Guideline for file content of biological products submitted for registration & re-registration file

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1. Introduction

The registration / re-registration files of biological products submitted should be in the common technical document (CTD) format which contains 5 modules, Module 1 of the Common Technical Document (CTD) contains the required regional administrative and regulatory information that need to be submitted. This guideline defines its structure and content, outlines the required documents, and specifies additional documentation requirements to ensure compliance with EDA regulations.

The documents described in this guideline should be prepared and submitted by the Marketing Authorization Holders (MAHs) for the new registration and re-registration of biological products in accordance with EDA Chairman Decree No. 343/2021 and the regulatory guideline for mechanisms and rules of implementing the decree of Egyptian Drug Authority's Chairman No. (343) / 2021 Code: EDREX.GL. BioInn.001.

2. Scope

This guideline defines & covers all regulatory requirements for the administration information file (Module 1) of biological products dossier submission to EDA and applies only to Egypt-specific information, excluding the data addressed in the other modules of the CTD (M2-M5) as established under ICH M4.

3. Abbreviations

ACO	Addendum to clinical overview
ATC	Anatomical Therapeutic Chemical
COO	Country Of Origin
CPP	Certificate of Pharmaceutical Product
CTD	Common Technical Document
EDA	Egyptian Drug Authority
EMA	European Medicines Agency
FDA	Food and Drug Administration
GMP	Good Manufacturing Practice
HDPE	High Density Polyethylene Glycol
ICH	International Council for Harmonization
MAHs	Marketing Authorization Holders
PIL	Patient Information Leaflet
PT	Preferred team
PSMF	Pharmacovigilance System Master File
PSUR	Periodic Safety Updated Report
RMP	Risk Management Plan
SOC	System Organ Class
SmPC	Summary of Product Characteristics

4. Definitions

Biological products: are products containing one or more active ingredient 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 update and/or international standard and reference.

Biosimilar: A biological product that is shown to be highly similar in terms of its quality, safety and efficacy to an already licensed reference product.

Imported products are biological products whether fully manufactured abroad or manufactured abroad and secondary packaged in factories within the Arab Republic of Egypt

Local products: are biological products manufactured in factories inside the Arab Republic of Egypt or the products imported in bulk form that are formulated and/or primary filled in the Arab Republic of Egypt.

Certificate of pharmaceutical products (CPP): a certificate issued by national regulatory authority in the country of origin for a single pharmaceutical product in the format recommended by the world health organization and establishes the status of the pharmaceutical product and the applicant for this certificate in the exporting country.

Common Technical Document (CTD): is a common format for the technical documentation included in an application for the registration of a human pharmaceutical product. The CTD file is divided into five main modules: Module 1: administrative information, Module 2: overviews and summaries of Modules 3-5, Module 3 Quality (pharmaceutical documentation), Module 4: Non-clinical reports (pharmacology/toxicology), Module 5: Clinical reports.

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 biosimilar.

Pharmacovigilance: The science and activities relating to 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.

5. Main topic

5.1 Required documentation for module 1 for new registration of biological products

Detailed requirements are illustrated in **Annex I**

5.2 Required documentation for module 1 for re-registration of biological products

Detailed requirements are illustrated in **Annex II**

5.3 Requirements for pack submission for new registration or re-registration of biological products

I- General considerations

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.

II- Information that should be illustrated on the pack of biological products (whether new registration or re-registration pathway):

- **Product Trade Name**, the company writes the trade name typically as in CPP**, inquiry approval, application form for biological products, and product insert. The generic name shall be printed in letters that are at least half as large as the letters comprising the trade name. If the trade name is a registered trade name®, the company will submit the approval certificate.
- **Active ingredients or generic name**, the company should mention their quantities or strengths identical to the approved product insert, the product composition certificate submitted with the file and Certificate of Pharmaceutical Product (CPP)**
- **The Pharmaceutical Dosage Form** (e.g.: PFS, Vial, PFP,), identical to inquiry approval, biological application forms, product insert, CPP**.
- **Full List of all inactive ingredients**, identical to the product composition certificate submitted with registration/ re-registration file, approved product insert, CPP**.
- **NOTE:** the applicant should mention the excipients with known side effect or have safety/efficacy precautions.
- **Route of administration (e.g.: IV, IM. SC, infusion…)**, as mentioned in CPP**, product insert and approved from scientific committee.
- **Multilingual or English-language 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** it should be mentioned.
- If the dosage form or the product is related **to special population** (infants, 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, each unit with its number of units should be mentioned.
- **Different concentration** should have **different printing colors** for easier identification and avoid medication error.
- **Manufacturer of the finished product:** site address should be mentioned and identical to GMP, manufacturing license, CPP** and biological product application.
  NOTE: it is acceptable for shorting the details of Finished product manufacturer on the outer pack to reflect the site name – city – country if the space limitation is a barrier.

For example:

Full detailed site: manufacturer name, Puerto Rico (PR) 01234-USA

- Shortened site: manufacturer name, Puerto Rico -USA
- **Solvent manufacturing site** (if needed): site address advisable to be mentioned and identical to GMP, manufacturing license, CPP** 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 - If the batch releaser is identified on the label, the name shall be qualified by the phrase **"Batch Releaser site is……..".**
c- If the Secondary packager is identified on the label; the name shall be qualified by the phrase: **"Packaged by ……."**.
If the imported product pack is a country of origin, international or shared pack: **
The company should stamp the manufacturing site by inkjet on the outer pack (according to technical committee 9/7/2020) in case of not mentioning the manufacturer of finished product

- **Product license holder**: company address should be mentioned and identical to request inquiry approval, manufacturing license, CPP** and biological product application.
- **The importer**:** company name and 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 EDA chairman decree 161/2025).
- **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.

** For imported products only

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:

- Generally oriented in the same direction.
- Placed in the same field of vision (i.e., readable without having to turn or rotate the container).
- 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 decreases, 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, which 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:

1. For new registration products or re-registration products the review and approval process starts after inspection approval, stability approval, and product insert approval are issued.
2. If comments are present, the registration administration sends an email with the required documents.
3. Once documents are completed the submitted layouts will be approved by signing and stamping the layouts and writing the obligations that should be stated on outer and inner labels.

5.4 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 summary of product characteristics (SmPC)) 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 effects 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 SmPC, 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 get 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}>

< {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:**

- **General Administration for Pharmaceutical Vigilance**

Address: 21 Abd El Aziz Al Soud Street, El-Manial, Cairo, Egypt, And PO Box: 11451
Telephone: (+2)02 25354100, Extension: 1470
Fax: +202 – 23610497
Email for reporting: pv.followup@edaegypt.gov.eg
Website for reporting: **https://vigiflow-eforms.who-umc.org/eg/med**
Hotline: 15301
QR code:

SCAN ME

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 SmPC and PIL can easily be tracked for updates and review. Each SmPC and PIL should be reviewed every 5 years or when necessary.

5.5 Summary of Product Characteristics (SmPC)

During the evaluation process, applicants may present SmPCs 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 SmPC 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 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 SmPC 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 must 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 minimization 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 considered, 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 based on increasing human experience in exposed pregnancies which eventually supersede 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

Based on the pharmacodynamic profile, Adverse Reactions reported 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-authorization 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 SmPC.
- 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 of ensuring appropriate information for 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.
- 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 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 reactions 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-authorization safety studies or spontaneous reporting).

The table should be presented according to the MedDRA system organ classification. 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. Generally, any adverse reaction 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 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 characterizing specific adverse reactions which may be useful to prevent, assess or manage the occurrence of an adverse reaction in clinical practice.

This section should include information characterizing individual serious and/or frequently 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 related to the same therapy, 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 for 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:

General Administration for Pharmaceutical Vigilance
Address: 21 Abd El Aziz Al Soud Street, El-Manial, Cairo, Egypt, And PO Box: 11451
Telephone: (+2)02 25354100, Extension: 1470
Fax: +202 – 23610497
Email for reporting: pv.followup@edaegypt.gov.eg
Website for reporting: **https://vigiflow-eforms.who-umc.org/eg/med**
Hotline: 15301
QR code:

SCAN ME

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, Anatomical Therapeutic Chemical (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; T_{max}; 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 pharmacokinetics is 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 incompatibility 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 incompatibility 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", "High Density Polyethylene Glycol (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}>

< {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}

6. References:

- Egyptian pharmacy law (127/1955)
- Egyptian Drug Authority establishing decree (151/2019)
- Prime minister decree at (777/2020)
- EDA Chairman Decree (343/2021)
- Ministerial decree 250/2015
- EDA Chairman Decree no. 38/2022 regarding amendment of article no. 4 of EDA Chairman Decree no. 343/2021.
- Regulatory Guideline of Mechanisms and Rules of Implementing the Decree of Egyptian Drug Authority's Chairman No. (343) of 2021.
- WHO SUMMARY OF PRODUCT CHARACTERISTICS (SmPC) TEMPLATE
- WHO patient information leaflet (PIL) template

7. Annexes:

Annex I Required documentation for module 1 for new registration of biological products

Annex II Required documentation for module 1 for re-registration of biological products

Annex III Template for PIL

Annex IV Template for SmPC

8. History table

History Table

Version No.	Issue date	Summary of changes
5	25/5/2026	Updated requirements for Module 1 documentation for new registration and re-registration of biological products, aligned with the eCTD format.

Annex I Required documentation for module 1 for new registration of biological products

	1. Administrative information file (Module 1)
1	Cover letter on applicant head letter signed and stamped by the registration general manager for file submission for registration
2	Application form for registration of biological products signed by the applicant last paper only & stamped each paper
3	**Product Information** • SmPC • Labelling and package leaflet o Proposed English insert marketed in country of origin (Numbered) o 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) o Comparative table between reference insert & proposed insert (in case of proposed insert is different than reference insert) o Innovator product insert in case of biosimilar products o In case of non-reference country imported products & local products only: o Reference model insert o Scientific reference (Literature & Trials) المرجع العلمي لكافة البيانات العلمية المذكورة بالنشرة من خلال الدراسات الشركة التي قامت بها و/او Literature o In case of local products only: o Proposed English Insert (Numbered) o Comparative table between current & proposed insert and scientific reference for every part in the insert • Mock up *(layouts for outer and inner label)* o 1 pack and 7 layouts for each concentration from each manufacturing site (if more than one site). o 1 label and 7 layouts for each concentration from each manufacturing site (if more than one site). 1. The manufacturer is specified 2. The trade name is specified 3. Generic name with strength is specified 4. Batch number is specified 5. Manufacturing date is specified 6. Expiry date is specified

4	**Documents related to pharmacovigilance:** • Cover letter signed by QPPV/LSR (E-signature is accepted without additional stamp) • Latest valid PSMF assessment report/Confirmation e-mail of PSMF document(s) receival. • The latest PSUR(s) (for imported products). • The most updated EU/Global/Core-Risk Management Plan (RMP) (for imported products) • The Egyptian display of EU-RMP/ Global/ Core-RMP (for imported products). • Egyptian integrated RMP (for local products).
5	**Legal documents:** • Letter of Attorney for Company representative • **Manufacturing License for all manufacturers** 1. Valid 2. Authenticated (From Embassy), original or true copy (authentication on the certificate) 3. The name of plant by its address should be specified 4. The invalidation date should be mentioned 5. The production lines are specified 6. Issued from the reference regulatory authority of the specified country (Note: electronic version is acceptable **if Manufacturing License available at EUDRA website – not required to be legalized)**. • **GMP certificate(s) 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)/ Alternative documents** 1. Valid 2. Authenticated (From Embassy), original or true copy (authentication on the certificate) (Note: electronic version is acceptable **if GMP available at EUDRA website – not required to be legalized)**. 3. The name of plant by its address should be specified 4. The date of last inspection should be specified 5. The invalidation date should be mentioned 6. The production lines are specified • The commercial register • Toll manufacturer license issued from EDA • Updated scientific office license issued from EDA • Importers register licenses for all importers issued from EDA • Storage license issued from EDA • Authorization letter / Agency agreement 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 • Manufacturing Agreement if applicable • Packaging Agreement *(or Original Authorization letter from the abroad mother company to a local company for product registration and packaging with a local licensed packaging site)* • Storage Agreement • Other Agreements (e.g. Toll manufacturing contract): the manufacturing contract specifying the intended product should be submitted & certified as truly signed • Termination / Waiver (if exist). • Updated Tax card • List of distributors for the submitted product in Egypt mentioning the responsibility for Lot release activity • A pledge acknowledging his commitment to the provisions of the intellectual property protection law No. 82 of 2002 on applicant letter head • Pharmacovigilance agreement between the MAH & the service provider covering all the Pharmacovigilance activities including the concerned product(s)
6	**EDA Approvals (if any):** • Inquiry approval • Exemption approval • Pricing certificate • Inspection report • Stability protocol approval • Pre-approved letters from EDA concerning the product • Registration license for the solvent
7	**Declarations:** • 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 • Ph. Eur. Certificate(s) of suitability for TSE. • TSE/BSE supplier safety declaration stating the safety of the substances used in the product manufacturing (if CEP not available) • Original letter from the company mentioning that product is TSE free and mentioning countries of origin of source materials • Raw materials storage responsibility declaration (for local products on applicant head letter) • Excipient/s Supplier name & origin for human or animal origin excipient • Declaration from the MAH declares the trade name of the albumin used as stabilizer. • Certificate of batch release from reference regulatory authority for albumin used as stabilizer • If the plasma derivative product manufacturer is not approved in Egypt: Plasma derivative supplier safety and efficacy commitment

	• Declaration letter (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 and that the proposed pack is the most updated (in case of proposed pack is identical to COO pack write most updated and marketed) • Declaration letter from MAH that the submitted product insert is the most updated & marketed in COO (product insert status). • Declaration letter from the License holder declaring that the submitted SMF is the most updated and approved signed, stamped. • The company is committed to ensure that the product will be stored at the proper storage condition according to the submitted stability study • Stability summary sheet • Other declarations requested by EDA (e.g. 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 (for local manufacturers only) • Stability testing site (for DS/DP/Solvent/Intermediates): 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.
8	**<u>Documents related to imported products:</u>** • **Certificate of Pharmaceutical Product (CPP) Note eCPP (if issued from reference country – not required to be legalized)** 1. Original, Authenticated from embassy 2. Valid 3. The Arab Republic of Egypt is mentioned as importing country 4. Number of product license & Date of issue are specified 5. Dosage form (s) and strength (s) are specified. 6. License holder (address, city, country) & Role of license holder are specified 7. Product marketed in the COO 8. 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) 9. Pack Presentation and pack size(s) of the product is (are) specified (could be as an attachment) 10. Active Ingredient(s) by its salt or hydrate form (if any) & Inactive Ingredient(s) with its (their) quantity (ies) per unit dose is (are)specified, along with function or role (could be as an attachment). 11. Shelf-life & storage conditions of the product are specified (could be as an attachment) 12. SmPC 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) • List of affiliates / Subsidiaries stating relation between mother company, license holder, MAH and affiliates related to the product in compliance with CPP (if needed)
9	**Documents related to reliance:** • Sameness letter • Unredacted assessment report along with other relevant supporting documents from the reference regulatory authority such as: reports pertaining to post-approval variations, post marketing commitments, supporting documents on comparative safety and efficacy studies submitted to the reference regulatory authority **and/or** questions & answer documents between applicant and the reference regulatory authority with all annexes • Reference regulatory authority Variation application with annexes • Correspondences between the applicant and the reference regulatory authority relating to safety and efficacy or queries, the risk management plan, or benefit-risk decisions should be provided • List of variations after first MA issued from country-of-origin reference regulatory authority
10	**Composition documents** •**Composition Certificate** 1. Original 2. For imported products composition certificate should be authenticated (From Embassy) or notarized (if not attached to CPP) 3. On license holder letter head 4. Signed & stamped by the license holder (E-signature is accepted without additional stamp) 5. Trade name of the product is specified 6. Dosage form of the product is specified 7. Active ingredient(s) & Inactive ingredient with its (their) quantity(ies) per unit dose is (are) specified 8. Specifications of active & inactive ingredients are mentioned (e.g. in house specification, USP, EU, JP, British pharmacopeia) 9. The overage & overfill should be mentioned 10. Identical to CPP & CTD
11	**Certificate of Analysis:** **A) Active ingredients: (one COA for each manufacturing site)** •Original •Signed and stamped by the company or the concerned center or laboratory that held the analysis (E-signature is accepted without additional stamp)

	•Product name, strength and form are specified •Manufacturing date is specified •Expiry date is specified •Batch number is specified **B) <u>Excipients:</u>** •Signed and stamped by the Company or the concerned center or laboratory that held the analysis Product name, strength and form are specified (E-signature is accepted without additional stamp) • Manufacturing date is specified • Expiry date is specified • Batch number is specified **C) <u>Finished product (one COA for each manufacturing site (if present)</u>** • Original & valid while submission •Signed and stamped by the company or the concerned center or laboratory that held the analysis (E-signature is accepted without additional stamp) • Product name, strength and form are specified • Manufacturing date is specified • Expiry date is specified • Batch number is specified **<u>D) Solvent (one COA for each manufacturing site (if present)</u>**
12	**<u>Proof of Payment for each relevant administration</u>**
13	**<u>Documents related to analysis:</u>** •Detailed standard operating procedures (SOP) Contain information related to: equipment used, proper quantities used in each step in procedure and mention the dilution of the sample and standard, the detailed description of calculation mentioning any used equation or software •Summary protocol for vaccines and Plasma derived medicinal products
14	**<u>Documents related to Plasma derived medicinal products:</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) •HIV-1, HIV-2, HBsAG, HCV freedom legalized certificate for the plasma •Certificate of plasma batch release from reference regulatory authority •Plasma master file approval from country-of-origin reference regulatory Authority
15	**<u>Scientific advice report (if any)</u>**
16	**<u>Scientific template (main and summary data)</u>**
17	**<u>Documents related to local products:</u>** 1-A valid importation approval (For imported drug substance)

	2-Sampling record (for finished product), include the following: A. Batch no. (same as in COA & one of stability batches) B. Batch scale (pilot or production) C. Batch Manufacturing date
18	**<u>Documents related to inspection:</u>** • Site master file (for manufacturer of active substance, manufacturer of finished, manufacturer of solvent, primary & secondary packager and batch releaser) including: 1. Covering letter from the License holder declaring that the submitted SMF is the most updated and approved signed, stamped 2. Relevant Premises & utilities information about each site. 3. Current status of the manufacturing site(s) with respect to current good manufacturing practice (cGMP) requirements. 4. Legible color printouts of water treatment and air-handling systems, including pipeline and instrumentation drawings in A3 or A2 format. (if applicable) 5. List of all the products and dosage forms manufactured on- the same site especially same production lines • Latest full inspection report(s) by stringent regulatory authority (past 3 years) with their outcomes. •List of each site where the product (drug substance and drug product), if authorized, is or would be manufactured. • One completed batch manufacturing and packaging record or master batch manufacturing record (in case of vaccines, summary protocol could be accepted instead). • List of any recalls with quality defects (past 3 years), if found. • Any warning letter or equivalent regulatory action (production- line specific) (if found). • Last annual product quality review. • Cold chain storage & transportation procedures including the allowed excursion during transportation for the product or declaration with cold chain storage and transportation conditions.

Annex II: Required documentation for module 1 for Re- registration of biological products

1. Administrative information file (Module 1)	
1	Cover letter on applicant head letter signed and stamped by the registration general manager for file submission for Re-registration
2	Application form for renewal of biological products signed by the applicant last paper only & stamped each paper
3	**Product Information** • SmPC • Labelling and package leaflet o 7 Copies of current approved insert o Tracking version for insert (Colored, numbered) • Mock up *(layouts for outer and inner label)* o 1 pack recently marketed in Egyptian market and 7 layouts) N.B If there is updated pack approved previously from variation unit, the company will submit the post approval change decision and declaration that the pack is the most updated one and this will be attached with renewal license. If the trade name is a registered trade name® , the company will submit the approval certificate o 1 label that recently marketed in Egyptian market and 7 The manufacturer is specified
4	**Documents related to pharmacovigilance:** • Cover letter signed by QPPV/LSR (E-signature is accepted without additional stamp). • Latest valid PSMF assessment report/Confirmation e-mail of PSMF document(s) receival. • The ACO including domestic data. • The most updated EU/Global/Core-Risk Management Plan (RMP) (for imported products). • The Egyptian display of EU-RMP/ Global/ Core-RMP (for imported products). • Egyptian integrated RMP (for local products).
5	**Legal documents:** • Letter of Attorney for Company representative • **Manufacturing License** 1. Valid 2. Authenticated (from embassy), original or true copy (authentication on the certificate) 3. The name of plant by its address should be specified 4. The invalidation date should be mentioned 5. The production lines are specified 6. Issued from the reference regulatory authority of the specified country

	(Note: electronic version is acceptable **if GMP available at EUDRA GMP website – not required to be legalized)**. • **GMP certificate(s): 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)** 1. Authenticated (from embassy), original or true copy (authentication on the certificate) (Note: electronic version is acceptable **if GMP available at EUDRA GMP website – not required to be legalized)** 2. Valid 3. The name of plant by its address should be specified 4. The date of the last inspection should be specified 5. The invalidation date should be mentioned 6. The production lines are specified • The commercial register • Toll Manufacturer License issued from EDA • Updated Scientific Office License issued from EDA • Importers register license issued from EDA • Storage License issued from EDA • Authorization letter / Agency agreement 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 • Manufacturing Agreement if applicable • Packaging Agreement *(or Original Authorization letter from the abroad mother company to a local company for product registration and packaging with a local licensed packaging site)* • Updated Storage Agreement • Other Agreements (e.g. Toll manufacturing contract): the manufacturing contract specifying the intended product should be submitted & certified as truly signed • Updated Tax card • List of distributors for the submitted product in Egypt mentioning the responsibility for Lot release activity • A pledge acknowledging his commitment to the provisions of the intellectual property protection law No. 82 of 2002 on applicant head letter • Pharmacovigilance agreement between the MAH & the service provider covering all the Pharmacovigilance activities including the concerned product(s)

6	**EDA Approvals (If any):** • Pricing Certificate • Inspection Report • Registration license for the solvent • Variation approvals
7	**Declarations:** • 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 • Ph. Eur. Certificate(s) of suitability for TSE. • TSE/BSE supplier safety declaration (if CEP not available) Original letter from the company mentioning that Product is TSE free and mentioning Countries of origin of source material • Raw materials storage responsibility declaration (for local products on applicant head letter) • Excipient/s Supplier name & origin for human or animal origin excipient • Declaration from the MAH declares the trade name of the albumin used as stabilizer. • Certificate of batch release of reference regulatory authority for this albumin used as stabilizer • If the plasma derivative product manufacturer is not approved in Egypt: Plasma derivative supplier safety and efficacy commitment. • Official declaration letter (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 and that the proposed pack is the most updated (in case of proposed pack is identical to COO pack write most updated and marketed) • Declaration from MAH that the submitted product insert is the most updated & marketed in COO (insert product status). • Declaration letter from the License holder declaring that the submitted SMF is the most updated and approved signed, stamped. • The company is committed that the product will be stored at the proper storage condition according to the submitted stability study • Stability summary sheet • Other declarations requested by EDA (e.g. 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 (for local manufacturers only), • Declaration letter from licence holder /applicants stating all variations • A declaration from the license holder mentioning the product name declare that the submitted CTD (version number & date) at the renewal process is the most updated and complete version.

8	**Documents related to Imported products:** 1. **Certificate of Pharmaceutical Product (CPP)** Note eCPP (if issued is from reference country – not required to be legalized) 2. Original, Authenticated from embassy 3. Valid 4. The Arab Republic of Egypt is mentioned as importing country 5. Number of product license & date of issue are specified 6. Dosage form (s) and strength (s) are specified. 7. License holder (address, city, country) & role of license holder are specified 8. Product marketed in the COO 9. 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) 10. Pack Presentation and pack size(s) of the product is (are) specified (could be as an attachment) 11. Active Ingredient(s) by its salt or hydrate form (if any) & Inactive Ingredient(s) with its (their) quantity (ies) per unit dose is (are)specified, along with function or role (could be as an attachment). 12. Shelf-life & Storage conditions of the product are specified (could be as an attachment) 13. SmPC 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) • List of affiliates / Subsidiaries stating relation between mother company, license holder, MAH and affiliates related to the product in compliance with CPP (if needed)
9	**Composition documents** **1. Composition Certificate** 2. Original * for imported products authenticated (from Embassy) or notarized (if not attached to CPP) 3. On license holder letter head 4. Signed & stamped by the license holder (E-signature is accepted without additional stamp) 5. Trade name of the product is specified 6. Dosage form of the product is specified 7. Active ingredient (s) & inactive ingredient with its (their) quantity (ies) per unit dose is (are) specified 8. Specifications of Active & inactive ingredients are mentioned (e.g. in house specification, USP, EU, JP, British pharmacopeia) 9. The overage & overfill should be mentioned 10. Identical to CPP & CTD

10	**<u>Certificate of Analysis</u>** **A) <u>Active ingredients (one COA for each manufacturing site):</u>** • Original •Signed and stamped by the company or the concerned center or laboratory that held the analysis (E-signature is accepted without additional stamp) • Product name, strength and form are specified • Manufacturing date is specified • Expiry date is specified • Batch number is specified **B) <u>Excipients:</u>** •Signed and stamped by the Company or the concerned center or laboratory that held the analysis (E-signature is accepted without additional stamp) • Product name, strength and form are specified • Manufacturing date is specified • Expiry date is specified • Batch number is specified **C) <u>Finished product for each manufacturing site (if present)</u>** • Original & valid while submission •Signed and stamped by the company or the concerned center or laboratory that held the analysis (E-signature is accepted without additional stamp) • Product name, strength and form are specified • Manufacturing date is specified • Expiry date is specified • Batch number is specified **D) <u>COA of solvent for each manufacturing site (if present)</u>**
11	**<u>Proof of Payment for each relevant administration</u>**
12	**<u>Documents related to Plasma derived medicinal products:</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) •HIV-1, HIV-2, HBsAG, HCV freedom legalized certificate for the plasma •Certificate of plasma batch release from reference regulatory authority •Plasma master file approval from country-of-origin reference regulatory authority

13	**<u>Documents related to inspection:</u>** • Site master file (for manufacturer of active substance, manufacturer of finished, manufacturer of solvent, primary & secondary packager and batch releaser) including: 1. Covering letter from the License holder declaring that the submitted SMF is the most updated and approved signed, stamped. 2. Relevant Premises & utilities information about each site. 3. Current status of the manufacturing site(s) with respect to current good manufacturing practice (cGMP) requirements. 4. Legible color printouts of water treatment and air-handling systems, including pipeline and instrumentation drawings in A3 or A2 format. (if applicable) 5. List of all the products and dosage forms manufactured on- the same site especially same production lines. • Latest full inspection report(s) by stringent regulatory authority (past 3 years), with their outcomes. • List of each site where the product (drug substance and drug product), if authorized, is or would be manufactured. • One completed batch manufacturing and packaging record or master batch manufacturing record (in case of vaccines, summary protocol could be accepted instead). • List of any recalls with quality defects (past 3 years), if found • Any warning letter or equivalent regulatory action (production- line specific) (if found). • Last annual product quality review • Cold chain storage & transportation procedures including the allowed excursion during transportation for the product or declaration with cold chain storage and transportation conditions.

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 names
6. Contents of the pack and other information

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

General Administration for Pharmaceutical Vigilance
Address: 21 Abd El Aziz Al Soud Street, El-Manial, Cairo, Egypt, And PO Box: 11451
Telephone: (+2)02 25354100, Extension: 1470
Fax: +202 – 23610497
Email for reporting: pv.followup@edaegypt.gov.eg
Website for reporting: **https://vigiflow-eforms.who-umc.org/eg/med**
Hotline: 15301
QR code:

SCAN ME

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 SmPC

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC) TEMPLATE

1.NAME OF THE MEDICINAL PRODUCT

2.QUALITATIVE AND QUANTITATIVE COMPOSITION

3.PHARMACEUTICAL form

4.Clinical particulars

4.1 Therapeutic indications
4.2 Posology and 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:

General Administration for Pharmaceutical Vigilance
Address: 21 Abd El Aziz Al Soud Street, El-Manial, Cairo, Egypt, And PO Box: 11451
Telephone: (+2)02 25354100, Extension: 1470
Fax: +202 – 23610497
Email for reporting: pv.followup@edaegypt.gov.eg
Website for reporting: **https://vigiflow-eforms.who-umc.org/eg/med**
Hotline: 15301
QR code:

SCAN ME

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 SmPC.

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 Pharmacies