicament
− A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.
− Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
− The doctor and the pharmacist are experts in medicine, its benefits and risks.
− Do not, by yourself, interrupt the period of treatment prescribed for you.
− Do not repeat the same prescription without consulting your doctor.
− Keep all medicaments out of reach of children.

Council of Arab Health Ministers
Union of Arab Pharmacists
This patient information leaflet is approved by the Egyptian Drug Authority.

-In exceptional cases, alternative headings may be acceptable, especially for those headings containing <take><use> or where a different wording would be more appropriate for the product concerned e.g. to better reflect the user of the product. This should not in any case impact on the content required for the section concerned. Applicants should justify the use of alternative headings (e.g. by reference to user testing results). For certain medicinal products not all items may be relevant, in this case the corresponding heading should not be included.
It is important that the SPC and PIL can easily be tracked for updates and review. Each SPC and PIL should be reviewed every 5 years or when necessary.

4.6 Summary of Product Characteristics (SPC)

During the evaluation process, applicants may present SPCs for different strengths in one document, clearly indicating with grey-shaded titles the strength or presentation to which alternative text elements refer. However, a separate SPC per strength and per pharmaceutical form, containing all pack-sizes related to the strength and pharmaceutical form concerned will have to be provided by the applicant.

ADD: Black Box Warning if applicable.

A black box warning is designed to call attention to serious or life-threatening risks. This section can be adapted from the US FDA professional product information leaflet.

Bracketing convention:
{Text}: Information to be filled in.

<Text>: Text to be selected or deleted as appropriate.

1. Name of the medicinal product

The name should be followed by both the strength and the pharmaceutical form.
{(Invented) name strength pharmaceutical form

2. Qualitative and quantitative composition

-Full details of the qualitative and quantitative composition in terms of the active substance(s) and excipients.
-The following standard statement should be included at the end of the section, i.e. „For a full list of excipients, see section 6.1.
If a diluent is part of the medicinal product, information should be included in the relevant sections (Usually sections 3, 6.1, 6.5 and 6.6).

3. Pharmaceutical form

-Full description of the pharmaceutical form should be provided.
-A visual description of the appearance of the product (color, markings, etc.) is given, including information on pH and osmolarity as required e.g.:
"Tablet White, circular flat bevelled-edge tablets marked "100" on one side".
-In case of tablets designed with a score line, information should be given whether or not reproducible dividing of the tablets has been shown. e.g.:
<The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.>
<The tablet can be divided into equal halves.>.

4. Clinical particulars

4.1 Therapeutic indications

- The indication(s) should be stated clearly and concisely and should define the target disease or condition distinguishing between treatment (symptomatic, curative or modifying the evolution or progression of the disease), prevention (primary or secondary) and diagnostic indication. When appropriate it should define the target population especially when restrictions to the patient populations apply.
-It should be stated in which age groups the product is indicated, specifying the age limits, e.g. 'X is indicated in <adults><neonates><infants><children> <adolescents> <aged x to y <years, months>>.
-If the product's indication depends on a particular genotype or the expression of a gene or a particular phenotype, this should be stated in the indication.

4.2 Posology and method of administration

-In case of restricted medical prescription start this section by specifying the conditions.
-The dosage should be clearly specified for each method/route of administration and for each indication, as appropriate.
- Dose recommendations (e.g. mg, mg/kg, mg/m^2) should be specified per dose interval for each category where appropriate (specify age/weight/body surface area of subsets of the population as appropriate). Frequency of dosing should be expressed using time units (e.g. once or twice daily or every 6 hour) and, to avoid confusion, abbreviations e.g. OD or BID should not be used.

Where appropriate, the following points should be addressed:
- The maximum recommended single, daily and/or total dose,
- The need for dose titration,
- The normal duration of use and any restrictions on duration and, if relevant, the need for tapering off, or advice on discontinuation,
- Advice on action to be taken if one or more dose(s) is (are) missed, or e.g. in case of vomiting (the advice should be as specific as possible, taking into consideration the recommended frequency of dosing and relevant pharmacokinetic data)
- Advice on preventive measures to avoid certain adverse drug reactions (e.g. administration of antiemetic),
- The intake of the product in relation to drink and food intake, e.g. with alcohol, grapefruit or milk,
- Advice regarding repeat use, with any information on intervals to be observed between courses of treatment, as appropriate.
- Interactions requiring specific dose adjustments with cross-reference to other appropriate sections of the SPC and it may also be relevant to recommend not to prematurely discontinue a treatment in case of specific non-serious adverse reaction(s) that are frequent but transient or manageable with dose-titration. Dosage adjustments or other posology related information on special populations should be presented here, in well-defined sub-sections ordered by importance, e.g. regarding: elderly population; pediatric population; renal impairment; hepatic impairment, patients with a particular genotype; other relevant special population (e.g. patients with other concomitant disease or overweight patients).

Method of administration
Any special precautions related to the manipulation or administration of the product (e.g. cytotoxic products) by healthcare professionals (including pregnant healthcare professionals), the patient or carers should be mentioned here under a specific sub-heading (<Precaution to be taken before manipulating or administering the product.
The route of administration and concise relevant instruction for correct administration and use should be given here.

4.3 Contraindications
Situations where the medicinal product must not be given for safety reasons, i.e. contraindications, are the subject of this section. Such circumstances could include a particular clinical diagnosis, concomitant diseases, demographic factors (e.g. gender, age) or predispositions (e.g. metabolic or immunological factors, a particular genotype and prior adverse reactions to the medicine or class of medicines). The situations should be unambiguously, comprehensively and clearly outlined. Only if pregnancy or breastfeeding is contraindicated, should it be mentioned here. Hypersensitivity to the active substance or to any of the excipients or residues from the manufacturing process should be included, as well as any contraindication arising from the presence of certain excipients.

4.4 Special warnings and precautions for use
- The order of warnings and precautions should be determined by the importance of the safety information provided.
-The exact content of this section will be different for each product and the therapeutic conditions it is intended to treat. It is however suggested that the following items should be included where relevant to the specific product.
-Information on a specific risk should be given in section 4.4 only when the risk leads to a precaution

for use or when healthcare professionals have to be warned of this risk. Patient groups in which use of the medicinal product is contraindicated should be mentioned in section 4.3 only and not to be repeated here.

The following should be described:

- The conditions, in which the use of the medicinal product could be acceptable, provided that special conditions for use are fulfilled. In particular, specific risk minimisation measures requested as part of a Risk Management Plan to ensure safe and effective use should be described in this section. (For example; "Liver function should be monitored before initiation of treatment and monthly thereafter", "Patients should be advised to immediately report any symptoms of depression and/or suicidal ideation", "Women of childbearing potential should use contraception", …)

- Special patient groups that are at increased risk or are the only groups at risk of experiencing product or product class-related adverse reactions (usually serious or common), e.g. elderly, children, patients with renal or hepatic impairment (including the degree of impairment, e.g. mild, moderate or severe), patients having an anaesthesic or patients with cardiac failure (including in this case the NYHA Classification for example). Cross-reference to section 4.8 on the differential effects in terms of frequency and severity of the specified adverse reaction should be provided.

-Serious adverse reactions to which healthcare professionals need to be alerted, the situations in which these may occur and the action that may be required, e.g. emergency resuscitation.

-If there are particular risks associated with starting the medicinal product (e.g. first dose effects) or stopping it (e.g. rebound, withdrawal effects), these should be mentioned in this section, together with the action required for prevention.

-Any measures which can be taken to identify patients at risk and prevent the occurrence, or detect early the onset or worsening of noxious conditions. If there is a need for awareness of symptoms or signs representing early warning of a serious adverse reaction, a statement should be included.

-Any need for specific clinical or laboratory monitoring should be stated. Recommendation for monitoring should address why, when and how the monitoring should be conducted in clinical practice. If dose reduction or other posology is recommended in such circumstances or conditions, this should be included in section 4.2 and cross-referenced here.

-Any warnings necessary for excipients or residues from the manufacturing process.

-Subjects or patients with a specific genotype or phenotype might either not respond to the treatment or be at risk of a pronounced pharmacodynamic effect or adverse reaction. These may arise because of non-functioning enzyme alleles, alternative metabolic pathways (governed by specific alleles), or transporter deficiencies. Such situations should be clearly described if known.

-Any particular risk associated with an incorrect route of administration (e.g. necrosis risk with extravasation of intravenous formulation, or neurological consequences of intravenous use instead of intramuscular use), should be presented, with advice on management if possible.

-In exceptional cases, especially important safety information may be included in bold type within a box.

- Any adverse reactions described in this section or known to result from conditions mentioned here should also be included in section 4.8.

- Specific interference with laboratory tests should be mentioned when appropriate, e.g. Coombs test and Beta-lactams. They should be clearly identified with a subheading,
e.g. "Interference with serological testing".

-In general, descriptions of warnings and precautions regarding pregnancy and breast-feeding, ability to drive and use machines, and other aspects of interactions should be dealt with in sections 4.6, 4.7 and 4.5, respectively. However, in specific cases of major clinical importance it might be more appropriate to describe specific precautionary measures in this section, e.g. contraception measures,
Or when concomitant use of another medicine is not recommended, and with cross reference to section 4.5, 4.6, or 4.7.

Paediatric population:
When the product is indicated in one or more subsets of the paediatric population and there are warnings and precautions for use that are specific to the paediatric population or any subset of the paediatric population, they should be identified under this subheading. Any necessary warning or precaution in relation to long-term safety (e.g. on growth, neuro-behavioural development or sexual maturation) or specific monitoring (e.g. growth) in the paediatric population should be described. When long-term safety data are necessary but not yet available, it should be stated in this section. Warnings should be included in case of possible significant or long-lasting impact on children‟s daily activities, such as learning ability or physical activities, or in case of impact on appetite or sleep pattern.
- If no interaction studies have been performed, this should be clearly stated.

4.5 Interaction with other medicinal products and other forms of interaction
-This section should provide information on the potential for clinically relevant interactions based on the pharmacodynamics properties and in vivo pharmacokinetic studies of the medicinal product, with a particular emphasis on the interactions, which result in a recommendation regarding the use of this medicinal product.
-Interactions affecting the use of this medicinal product should be given first, followed by those interactions resulting in clinically relevant changes on the use of others.

4.6 Fertility, Pregnancy and lactation
- Efforts should be made by the Marketing Authorization Applicant or Holder to provide the reasons for the recommendations for use in pregnant or lactating women and in women of childbearing potential. This information is important for the healthcare professionals informing the patient
- in the overall assessment, all available knowledge should be taken into account, including clinical studies and post-marketing surveillance, pharmacological activity, results from non-clinical studies, and knowledge about compounds within the same class.
- Efforts should be made to update the recommendations for use during pregnancy and lactation on the basis of increasing human experience in exposed pregnancies which eventually supersede the animal data.

The following should be mentioned:

- Women of childbearing potential / Contraception in males and females.
- Pregnancy
- Breastfeeding
- Fertility

4.7 Effects on ability to drive and use machines

-On the basis of the pharmacodynamic profile, reported Adverse Reactions and/or specific studies on a relevant target population addressing the performance related to driving or using machines**, specify whether the medicinal product has:**

A. no or negligible influence.
B. minor or moderate influence, or
C. major influence on these abilities.

Effects of the disease itself on these abilities should not be discussed.

4.8 Undesirable effects

- This section should include all adverse reactions from clinical trials, post-authorisation safety studies and spontaneous reporting for which, after thorough assessment, a causal relationship between the medicinal product and the adverse event is at least a reasonable possibility, based for example, on their comparative incidence in clinical trials, or on findings from epidemiological studies and/or on an evaluation of causality from individual case reports. Adverse events, without at least a suspected causal relationship, should not be listed in the SPC.
- the content of this section should be justified in the Clinical Overview of the marketing authorization application based upon a best-evidence assessment of all observed adverse events and all facts relevant to the assessment of causality, severity and frequency. This section should be regularly reviewed and, if necessary, updated with the aim to ensure appropriate information to health care professionals on the safety profile of the product. In addition, the whole section could be revised at the renewal of the marketing authorization, where the safety profile of most products is likely to be well established, and thereafter at each of the three-yearly PSUR.
-It is important that the whole section is worded in concise and specific language and does not include information such as claims regarding the absence of specific adverse reactions, comparative frequency statements other than as described below, or statements of general good tolerability such as “well tolerated”, “adverse reactions are normally rare”, etc. Statements on lack of proof of causal association should not be included.
-In order to provide clear and readily accessible information, **section 4.8 should be structured according to the following recommendations:**

a. Summary of the safety profile
b. Tabulated summary of adverse reactions
c. Description of selected adverse reactions
d. <Paediatric population>
e. <Other special population(s)>

a. Summary of the safety profile

The summary of the safety profile should provide information about the most serious and/or most frequently occurring adverse reactions.

If known, it may be helpful to indicate the timing when adverse reactions occur. For example, in order to prevent early discontinuation of a treatment, it may be important to inform about non-serious adverse reactions that are frequent in the beginning of the treatment but may disappear with its continuation. Another example would be to inform about adverse reaction associated with long-term use. Frequencies of cited adverse reactions should be stated as accurately as possible. This summary of the safety profile should be consistent with the important identified risks mentioned in the Safety Specification of the

Risk Management Plan. The information should be consistent with the Table of Adverse Reactions (see section b). Cross-reference should be made to section 4.4 if relevant risk minimization measures have been proposed in that section.
An example of an acceptable statement is given below:

"At the beginning of the treatment, epigastric pain, nausea, diarrhoea, headache or vertigo may occur; these reactions usually disappear within a few days even if treatment is continued. The most commonly reported adverse reactions during treatment are dizziness
And headache, both occurring in approximately 6% of patients. Serious acute liver injury and agranulocytosis may occur rarely (less than 1 case per 1,000 patients)"

b. Tabulated summary of adverse reactions
A single table (or structured listing) should list all adverse reactions with their respective frequency category. In some cases for common or very common reactions, and when it is necessary for the clarity of the information, frequency figures may be presented in the table.

Separate tables are acceptable in exceptional cases where the adverse reaction profiles markedly differ depending on the use of the product. For example, it might be the case for a product used for different indications (e.g. an oncology and a non-oncology indication) or at different posologies.

The table should be introduced with a short paragraph stating the source of the safety database (e.g. from clinical trials, post-authorisation safety studies or spontaneous reporting).

The table should be presented according to the MedDRA system organ classification. The system organ class (SOC) should be presented in the order shown in the annex. Adverse reactions descriptions should be based on the most suitable representation within the MedDRA terminology. This will usually be at the Preferred Term (PT) Level, although there may be instances where the use of Lowest Term Level or exceptionally group terms, such as High Level Terms may be appropriate. As a general rule, any adverse reactions should be assigned to the most relevant SOC related to the target organ. For example, PT „Liver function test abnormal" should be assigned to the SOC „Hepatobiliary disorders" rather than to the SOC „Investigations". Within each system organ class, the adverse reactions should be ranked under headings of frequency, most frequent reactions first. Within each frequency grouping, adverse reactions should be presented in the order of decreasing seriousness. The names used to describe each of the frequency groupings should follow standard terms established in each official language using the following convention: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

In exceptional cases, if a frequency cannot be estimated from the available data, an additional category frequency „not known" may be used. In case the expression "Frequency not known" is used, the following text should be added in the list of terms explaining the frequency categories: "not known (cannot be estimated from the available data)". The expressions isolated/single cases/reports should not be used.

Where additional details about an adverse reaction are described in section c), the reaction concerned should be highlighted, for example with an asterisk, and, "see section c)" should be included as a footnote.

Guidance on how to estimate the frequency of an adverse reaction is provided at the end of this Chapter of the guideline.

c. Description of selected adverse reactions

This section should include information characterising specific adverse reaction which may be useful to prevent, assess or manage the occurrence of an adverse reaction in clinical practice.
This section should include information characterising individual serious and/or frequently occurring adverse reactions, or those where there have been reports of particularly severe cases. The information should provide frequency and may describe for example reversibility, time of onset, severity, duration, mechanism of the reaction (if of clinical relevance), dose relationship, relationship with duration of exposure or risk factors. Measures to be taken to avoid specific adverse reactions or actions to be taken if specific reactions occur should be mentioned under section 4.4 and cross-referenced here.

Information on the occurrence of withdrawal reactions may be mentioned here with cross-reference to section 4.2 in case of need for tapering off or advice on discontinuation of the product. Mention should be made here of any differences between different dosage forms in respect of adverse reactions.

In the case of combination products, information should be included in this sub-section pointing out which particular adverse reactions are usually attributable to which active substance of the combination, where known.

Any adverse reactions resulting directly from an interaction should be mentioned here and cross referenced to section 4.5.

This section should also inform on adverse reactions with very low frequency or with delayed onset of symptoms which may not have been observed in relation to the product, but which are considered to be related to the same therapeutic, chemical or pharmacological class. The fact that this is a class attribution should be mentioned.

Any adverse reaction specific to excipients or residues from the manufacturing process should be Included.

d. Paediatric population

A paediatric sub-section should always be included (unless irrelevant).
The extent and age characteristics of the safety database in children should be described (e.g. from clinical trials or pharmacovigilance data). Uncertainties due to limited experience should be stated. If the observed safety profile is similar in children and adults this could be stated: e.g. “Frequency, type And severity of adverse reactions in children are <expected> to be the same as in adults”. Similarly, it is appropriate to state whether the safety profiles in the different paediatric subsets are similar or not.

Any clinically relevant differences (i.e. in nature, frequency, seriousness or reversibility of adverse reactions) between the safety profiles in adult and paediatric populations, or in any relevant age groups, should be described and presented by age group. If there is a need for specific monitoring, this should be highlighted by cross-referencing to section 4.4. For clinically relevant differences, a separate table listing such adverse reactions by frequency can be added and presented by relevant age groups if appropriate. If some paediatric adverse reactions are considered common (≥1/100 to <1/10) or very

common (≥1/10), the frequencies should be provided in parentheses. In case of major difference with the safety profile in adults, a summary of the safety profile in children could be presented to facilitate the presentation of the information. Available information, from any source scientifically validated, on long-term safety in children (e.g. on growth, mental development and sexual maturation) should also be summarized, whether positive or negative, with cross-reference to section 5.1 if appropriate. Any risk factors such as duration of treatment or period at risk should be specified.

If relevant, symptoms of neonatal withdrawal should be listed in a separate paragraph with cross Reference with 4.6.

e. Other special populations

This section may include information on any clinically relevant differences (i.e. in nature, frequency, seriousness or reversibility of adverse reactions, or need for monitoring) specifically observed in other special populations such as elderly, patients with renal impairment, patients with hepatic impairment, patients with other diseases or a specific genotype. Cross-reference to other sections such as 4.3, 4.4 or 4.5 may be added as appropriate.

Adverse reactions may also be related to genetically determined product metabolism. Subjects or patients deficient in the specific enzyme may experience a different rate or severity of adverse reactions. This should be mentioned and where relevant correlated with data from clinical trials.

To reports any side effect(s):

• Egypt:

- Egyptian Pharmacovigilance Centre (EPVC):

Adress: 21 AbdelAziz Al Saoud St., Manial ElRawda, Giza, Egypt.
e-mail for reporting: pv.followup@edaegypt.gov.eg
Website for reporting: www.edaegypt.gov.eg
Hotline: 15301
Sean QR code:

4.9 Overdose

-Describe acute symptoms and signs and potential sequelae of different dose levels of the medicinal product based on all available information including accidental intake, mistakes and suicide attempts by patients.

-Taking into account all relevant evidence, describe management of overdose in man, e.g. in relation to monitoring or use of specific agonists/antagonists, antidotes or methods to increase elimination of the medicinal product such as dialysis.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Describe the following:

-Pharmacotherapeutic group: {group}, ATC code: {code}. If an ATC code is not yet available, this should be mentioned as „not yet assigned".

-Mechanism of action (if known).
- Pharmacodynamic effects.
-Clinical efficacy and safety.

5.2 Pharmacokinetic properties

-Pharmacokinetic properties of the active substance(s) relevant for the advised dose, strength and the pharmaceutical formulation marketed should be given in this section. If these are not available, results obtained with other administration routes, other pharmaceutical forms or doses can be given as alternative.
-Basic primary pharmacokinetic parameters, for instance bioavailability, clearance and half-life, should be given as mean values with a measure of variability.
- Pharmacokinetics items, which could be included in this section when relevant, are given below.
a. General introduction, information about whether the medicinal product is a pro-drug or whether there are active metabolites, chirality, solubility etc.
b. General characteristics of the active substance(s) after administration of the medicinal product formulation to be marketed.

***Absorption*:** complete or incomplete absorption; absolute and/or relative bioavailability; first pass effect; Tmax; the influence of food; in case of locally applied medicinal product the systemic bioavailability.

Distribution: plasma protein binding; volume of distribution; tissue and/or plasma concentrations; pronounced multi-compartment behavior.

Biotransformation: degree of metabolism; which metabolites; activity of metabolites; enzymes involved in metabolism; site of metabolism; results from in vitro interaction studies that indicate whether the new compound can induce/inhibit metabolic enzymes.

Elimination: elimination half-lives, the total clearance; inter and/or intra-subject variability in total clearance; excretion routes of the unchanged substance and the metabolites.

Linearity/non-linearity: linearity/non-linearity of the pharmacokinetics of the new compound with respect to dose and/or time; if the pharmacokinetics are nonlinear with respect to dose and/or time, the underlying reason for the non-linearity should be presented.
- Additional relevant information should be included here.

a. Characteristics in patients

-Variations with respect to factors such as age, gender, smoking status, polymorphic metabolism and concomitant pathological situations such as renal failure, hepatic insufficiency, including degree of impairment. If this influence on the pharmacokinetics is considered to be clinically relevant, it should be described here in quantitative terms (cross-referral to 4.2 when applicable).

b. Pharmacokinetic/pharmacodynamic relationship(s)

Relationship between dose/concentration/pharmacokinetic parameter and effect (either true endpoint, validated surrogate endpoint or a side effect).

- Contribution (if any) of metabolite(s) to the effect.

5.3 Preclinical safety data

-the results of the non-clinical testing should be described in brief and qualitative statements as outlined in the following example statements:

- <Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction.>

- <Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.>

- <Adverse reactions not observed in clinical studies, but seen in animals at exposure levels similar to clinical exposure levels and with possible relevance to clinical use were as follows:>

Conclusions on the environmental risk assessment on the product should be included where relevant, with reference to section 6.6.

6. Pharmaceutical particulars

6.1 List of excipients

- A list should be given of the excipients, expressed qualitatively only. All excipients, which are present in the product, should be included, even those present in small amounts, such as printing inks.
- Each to be listed on a separate line according to the different parts of the product.

6.2 Incompatibilities

-Information on physical and chemical incompatibilities of the medicinal product with other products with which it is likely to be mixed or co-administered should be stated.
- Statements concerning compatibility of the product with other medicinal products or devices should not be included in this section but in section 6.6. Statements concerning pharmacological incompatibilities with food should be included in section 4.5.
- If appropriate, the standard statement, "Not applicable", should be included.
- For certain pharmaceutical forms, e.g. parenterals, either of the following standard statements should be included as appropriate:

- <In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.>

- <This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.>

6.3 Shelf life

-Information on the finished product shelf life and on the in-use stability after 1st opening and/or reconstitution/dilution should appear here. Only one overall shelf life for the finished product is to be

given even if different components of the product may have a different shelf life (e.g. powder & solvent).
<...> <6 months> <...> <1 year> <18 months> <2 years> <30 months> <3 years> <...>

6.4 Special precautions for storage
-General storage conditions of the finished product should appear here, together with a cross-reference to section 6.3 where appropriate:
<For storage conditions of the <reconstituted> <diluted> medicinal product, see section 6.3.>
6.5 Nature and contents of container
-The material of construction of the immediate container should be stated ("Type I glass vials", "PVC/Aluminium blisters", "HDPE bottles"); and any other component of the product should be listed, e.g. needles, swabs, measuring spoons, inhaler devices, desiccant. The container of any solvent provided with the medicinal product should also be described. Excessive detail, e.g., concerning the color of the stopper, the nature of the heat-seal lacquer, should usually not be included. Examples on the text in this section:
"<Volume> ml suspension in a pre-filled syringe (type I glass) with plunger stopper (chlorobutyl rubber) with or without needle in pack sizes of 5 or 10"

"HDPE bottle with a child-resistant closure and a silica gel desiccant. Pack-sizes of 30, 60 or 90 film coated tablets"
-All pack sizes must be listed. Pack sizes mentioned should include the number of units, number of doses (for e.g. multi-dose vaccines, inhalers, etc.), total weight or volume of the immediate container, as appropriate, and the number of containers present in any outer carton. If applicable, add:

<Not all pack sizes may be marketed.>

6.6 Special precautions for disposal <and other handling>
-Include practical instructions for preparation and handling of the product, where applicable, including disposal of the medicinal product, and waste materials derived from the used medicinal product.
- If applicable, e.g. for cytotoxics, the following standard statement should be included, „Any unused product or waste material should be disposed of in accordance with local requirements"

- If there are no special use or handling instructions for the pharmacist or other healthcare professionals, the following standard statement should be included:

<No special requirements.>

7. Marketing authorization holder
{Name and address}
< {tel}>
< {Fax}>
< {E-mail}
8. Marketing authorization number(s)
9. Date of first Authorization/ renewal of the authorization
< {DD/MM/YYYY}> < {DD month YYYY}>
10. Date of revision of the text
{MM/YYYY

5. Glossary:

ACO	Addendum to clinical overview
ATC	Anatomical Therapeutic Chemical
CCDS	Company core data sheet
COO	Country of origin
CPP	Certificate of Pharmaceutical product
CTD	Common Technical Documentation
DR	Document Review
EDA	Egyptian Drug Authority
EMA	European Medicines Agency
EPVC	Egyptian pharmacovigilance center
FDA	Food and drug administration
GA	General administration
GMP	Good Manufacturing Practice
GVP	Good Pharmacovigilance Practice
HDPE	High Density Polyethylene Glycol
ICH	International Council for Harmonization
IV	Intravenous
MAH	Marketing Authorization holder
MEdDRA	Medical Dictionary for Regulatory Activities
OD	Once daily
PIL	Patient information leaflet
PT	Preferred team
PSMF	Plasma site master file
PSUR	Periodic Safety Updated Report
RMP	Risk management Plan
SOC	System organ class
SPC	Summary of product characterization
U.S	United state
WHO	World health organization

6. Reference:

- 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.
- EDA chairman decree 99/2022 for service considerations update
- https://extranet.who.int/pqweb/sites/default/files/documents/110%20Annotated%20SmPC%20template_Oct2016_0.docx
- https://extranet.who.int/pqweb/key-resources/documents/patient-information-leaflet-pil-template

7. Annexes

Annex I	Checklist for documents of new biological products registration file
Annex II	Checklist for documents of re-registration biological Products file
Annex III	Template for PIL
Annex IV	Template for SPC

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	**Applicant profile submitted & updated**		
2	**Index**		
3	**Covering letter on applicant head letter signed and stamped bythe registration general manager for file submission for registration**		
4	**Copy of Inquiry approval**		
5	**Copy of pricing certificate or proof of pricing file submission in case of reliance or fast track pathway**		
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 andupdated 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 andthis letter should be certified as truly signed**		
10	**Payment receipt (according to last update of fees decree)**		
11	**Application form for registration of biological medicinal productsSigned & Stamped by the Applicant (each paper)**		
12	**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 orhydrate form (if any))		
13	**For Imported products: CPP issued by Competent Authorities inCountry 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).		
14	**GMP of all the manufacturers involved in the productionprocess (Manufacturer of active substance, Manufacturer of finished, Manufacturer of solvent, primarypackager, 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		
15	**Copy of Manufacturing license for All manufacturing sites**		
	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		
16	**TSE/BSE free declaration for products contain animal-derivedmaterials 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		
17	**Certificate of suitability (applicable in case the presence ofanimal materials susceptible to transmit TSE)** **if not applicable: Supplier official declaration(s) stating the safety of the substances used in the product manufacturing**		
18	**<u>In cases of imported bulk products and packing in local</u> <u>manufacturing site:</u>** the packaging contract between the foreign manufacturing company and the local packaging site should Submitted		
19	**<u>In case of Toll manufacturing:</u> the manufacturing contract specifying the intended product should be submitted should be certified as truly signed**		
20	**<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		
21	**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 andothers) they should be mentioned		

	English speaking pack (in addition to Arabic language in case of local products)		
22	**Inner Label of the product (1 original label and 7 layouts)**		
	The manufacturer should be specified		
	The trade names		
	Generic Name with strength		
	Batch number is specified		
	Manufacturing date is specified		
	Expire date is specified		
23	**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**		
24	**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 embassyabroad**		
25	**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**		
26	**<u>In case of imported bulk naked vial</u> that manufactured abroadand 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)**		
27	**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 thecompletion of distribution**		
28	**Submitting a pledge acknowledging his commitment to the provisions of the Intellectual Property Protection Law No. 82 of2002**		
29	**- Submit the updated scientific office license, importer register for all importers, Updated Storage License for all Storage sites, updated Tax card & Commercial register** **- List of distributors for the submitted product in Egypt mentioning the responsibility for Lot release activity.**		
30	**Product insert**		
Second: Ingredients & packaging materials			
A) Active ingredients:			
31	**Specifications of the active ingredients and the relevant tests.**		
32	**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:			
33	**Specifications of the inactive ingredients and the relevant tests.**		
34	**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		
35	**Supplier name & origin**		
36	**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			
37	**Specifications of the finished product and the relevant tests**		
38	**Certificate of Analysis of finished products for eachmanufacturing site (if present)**		
	Original & valid while submission		
	Signed by the Company or the concerned center or laboratory that held the analysis (**<u>Authenticatedand Notarized</u>**)		
	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		
39	**COA of solvent for each manufacturing site (if present)Authenticated and Notarized)**		
40	**CD containing Complete & updated CTD**		
41	**<u>In case of reliance products (level 2 file submission)</u>, the following are generally required:** 1- Complete CTD file, with detailed SOPs, the dossier should be the same as that submitted to the reference drug regulatory agency for modules 2-5 2- all annexes and appendices related to safety and efficacy issues of the product with full details 3- a declaration letter by the product owner/applicant stating that all aspects of the product's quality, safety and efficacy are identical to the currently approved by the reference agency with the same dose, indication, warnings and precaution.		
42	**<u>In case of reliance products (level 1 file submission), the following are required:</u>** 1- full assessment report along with other relevant supporting documents from the reference		

	regulatory agency such as: reports pertaining to post-approval variations, post marketing commitments, supporting documents on comparative safety and efficacy studies submitted to the reference agency 2- questions & answer documents between applicant and the reference agency with all annexes 3- any correspondences between the applicant and the reference agency relating to safety and efficacy or queries, the risk management plan, or benefit-risk decisions should be provided		
43	**<u>If the materials entering in the product formulation are from blood derivatives, thefollowing will be presented:</u>**		
	Plasma Master file that contains information of plasma source starting from collection passing all production process & in- process control & Viral safety		
	Official certificates declaring plasma source (legalized in case ofblood 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)		

		Check	Notes
	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	*** the following to be submitted if applicable:** **- 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	**List of each site where the product (Drug Substance and Drug Product), if authorized, is or would be manufactured.**		
9	**Copy of inquiry approval**		
10	**Copy of application form for biological products**		

		Check	Notes
	File III: Quality file		
1	**Copy of inquiry**		
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,)**		
8	**Add the sections No. 40 & 41 mentioned in core file section**		
9	**<u>In case of reliance products (level 1 file submission), the following are required:</u>** 1- Full assessment report along with other relevant supporting documents from the reference regulatory agency such as: reports pertaining to post-approval variations, post marketing commitments, supporting documents on comparative safety and efficacy studies submitted to the reference agency 2- Questions & answer documents between applicant and the reference agency with all annexes 3- Any correspondences between the applicant and the reference agency relating to safety and efficacy or queries, the risk management plan, or benefit-risk decisions should be provided **<u>In case of reliance products (level 2 file submission), the following are required:</u>** 1- Complete CTD file, with detailed SOPs, the dossier should be the same as that submitted to the reference drug regulatory agency for modules 2-5 2- All annexes and appendices related to safety and efficacy issues of the product with full details 3- a declaration letter by the product owner/applicant stating that all aspects of the product's quality, safety and efficacy are identical to the currently approved by the reference agency with the same dose, indication, warnings and precaution.		

		Check	Notes
File IV: Stability file			
A. Requirements of Stability file for Imported Biological Products			
Administrative documents			
1	**Service consideration (except reliance pathway)**		
2	**Summary sheet (Word + signed & stamped PDF)**		
3	If there are any differences regarding the shelf-life and/or storage conditions in the submitted stability file then: a declaration signed & stamped from MAH clarifying the required shelf-life, storage conditions, in-use, after reconstitution and dilution, incompatibilities and precautions for handling is needed. (The declaration must be legalized in case of imported products from non-reference countries)		
4	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.		
5	**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)		
6	Stability testing site: If not stated in Manufacturers section in CTD or if more than one stability testing site is mentioned then a signed & stamped declaration from the MAH/manufacturer clarifying the stability testing site is required.		
Requirements for the drug substance			
1	**Certificate of analysis (C.O.A) of recently manufactured drug substance (manufacturing date within 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".		
3	**N.B:** - If the Active substance has more than one manufacturer, stability studies must be submitted from each manufacturer. - Pilot scale batches can be provided with an undertaking by the MAH/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 undertaking and batch numbers (in case of on-going stability on production batches). - The stability protocol used for studies on production scale batches shouldbe 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 HPLCanalysis) or (last time interval by HPLC in case of any other method of analysis) for all batches included in all stability studies		
	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 reconstitutionshould 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 orproduction 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.		
4	**<u>The stability studies must be performed as follows:</u>** - 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 orsize, unless bracketing is applied. - If FP has more than one manufacturer/ primary packager, all stabilitystudies must be submitted from each manufacturer/ primary packager. - Stability studies should include samples maintained in the inverted orhorizontal 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 asigned 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-termstability 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 HPLCanalysis) or (last time interval by HPLC in case of any other method of analysis) for all batches included in all stability studies.		
B. Requirements for Stability file of Local Biological Products			
Administrative documents:			
1	Summary sheet (Word) + signed & stamped pdf.		
2	Payment receipts		
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).		
4	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.		
Requirements for the active substance			
1	Valid importation permit (موافقة استيرادية سارية)		
2	An undertaking letter from the applicant mentioning: ➢ Active substance manufacturer name & full address ➢ Batch number of finished product batches.		
3	Stability testing site: If not stated in Manufacturers section in CTD or if more than one stability testing site is mentioned then a signed & stamped declaration from the MAH/manufacturer clarifying the stability testing site is required.		
4	A declaration letter from the active substance manufacturer clarifying: ➢ The stability testing site (name & address) mentioning API batch numbers.		
5	Full S-Part from Module 3		
6	An undertaking by the applicant that the submitted S-Part is authentic & accurate. (تعهد صحة البيانات)		
7	C.O.A of recently manufactured active 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".		
8	**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 active 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.		
9	**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 an undertaking by 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 undertaking 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.		
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 (Same as stability 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): an undertaking by 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 substance 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 Undertaking. - In case of issuing stability approval for pilot scale batches: an undertaking 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 undertaking. - 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.).		
13	**Important notes:** ➢ In case of more than one manufacturer, all stability studies must be submitted from each manufacturer. ➢ Pilot scale batches can be provided with an undertaking by 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 undertaking. ➢ 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 photostability 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.		

		Check	Notes
File V : Scientific File Documents			
A- Administrative Part			
1	Product leaflet in case of first time approval/ approved insert in case of re-reg.		
2	International accreditation (EMA, FDA, TGA, MHLD/PMDA, WHO)		
3	Reference (BNF, Vidal, Compendium Swiss, Rote liste)		
4	Approved price or suggested price (only in cases of reliance file, fast track) &pricing receipt (signed and stamped on company Letter head)		
5	**if plasma derived product (plasma master file &viral inactivation)**		
6	Summary of product characteristics		
7	Scientific template (main and summary data)		
8	CD containing Module2 , Module 4 and Module 5 and contents of all the scientific dossier		
9			
B-Plasma Master File			
1	Cover Letter (signed and stamped with all registered and under registration products in Egypt)		
2	Health authority approval on plasma master file		
3	Certificate of plasma release from national regulatory released same year of PMF		

	submission.		
4	Service considerations		
5	Soft copy of Plasma Master File		
6	For imported finished blood products containing plasma from non-reference countries (not holding GMP from ref. countries or from recognized international accreditation (PPTA/IQPP)): EDA inspection approval for collection centers & finished product factory should be submitted.		
C- Package leaflet			
In Case of imported reference country			
Innovator products			
1	*Proposed* English Insert marketed in Country of Origin (Numbered)		
2	*Proposed* translated Arabic Insert, translated from a Certified translation office, except (Vaccines- Immunosuppressant- IV infusion products- Hospital use only - Immunological products- Contrast agents except iodinated one)		
3	SmPC "summary of product characteristics" and/or CCDS "companycore data sheet"		
4	Comparative table between reference insert & proposed insert (in case of proposed insert is different than reference insert)		
5	Declaration from *MAH* that the submitted insert is the most updated & marketed in COO (insert status)		
6	Module 2-5 soft copy (In case of insert update)		
Biosimilar products			
1	*Proposed* English Insert marketed in Country of Origin (Numbered)		
2	*Proposed* translated Arabic Insert, translated from a Certified translation office, except (Vaccines- Immunosuppressant- IV infusion products- Hospital use only - Immunological products- Contrast agents except iodinated one)		
3	Innovator product insert		
4	SmPC "summary of product characteristics" and/or CCDS "company core data sheet"		
5	Declaration from *MAH* that the submitted insert is the most updated & marketed in COO (insert status)		
6	Comparative table between reference insert & proposed insert (in case of proposed insert is different than reference insert)		
7	Module 2-5 soft copy (In case of insert update)		
In case of imported product from non-reference country			
Standalone product:			
1	*Proposed* English Insert marketed in Country of Origin (Numbered)		
2	*Proposed* translated Arabic Insert, translated from a Certified translation office, except (Vaccines- Immunosuppressant- IV infusion products- Hospital use only - Immunological products- Contrast agents except iodinated one)		
3	SmPC "summary of product characteristics" and/or CCDS "company core data sheet"		
4	Declaration from *MAH* that the submitted insert is the most updated & marketed in COO (insert status)		
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 او/و literatures		
7	Comparative table between reference insert & proposed insert (in case of proposed insert is different than reference insert)		
8	Module 2-5 soft copy (In case of insert update)		
	Biosimilar Product		
1	*Proposed* English Insert marketed in Country of Origin (Numbered)		
2	*Proposed* translated Arabic Insert, translated from a Certified translation office, except (Vaccines- Immunosuppressant- IV infusion products- Hospital use only - Immunological products- Contrast agents except iodinated one)		
3	SmPC "summary of product characteristics" and/or CCDS "company core data sheet"		
4	Declaration from *MAH* that the submitted insert is the most updated & marketed in COO (insert status)		
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 literatures		
7	Comparative table between reference insert & proposed insert (in case of proposed insert is different than reference insert)		
8	Innovator product insert		
9	Module 2-5 soft copy (In case of insert update)		
	In case of local products		
1	*Proposed* English Insert (Numbered)		
2	*Proposed* translated Arabic Insert, translated from a Certified translation office, except (Vaccines- Immunosuppressant- IV infusion products- Hospital use only - Immunological products- Contrast agents except iodinated one)		
3	SmPC "summary of product characteristics"		
4	Reference model insert نموذج النشرة المرجعي التى قامت الشركة بكتابة نشرتها بناءاً عليه		
5	Scientific reference (Trials & Literature): المرجع العلمي لكافة البيانات العلمية المذكورة بالنشرة من خلال الدراسات التى قامت بها الشركة و/او ال literatures		
6	Declaration from *MAH* that the submitted insert is the most updated (insert status, mention revision date)		
7	Innovator product insert (in case of biosimilar)		
8	Comparative table between reference insert & proposed insert (in case of proposed insert is different than reference insert)		
9	Comparative table between current & proposed insert and scientific reference for every part in the insert		
10	Module 2-5 soft copy (In case of insert update)		
	D- Albumin used as stabilizer Requirements		
1	EMA Approval if the plasma master file has an approval from EMA		

2	Certificate of batch release of health authority for this albumin used as astabilizer.		
3	Declaration from the MAH declares the trade name of the albumin used as astabilizer.		
4	**GENERAL INFORMATION (SUMMARY)** 1- Plasma-Derived Products' List 2- Overall Safety Strategy 3- General Logistics		
5	**TECHNICAL INFORMATION ON STARTING MATERIALS** 1- PLASMA ORIGIN 2- Information on centers or establishments in which blood/ plasmacollection is carried out, including inspection and approval, and epidemiological data onblood transmissible infections 3- Information on centers or establishments in which testing of donationsand 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 finishedproducts and vice versa		
6	**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.		
7	Technical characteristics of bags for blood and plasma collection, including information on anticoagulant solutions used.		

			check Notes
File VI- PV requirements			
A- Imported products **(**Soft copy searchable text PDF should be provided)			
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 + "pink receipt" صورة ضوئية من أصل ايصال سداد . 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 التقرير/ التقارير المجمعة الدورية لمأمونية المستحضر (PSUR) طبقا 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 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 رقم 6 / 2021)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 including the concerned product(s) N.B: Starting form 15/05/2022, EPVC will not receive the PV agreement without the inclusion of the concerned product."		
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		
	B- Local products **(**Soft copy searchable text PDF should be provided)		
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 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 رقم 6 / 2021 (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 including the concerned product(s) N.B: Starting form 15/05/2022, EPVC will not receive the PV agreement without the inclusion of the concerned product."		
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** صورة ضوئية من "+pink receipt" وفي هذه الحالة يتعين على الشركة تقديم صورة ضوئية من أصل ايصال سداد ** مقابل الخدمات المقدمة من الادارة المركزية **(Application number)** لكل "yellow receipt" أصل ايصال سداد للرعاية الصيدلية مختوم ا بختم اليقظة بقيمة 1000 جنيه مصري "لا تشمل ضريبة القيمة المضافة" عن طلب تقييم التقرير/ 2022/ طبقا لقرار السيد الاستاذ الدكتور رئيس الهيئة رقم 99 (PSUR) التقارير المجمعة الدورية لمأمونية المستحضر		

Annex II
Check list for documents of Re-registration biological products file

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

		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		
4	Copy of the updated pricing certificate		
5	C.D. containing all content of the 3 files (core, inspection, quality)		
6	A certification that all data in the file is true and accurate and updated and identical to the CD		
7	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 the last update of fees decree)		
10	Original List OF variations from the MA holder		
11	Application form for Renewal of biological medicinal products Signed & Stamped by the Applicant (each paper)		
12	**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))		
13	**<u>For Imported products:</u> CPP issued by Competent Authorities in Country of Origin**		
	Original		
	Authenticated <u>from Embassy</u>		
	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).		

14	**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		
15	**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		
16	Outer label of the Product (1 original pack recently marketed in Egyptian market and 7 layouts)		
17	Inner Label of the product (1 original label that recently marketed in Egyptian market and 7 layouts)		
18	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		
19	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		
20	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		
21	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)		

22	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		
23	Submitting a pledge acknowledging his commitment to the provisions of the Intellectual Property Protection Law No. 82 of 2002		
24	Submit the updated scientific office license, importer register for all importers, Updated Storage License for all Storage sites, updated Tax card & Commercial register		
25	- 7 Copies of Current approved insert - Module 2-5 soft copy (In case of insert update) & Tracking version for insert (Colored, numbered)		
26	CD containing Complete & updated Module 3		
27	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		
28	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)		
29	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)		
30	COA for active substance & finished Product (solvent if needed)		
31	TSE free certificate from license holder		
32	If the materials entering in the product formulation are from blood derivatives, the following will be presented:		
	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)		

		Check	Notes
File II: Inspection file			
1	**Updated 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	*** the following to be submitted if applicable:** - 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 reports 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.		

		Check	Notes
File III: Quality file			
1	Copy of application form for biological products		
2	List of Variation		
3	Summary protocol (for blood products & vaccines)		
4	Complete updated CTD		
5	Certificate of Analysis for Drug substance & Finished product & solvent (if solvent present)		

		check	Notes
File VI- PV requirements			
A. Imported products **(**Soft copy searchable text PDF should be provided)			
1	Delegation letter		
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	"yellow receipt" سداد ايصال أصل ضوئية من صورة + "pink receipt" سداد ايصال أصل من ضوئية صورة بختم ا مختوم الصيدلية للرعاية المركزية الادارة من المقدمة مقابل الخدمات **(File number)** لكل "receipt المعلومات تحديث تقييم ملحق طلب عن "المضافة القيمة ضريبة تشمل لا" مصري جنيه 1000 اليقظة بقيمة / 99 رقم الهيئة رئيس الدكتور الاستاذ السيد لقرار طبقا(ACO) التسجيل إعادة إطار في المقدم الإكلينيكية ، 2022		
5	"yellow receipt" سداد ايصال أصل ضوئية من صورة + "pink receipt" سداد ايصال أصل من ضوئية صورة بختم ا مختوم الصيدلية للرعاية المركزية الادارة من المقدمة مقابل الخدمات **(File number)** لكل "receipt (RMP) المخاطر إدارة تقييم خطة طلب عن "المضافة القيمة ضريبة تشمل لا" مصري جنيه 1000 اليقظة بقيمة المادة/المستحضر اسم بالايصال موضحا2021 / 6 الهيئة رقم رئيس الدكتور الاستاذ السيد لقرار طبقا)المستحضر صاحبة الشركة اسم /التقديم اطار/الشكل الصيدلي – التركيز/الفعالة		
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 activities including the concerned product(s) N.B: Starting form 15/05/2022, EPVC will not receive the PV agreement without the inclusion of the concerned Product."		
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. the company should submit the following: □ Sales data and interval patient exposure in Egypt (for each Year of the reporting interval separately). □ Data in summary tabulations in Egypt during the reporting interval (in a table organized by MedDRA SOC) & the		

	Number of cases reported in Egypt during the interval. N.B: Starting form 01/05/2022, EPVC will not receive The ACO without the above mentioned items."		
10	The most updated "EU/Global/Core-Risk Management Plan (RMP)"of the product.		
11	The Egyptian display of EU-RMP		
	B. Local products **(**Soft copy searchable text PDF should be provided)		
1	Delegation letter		
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	مقابل **(File number)** لكل "pink receipt" + "yellow receipt" سداد ايصال أصل من ضوئية صورة تشمل لا"مصري جنيه 1000 بقيمة اليقظة بختم ا مختوم الصيدلية للرعاية الادارة المركزية من المقدمة الخدمات التسجيل إعادة إطار في المقدم المعلومات الإكلينيكية تحديث ملحق تقييم طلب عن "المضافة القيمة ضريبة (ACO) 99 / 2022 رقم الهيئة رئيس الاستاذ الدكتور السيد لقرار طبقا		
5	مقابل **(File number)** لكل "yellow receipt + pink receipt" سداد ايصال أصل من ضوئية صورة لا تشمل" مصري جنيه 500 بقيمة اليقظة بختم ا مختوم الصيدلية للرعاية الادارة المركزية من المقدمة الخدمات رئيس الدكتور الاستاذ السيد لقرار ا طبق(RMP) المخاطر إدارة خطة تقييم طلب عن "المضافة القيمة ضريبة /التقديم اطار/الشكل الصيدلي – التركيز/الفعالة المادة/المستحضر اسم بالايصال موضحا(2021 / 6 رقم الهيئة)المستحضر صاحبة الشركة اسم		
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 including the concerned product(s) N.B: Starting form 15/05/2022, EPVC will not receive the PV agreement without the inclusion of the concerned Product."		
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		

Annex III: Template for PIL

{(Invented) name strength pharmaceutical form}
{Active pharmaceutical ingredient(s)}

Read all of this leaflet carefully before you start <taking> <using> this medicine.

- Keep this leaflet. You may need to read it again.

- If you have any further questions, ask your < health care provider.

- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.

- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your < health care provider>

In this leaflet:

1. What {product name} is and what it is used for
2. Before you <take> <use> {product name}
3. How to <take> <use> {product name}
4. Possible side effects
5. How to store {product name}
6. Contents of the pack and other information

- **To report any side effect(s):**

• Egypt:

- Egyptian Pharmacovigilance Centre (EPVC):

Adress: 21 AbdelAziz Al Saoud St., Manial ElRawda, Giza, Egypt.

e-mail for reporting: pv.followup@edaegypt.gov.eg

Website for reporting: www.edaegypt.gov.eg

Hotline: 15301

Sean QR code:

The following statements issued by the Council of Arab Health Ministers should be printed in the PIL.

This is a Medicament

− A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.
− Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
− The doctor and the pharmacist are experts in medicine, its benefits and risks.
− Do not, by yourself, interrupt the period of treatment prescribed for you.
− Do not repeat the same prescription without consulting your doctor.
− Keep all medicaments out of reach of children.

Council of Arab Health Ministers
Union of Arab Pharmacists

This patient information leaflet is approved by the Egyptian Drug Authority.

Annex IV: Template for SPC

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC) TEMPLATE
1.NAME OF THE MEDICINAL PRODUCT

2.QUALITATIVE AND QUANTITATIVE COMPOSITION

3.PHARMACEUTICAL form

4.Clinical particulars

4.1Therapeutic indications

4.2 Posology and method of administration

Posology
Method of administration

4.3 Contraindications

4.4 Special warnings and precautions for use

4.5 Interaction with other medicinal products and other forms of interaction
4.6 Pregnancy and lactation
4.7 Effects on ability to drive and use machines
4.8 Undesirable effects
- **To report any side effect(s):**

• Egypt:
- Egyptian Pharmacovigilance Centre (EPVC):

Adress: 21 AbdelAziz Al Saoud St., Manial ElRawda, Giza, Egypt.

e-mail for reporting: pv.followup@edaegypt.gov.eg

Website for reporting: www.edaegypt.gov.eg

Hotline: 15301

Sean QR code:

4.9 Overdose

5.PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

5.2 Pharmacokinetic properties

5.3 Preclinical safety data

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

6.2 Incompatibilities

6.3 Shelf life

6.4 Special precautions for storage

6.5 Nature and contents of container <and special equipment for use, administration or implantation>

6.6 Special precautions for disposal <and other handling>

7. MARKETING AUTHORISATION HOLDER/SUPPLIER

8.DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION

9.DATE OF REVISION OF THE TEXT

This summary of product characteristics is approved by the Egyptian Drug Authority.
The following statements issued by the Council of Arab Health Ministers should be printed in the SPC.

This is a Medicament
− A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.
− Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
− The doctor and the pharmacist are experts in medicine, its benefits and risks.
− Do not, by yourself, interrupt the period of treatment prescribed for you.
− Do not repeat the same prescription without consulting your doctor.
− Keep all medicaments out of reach of children.

Council of Arab Health Ministers
Union of Arab Pharmacists