Requirements of Stability file for Imported Biological Products

1. Administrative documents

1. Cover letter clarifying the purpose of submission.
2. Summary sheet ((Word) + signed & stamped pdf.)
3. Box Approval (in case of 343 or 820).
4. Valid legalized C.P.P that includes:
   - Trade name, dosage form, active ingredients & composition
   - Stating the license holder, manufacturers of the finished product.
5. SmPC (Must be in English. If not, official translation is required)
   - If SmPC is not attached to the CPP, then a declaration letter from global is required to confirm that this the most updated version marketed in the country of origin, with commitment to submit the legalized SmPC within 6 months from the date of commitment.
     N.B.: (If the CPP is from EMA or FDA, no legalization is needed).
   - If SmPC isn't available, then Patient Information Leaflet (PIL) from Mother Company is required.
   - If shelf life and storage conditions aren't present in SmPC or in case of storage conditions in SmPC is "it doesn't require any specialized conditions", then a declaration letter for the required storage conditions with exact temperature is required from Mother Company signed, stamped and legalized.
     N.B.: (If the CPP is from EMA or FDA, no legalization is needed).
   - If temperature storage is at (25 °C), a commitment from the applicant to store the product in warehouses and pharmacies at temperature not exceeding (25 °C) is required.
6. Signed & stamped declaration from global with the stability testing site for the submitted stability studies, mentioning the batch numbers.
7. Composition:
   - Composition from the C.T.D section "3.2.P.1"
   - It should be similar to Composition in C.P.P.
   - If the composition isn't present in C.P.P, so legalized composition is required.
   - Signed & stamped composition on company papers
   - Mentioning trade name, dosage form, strength
   - It should include a table that contain:
     (Function, reference to standard & grades (if applicable) of each ingredient)
8. If the responsibilities of the manufacturers from CTD section "3.2.P.3.1" does not clarify the manufacturers, Packagers (primary & secondary), batch releaser & stability testing site, than a signed & stamped declaration letter is required from Mother Company.
9. Commitment from the applicant that all the data are authentic & accurate (تعهد صحة البيانات).
10. Pack layout (marketed in country of origin).
11. Full Module 3 (For the drug substance & the drug product).

2. Requirements for the drug substance:

1. Certificate of analysis (C.O.A) of recently manufactured drug substance (5-10 years):
   - Clarifying the manufacturer name & address,
   - With manufacturing & expiry dates (corresponds to the required shelf life) and tested parameters following the same specifications as in section "3.2.S.4.1".
2. Stability studies:
   - Stability studies (Long-term & accelerated) & its protocol of 3 (pilot or production scale) batches carried out in the intended drug substance container-closure system, containing manufacturing site, manufacturing date and tested parameters that follows the same specifications as in section "3.2.S.4.1".

N.B:

- If the drug substance has more than one manufacturer, stability studies must be submitted from each manufacturer.
- Pilot scale batches can be provided with a commitment from the mother company to place the first three production scale batches into the long-term stability program after approval and submitting the study once completed mentioning the date of submission in the commitment and batch numbers (in case of on-going stability on production batches).
- The stability protocol used for studies on production scale batches should be the same as that for the pilot batches, unless otherwise scientifically justified.
- **For imported products from non-reference countries only:** Assay chromatograms should be submitted for each time point (in case of HPLC analysis) or (last time interval by HPLC in case of any other method of analysis) for all batches included in all stability studies.

3. Requirements for the drug product:

1. Certificate of analysis "C.O. A" of recently manufactured finished product (5-10 years):
   - Signed and Stamped
   - Clarifying the manufacturer and primary packager.
   - With manufacturing & expiry dates (corresponds to the required shelf life) and tested parameters that follows specifications as in CTD section "3.2.P.5.1".
   - **If the product is powder:** the color of powder before & after reconstitution should be mentioned in the COA and specifications, unless otherwise scientifically justified.
2. Certificate of analysis "C.O. A" of recently manufactured solvent (5-10 years), if applicable.
3. Stability studies:
   - **Long-term stability study** & its protocol of 3 (pilot or production scale) batches
   - **Accelerated stability study** & its protocol of 3 (pilot or production scale) batches
   - **In-use :(** after reconstitution / after dilution) stability study on at least two pilot scale batches
     (The age of one batch is at the beginning of shelf-life and the age of the other near the end of shelf-life)

- **Stability of solvent**: long-term and accelerated & its protocol of 3 (pilot or production scale) batches (If applicable).
- **Photo-stability study** on at least one pilot scale batch.
- **For Biosimilar products:** Side-by-side accelerated and stress studies carried out using a representative number of batches, comparing the biosimilar product to the reference product are mandatory to determine the similarity of the products by showing comparable degradation profiles. Any differences concerning the stability profile of the biosimilar product when compared to the reference product should be justified.

N.B:

- The stability studies must be performed as follows:
  - On the exact composition as that in the submitted CPP.
  - Carried out in the intended commercial drug product container-closure system
  - Contain name of the manufacturing site & primary packager
  - Contain manufacturing date (within 5- 10 years)
  - Contain tested parameters that follow specifications as in CTD section "3.2.P.5.1".
- If finished product has more than one strength, container type or size, stability study must be done on 3 batches (in case of new registration) or one batch (in case of renewal) for each individual strength, container type or size, unless bracketing is applied.
- If FP has more than one manufacturer/ primary packager, all stability studies must be submitted from each manufacturer/ primary packager.
- Stability studies should include samples maintained in the inverted or horizontal position (i.e., in contact with the closure), as well as in the upright position. (worst scenario)
- If the scale of batches (production / pilot) is not stated in the CTD, then a signed and stamped declaration is needed to clarify the scale of the submitted batches.
- Pilot scale batches can be provided with a commitment from the mother company to place the first three production scale batches into the long-term stability program after approval and submitting the study once completed mentioning the date of submission in the commitment and batch numbers (in case of on-going stability on production batches).
- The stability protocol used for studies on production scale batches should be the same as that for the pilot batches, unless otherwise scientifically justified.
- **For imported products from non-reference countries only:** Assay chromatograms should be submitted for each time point (in case of HPLC analysis) or (last time interval by HPLC in case of any other method of analysis) for all batches included in all stability studies.

Requirements for Inspection and Stability file of Local Biological Products

A. Administrative documents

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

- **In case of** performing the stability study in place rather than the manufacturer, attach the following:
  - Contract between the applicant and the place at which the stability study was performed (Authenticated by the legal counsel of EDA)
  - Copy of the license of the place at which the stability study was performed.

B. Requirements for finished product:

1. Composition:
   - Stamped and signed on applicant paper
   - Mentioning trade name, dosage form, strength
   - Mentioning function, reference to standard & grades (if applicable) of each ingredient.
2. Description of Manufacturing Process and Process Controls (name, dosage form)
3. Certificate of analysis "C.O. A" of 3 batches of finished product (and solvent, if applicable):
   - Signed and Stamped
   - It should mention trade name, strength, dosage form, pack size & description, the manufacturer & primary packager.
   - With manufacturing & expiry dates (corresponds to the required shelf life) and tested parameters as stated in specifications submitted in the file.
   - **If the product is powder:** the color of powder before & after reconstitution should be mentioned in the COA and specifications.
4. Declaration with the shelf-life & storage conditions of the product:
   - Signed &stamped from the manufacturer and to use the same wording of the proposed conditions as the reference product insert marketed in Egypt.
   - In case of storage temperature at (25 °C): a commitment from the applicant to store the product in warehouses and pharmacies at temperature not exceeding (25 °C) is required.
5. Pack description:
   - Signed &stamped from the manufacturer
   - Mentioning color, material of each component of primary pack, no. of units per secondary pack & its description.
6. Sampling record (محضر السحب), include the following:
   - Batch no. (same as in stability study)
   - Batch scale (pilot or production)
   - Manufacturing date of batches

7. Reference product insert marketed in Egypt.
8. Sample.
9. Finished product specification:
   - Tested parameters: Appearance and description, Identity, Purity and impurities, Potency, Sterility test or alternatives, etc….
   - Mentioning method of analysis and reference for each method.
   - Justification of specification
10. Method of analysis. (detailed procedures)
11. Validation of analytical procedure of active ingredient assay and related substances along with HPLC chromatograms for each parameter (in case of HPLC analysis)
12. Stability Studies:

a) Stability Summary and Conclusion
   - ⇨ Summarizing the following details for each study (Long-term, accelerated, In-use, after reconstitution, after dilution, photostability or solvent):
     - Storage conditions (temperature & relative humidity) and duration of the study.
     - Details of tested batches (Manufacturing date, manufacturer & primary packager of finished product, pack details, batch scale (pilot or production))
     - Study protocol in tabular format (Tested attributes as per specifications and the frequency of testing for each test)
     - Summary of test results and justification for any out-of-specification results.
     - Conclusion for shelf-life and storage conditions.

b) Post-approval Stability Protocol and Stability Commitment.
   - In case of issuing stability approval for pilot scale batches: a commitment to place the first three production scale batches into the long-term stability program after approval and submitting the study once completed mentioning the date of submission in the commitment.
   - The stability protocol used for studies on production scale batches should be the same as that for the pilot batches, unless otherwise scientifically justified.

c) Stability Data Tables and assay chromatograms for each time point (in case of HPLC analysis) or (last time interval by HPLC in case of any other method of analysis) for all batches included in all stability studies:
   - Each table should include the study type (long-term, accelerated, In-use, after reconstitution, after dilution, photostability), trade name & strength, batch number and pack size.
   - The shelf-life will be based on the stability data submitted (12 months data = shelf-life of 12 months, 18 months data = shelf-life of 18 months….etc.).

- **N.B:**

➢ In case of more than one manufacturer, all stability studies must be submitted from each manufacturer.

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

- The stability protocol used for studies on production scale batches should be the same as that for the pilot batches, unless otherwise scientifically justified.
- Required number of batches for each study:

1- Long-term and accelerated studies on 3 (pilot or production) batches.
2- In-use :(after opening / after reconstitution / after dilution) stability study on at least two pilot scale batches. (The age of one batch is at the beginning of shelf-life and the age of the other near the end of shelf-life).
3- Photo-stability study on at least one pilot scale batch.
4- Long-term stability study of solvent on 3 (pilot or production) batches.
   - The stability studies must be performed on the exact composition as that attached to transfer letter
   - In case of the finished product has more than one strength, container type or size, stability study must be done on 3 batches for each individual strength, container type or size, unless bracketing is applied.
   - In case of more than one manufacturer, all stability studies must be submitted from each manufacturer (except photo-stability study).

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

C. Requirements for the drug substance:

1- موافقة استيرادية سارية
2- A commitment letter from the applicant mentioning:
   - Drug substance manufacturer name & full address
   - Batch number of finished product batches.
3- A declaration letter from the drug substance manufacturer clarifying:
   - The stability testing site (name & address) mentioning drug substance batch numbers.
4- Full S-Part from Module 3.
5- A commitment from the applicant that the submitted S-Part is authentic & accurate.
   (تعهد صحة البيانات)

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

7- Stability Study:

- Stability studies "3.2.S.7.3"and assay chromatograms for each time point (in case of HPLC analysis) or (last time interval by HPLC in case of any other method of analysis) for all batches included in all stability studies (for all batches included in all stability studies):
  - Long-term and accelerated stability studies and its protocol of 3 (pilot or production) batches carried out in the intended drug substance container-closure system, containing manufacturing site, manufacturing date and tested parameters that follow the same specifications as in section "3.2.S.4.1", unless otherwise justified.

N.B:

- In case of more than one manufacturer, all stability studies must be submitted from each manufacturer.
- Pilot scale batches can be provided with a commitment from the manufacturer to place the first three production scale batches into the long-term stability program after approval and submitting the study once completed mentioning the date of submission in the commitment and batch numbers (in case of on-going stability on production batches).
- The stability protocol used for studies on production scale batches should be the same as that for the pilot batches, unless otherwise scientifically justified.