Requirements of Stability file for Imported Biological Products (Reference)

A. Administrative documents

B. Cover letter clarifying the purpose of submission +covering letter of the file content.
C. Summary sheet ((Word) + signed & stamped pdf.)
D. Transfer letter from the registration department (in case of 297) or box approval (in case of 820).
E. A copy of registration license + attached composition (in case of renewal).
F. Valid legalized C.P.P that includes:
   - Trade name, dosage form, active ingredients & composition
   - Stating the license holder, manufacturers of the finished product.

G. 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.

H. Signed & stamped declaration from global with the stability testing site for the submitted stability studies, mentioning the batch numbers.
I. Full Module 3 (For the drug substance & the drug product).
   - The required sections from CTD must be submitted in a separate folder, where each section in a separate pdf file.

J. Commitment from the applicant that all the data are authentic & accurate (تعهد صحة البيانات).
K. Copy for any previous approved variations related to the product information in the registration license, in a separate folder (In case of renewal only)

L. Requirements for the drug substance:

1. Manufacturer(s) section from CTD "3.2.S.2.1"
2. Description of Manufacturing Process and Process Control
3. 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".
4. Batch Analysis section from CTD "3.2.S.4.4"
5. Specification section from CTD "3.2.S.4.1"illustrating method of analysis and reference for each method.
   - Justification of Specification section from CTD "3.2.S.4.5"
6. Container Closure System section from CTD "3.2.S.6"

7. Stability section "3.2.S.7":
   - Stability Summary and Conclusion from CTD section "3.2.S.7.1"
   - Post-approval Stability Protocol and Stability Commitment from CTD section "3.2.S.7.2"
   - The stability protocol used for studies on production scale batches should be the same as that for the pilot batches, unless otherwise scientifically justified.

   - Stability studies:

- **In case of new registration:**

- 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".

- **In case of renewal:**

- Long-term stability study & its protocol of 1 production batch 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).

M. Requirements for the drug product:

1. 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)
2. The responsibilities of the manufacturers from CTD section "3.2.P.3.1"
   - That clarify the manufacturers, Packagers (primary & secondary), batch releaser & stability testing site
   - If any of them is not present in this section then a signed & stamped declaration letter is required from Mother Company.
3. Description of Manufacturing Process and Process Control
4. Release and shelf life specifications from CTD section "3.2.P.5.1"
   - "Illustrating method of analysis and reference for each method.
   - Justification of specification section from CTD "3.2.P.5.6"

5. 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.
6. Certificate of analysis "C.O. A" of recently manufactured solvent (5-10 years), if applicable.
7. Batch analysis section from CTD "3.2.P.5.4"
8. Pack layout (marketed in country of origin).
9. Container closure system from the C.T.D section "3.2.P.7":
   - That include full Pack description in details (primary pack description in terms of material, color, volume; secondary pack)
10. Stability section "3.2.P.8":
    - Stability Summary and Conclusion from CTD section "3.2.P.8.1"
    - Post-approval Stability Protocol and Stability Commitment from CTD section "3.2.P.8.2".
    - The stability protocol used for studies on production scale batches should be the same as that for the pilot batches, unless otherwise scientifically justified.

    - Stability studies:

- **In case of new registration:**
  - **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.

- **In case of renewal:**
  - **Long-term stability study** & its protocol of one production batch.
  - **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)
    (In case of shelf life & storage conditions aren't mentioned in registration license)

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).

- **If Biosimilar product:**
  Side-by-side accelerated and stress studies 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.

Requirements of Stability file for Imported Biological Products (Non-Reference)

A. Administrative documents

A. Cover letter clarifying the purpose of submission +covering letter of the file content.
B. Summary sheet ((Word) + signed & stamped pdf.)
C. Transfer letter from the registration department (in case of 297) or box approval (in case of 820).
D. A copy of registration license + attached composition (in case of renewal).
E. Valid legalized C.P.P that includes:
   - Trade name, dosage form, active ingredients & composition
   - Stating the license holder, manufacturers of the finished product.
F. 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.
   - 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.
   - 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.
G. Signed & stamped declaration from global with the stability testing site for the submitted stability studies, mentioning the batch numbers.
H. Full Module 3 (For the drug substance & the drug product).
   - The required sections from CTD must be submitted in a separate folder, where each section in a separate pdf file.
I. Commitment from the applicant that all the data are authentic & accurate (تعهد صحة البيانات).
J. Copy for any previous approved variations related to the product information in the registration license, in a separate folder (in case of renewal only)

K. Requirements for the drug substance:

1. Manufacturer(s) section from CTD "3.2.S.2.1"
2. Description of Manufacturing Process and Process Control
3. 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".
4. Analytical Procedures "3.2.S.4.2".
5. Validation of Analytical Procedures "3.2.S.4.3" :
   - For assay and related substances (with HPLC chromatograms for each parameter (in case of HPLC analysis).
6. Batch Analysis section from CTD "3.2.S.4.4"
7. Specification section from CTD "3.2.S.4.1"illustrating method of analysis and reference for each method.

- Justification of Specification section from CTD "3.2.S.4.5"

8. Container Closure System section from CTD "3.2.S.6"
9. Stability section "3.2.S.7":
   - Stability Summary and Conclusion from CTD section "3.2.S.7.1"
   - Post-approval Stability Protocol and Stability Commitment from CTD section "3.2.S.7.2"
   - The stability protocol used for studies on production scale batches should be the same as that for the pilot batches, unless otherwise scientifically justified.

- Stability studies:

- **In case of new registration:**

- 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".

- **In case of renewal:**

- Long-term stability study & its protocol of 1 production batch 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).

- 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.

L. Requirements for the drug product:

1. 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)

2. The responsibilities of the manufacturers from CTD section "3.2.P.3.1"
   - That clarify the manufacturers, Packagers (primary & secondary), batch releaser & stability testing site

- If any of them is not present in this section then a signed & stamped declaration letter is required from Mother Company.

3. Description of Manufacturing Process and Process Control
4. Analytical Procedures "3.2.P.5.2".
5. Validation of Analytical Procedures "3.2.P.5.3": (with HPLC chromatograms for each parameter (in case of HPLC analysis) or (degradation by HPLC in case of any other method of analysis)
6. Release and shelf life specifications from CTD section "3.2.P.5.1"
   - "Illustrating method of analysis and reference for each method.
   - Justification of specification section from CTD "3.2.P.5.6"
7. 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.
8. Certificate of analysis "C.O. A" of recently manufactured solvent (5-10 years), if applicable.
9. Batch analysis section from CTD "3.2.P.5.4"
10. Pack layout (marketed in country of origin).
11. Container closure system from the C.T.D section "3.2.P.7":
    - That include full Pack description in details (primary pack description in terms of material, color, volume; secondary pack)
12. Stability section "3.2.P.8":
    - Stability Summary and Conclusion from CTD section "3.2.P.8.1"
    - Post-approval Stability Protocol and Stability Commitment from CTD section "3.2.P.8.2".
    - The stability protocol used for studies on production scale batches should be the same as that for the pilot batches, unless otherwise scientifically justified.

    - Stability studies:

- **In case of new registration:**
  - **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.

- **In case of renewal:**
  - **Long-term stability study** & its protocol of one production batch.
  - **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)
(In case of shelf life & storage conditions aren't mentioned in registration license)

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).
- 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

- **If Biosimilar product:**
  Side-by-side accelerated and stress studies 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.

Requirements of Stability file for Local Biological Products

M. Administrative documents

N. Cover letter clarifying the purpose of submission + cover letter of the file contents.
O. Summary sheet (Word) + signed & stamped pdf.
P. Transfer letter from the registration department with attached composition.
Q. Registration license with attached composition (in case of renewal only)
R. Copy for any previous approved variations related to the product information in the registration license, in a separate folder (in case of renewal only)

S. Requirements for finished product:

1- Composition:
- Stamped and signed on applicant paper
- Identical to the attached one in transfer letter
- Mentioning trade name, dosage form, strength
- Mentioning function, reference to standard & grades (if applicable) of each ingredient.

2- Certificate of responsibility (C.O.R) stamped from the site at which the stability study was performed, mentioning the batch numbers for the submitted stability studies. (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.

3- Description of Manufacturing Process and Process Controls (name, dosage form)
4- Method of analysis. (detailed procedures)
5- Validation of analytical procedure of active ingredient assay and related substances along with HPLC chromatograms for each parameter (in case of HPLC analysis).
6- 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

7- Certificate of analysis "C.O. A":
- Signed and Stamped
- In case of new registration :3 C.O. As
- In case of re-registration :1 C.O.A
- C.O.A of solvent, if applicable
- 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.

8- 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.

9- Reference product insert marketed in Egypt.

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

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

12- Sample (in case of new only)

13- 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:**

➢ Required number of batches for each study:

1- Long-term and accelerated studies on 3 (pilot or production) batches (in case of new) or 1 production batch (in case of renewal).
2- In-use :(after reconstitution / after dilution) stability study on at least 2 pilot scale batches (in case of new) or 2 production batches (in case of renewal).

➢ (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. (in case of new only)

➢ The stability studies must be performed on the exact composition as that attached to transfer letter
➢ If the finished product has more than one strength, container type or size, stability study must be done on 3 batches (in case of new) or one batch (in case of renewal) for each individual strength, container type or size, unless bracketing is applied.
➢ In case of more than one manufacturer, all stability studies must be submitted from each manufacturer.

- **Additional studies in case of biosimilar product:**

➢ Side-by-side accelerated and stress studies 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.

T. 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- A copy of the following sections from CTD submitted in a separate folder, where each section in a separate pdf file:

a) Manufacturer(s) section "3.2.S.2.1"
b) Specification section "3.2.S.4.1" (mentioning method of analysis and reference for each method)
c) Analytical Procedures "3.2.S.4.2".
d) Validation of Analytical Procedures "3.2.S.4.3" for assay and related substances (with HPLC chromatograms for each parameter (in case of HPLC analysis).
e) Batch Analysis section "3.2.S.4.4"
f) Justification of Specification section "3.2.S.4.5"
g) Container Closure System section "3.2.S.6"
h) Stability section "3.2.S.7":
i. Stability Summary and Conclusion from CTD section "3.2.S.7.1"
ii. Post-approval Stability Protocol and Stability Commitment from CTD section "3.2.S.7.2"

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

iii. 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 (in case of new) or Long-term stability study and its protocol of one production batch (in case of renewal) 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).

- **If Biosimilar product:**

Side-by-side accelerated and stress studies 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.

Requirements of Variation Stability file for Imported Biological Products

1. Cover letter clarifying the purpose of submission.
2. Covering letter of the file contents.
3. Commitment from the applicant that all the data are authentic & accurate (تعهد صحة البيانات).
4. Summary sheet ((Word) + signed & stamped pdf.)
5. Transfer letter from the biological department.
6. A copy of registration license with attached composition.
7. Any variation approvals related to the product information in the registration license.
8. Variation approval from country of origin.
9. Valid legalized C.P.P includes trade name, dosage form, active ingredients & composition and stating the license holder, manufacturers of the finished product.
10. SmPC (Must be in English. If not, official translation is required) - If SmPC isn't available, then Patient Information Leaflet (PIL) from Mother Company is required.
11. Signed & stamped declaration from global with the stability testing site. (If not stated in Manufacturers section in CTD)
12. COA of the DS or DP (depends on variation).
13. The following CTD sections:
    - Manufacturers section (DS & DP)
    - Composition
    - Container closure system for the DS or DP (depends on variation)
    - Specifications for the DS or DP (depends on variation)
14. Stability study requirements mentioned in the transfer letter as per WHO guidelines.
    - In case of comparative pre-change & post-change stability studies are required, the pre-change stability should be completed (long-term &/or accelerated, depends on the type of studies required) on the number of batches defined in the transfer letter.

Requirements of Variation Stability file for Local Biological Products

1. Cover letter clarifying the purpose of submission.
2. Covering letter of the file contents.
3. Commitment from the applicant that all the data are authentic & accurate (تعهد صحة البيانات).
4. Summary sheet ((Word) + signed & stamped pdf.)
5. Transfer letter from the biological department.
6. A copy of registration license with attached composition.
7. Any variation approvals related to the product information in the registration license.
8. PIL
9. Finished product specification (physical, chemical, impurities, related substances & microbiological), mentioning method of analysis and reference for each method.
10. In case of DS variation: Signed & stamped declaration from global with the stability testing site. (If not stated in Manufacturers section in CTD), while in case of DP: 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).
11. COA of the DS or DP (depends on variation).
12. The following CTD sections (In case of DS variation):
    - Manufacturers section
    - Container closure system
    - Specifications
13. Stability study requirements mentioned in the transfer letter as per WHO guidelines.

Requirements of Stability study for Annual update of Imported Influenza vaccines

a) Cover letter clarifying the purpose of submission.
b) Covering letter of the file contents.
c) Commitment from the applicant that all the data are authentic & accurate (تعهد صحة البيانات).
d) Summary sheet ((Word) + signed & stamped pdf.
e) Transfer letter from the variation department.
f) A copy of registration license with attached composition.
g) Any variation approvals related to the product information in the registration license.
h) Valid legalized CPP includes trade name, dosage form, active ingredients & composition (strains for the upcoming season) and stating the license holder, manufacturers of the finished product.
i) SmPC (Must be in English. If not, official translation is required)
   - If SmPC isn't available, then Patient Information Leaflet (PIL) from Mother Company is required.
   - If shelf life and storage conditions aren't present in SmPC or in case of storage conditions in SmPC is "it doesn't require any specialized conditions", then a declaration letter for the required storage conditions with exact temperature is required from Mother Company signed, stamped and legalized.
   - In case of (EMEA or FDA) approved products: If the storage conditions in SmPC are "it doesn't require any specialized conditions", then a declaration letter for the required storage conditions and exact temperature, signed and stamped from Mother Company is required
j) Signed & stamped declaration from global clarifying the stability testing site, name & address (for DS & DP).

k) Requirements for the drug substance:

1. Manufacturer(s) section from CTD "3.2.S.2.1"
2. Specification section from CTD "3.2.S.4.1"
3. "C.O.A" for each new strain (for upcoming season):
   - 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".
5. Container Closure System section from CTD "3.2.S.6"
6. Stability section "3.2.S.7":
   i. Stability Summary and Conclusion from CTD section "3.2.S.7.1",
      - Containing stability protocol.
   ii. Post-approval Stability Protocol and Stability Commitment from CTD section "3.2.S.7.2"

iii. Stability studies:

- Carried out in the intended drug substance container-closure system.
- Containing manufacturing site, manufacturing date and tested parameters following the same specifications as in section "3.2.S.4.1".
- For new strains (in the previous season):
  - On-going Stability studies (updated to the last available time-point) of 3 production batches under real-time storage conditions (minimum 6 months) and accelerated storage conditions (minimum 3 months).
- For new strains (in the upcoming season):

  A commitment is required from the mother company to:
  - Place the first three production scale batches of monovalent bulk into the stability program (detailed in a post-approval stability protocol) under real-time and accelerated storage conditions after approval.
  - Submit the on-going Stability studies (updated to the last available time-point) with the next season submission.
  - Submit the studies once completed mentioning the date of submission in the commitment.

- N.B:

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

l) Requirements for the drug product:

1. Composition:
   - Composition from the C.T.D section "3.2.P.1" for new season
     - 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:
       (Ingredients with their grades, function of each ingredient, quantity & reference).
2. The responsibilities of the manufacturers from CTD section "3.2.P.3.1"
   - That clarify the manufacturers, Packagers (primary & secondary), batch releaser & Stability testing site
   - If any of them is not present in this section then a signed & stamped declaration letter is required from Mother Company.

3. Container closure system from the C.T.D section "3.2.P.7":
   - including full Pack description in details (number of units per pack, primary pack description in terms of material, color, volume; secondary pack)
4. Release and shelf life specifications from CTD section "3.2.P.5.1"
5. Signed and Stamped certificate of analysis "C.O.A" of finished product (for upcoming season):
   - clarifying the manufacturer, primary packager and to be released from the batch releaser
   - containing manufacturing & expiry dates (corresponds to the required shelf life)
   - tested parameters that follow same specifications from CTD section "3.2.P.5.1"

11. Stability section "3.2.P.8":

- Stability Summary and Conclusion from CTD section "3.2.P.8.1"
  - Contain stability protocol.
- Post-approval Stability Protocol and Stability Commitment from CTD section "3.2.P.8.2".
  - The stability protocol used for studies on upcoming season batches should be the same as that for the previous season batches, unless otherwise scientifically justified.
- Stability studies:
  - Carried out in the intended drug product container-closure system
  - Containing manufacturing site & primary packager
  - Manufacturing & expiry dates (corresponds to the required shelf life of the product)
  - Tested parameters follow same specifications from CTD section "3.2.P.5.1"
  - 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.
- Stability Data:

- Pre-change stability study (Any historical data):
  - Completed stability studies of 3 production batches (from any previous season) under real-time and accelerated storage conditions.
- Post-change stability study:
  - On-going Stability studies of 3 production batches (from the previous season) real-time storage conditions (minimum 6 months) and accelerated storage conditions (minimum 3 months).
  - For the upcoming season, a commitment is required from the mother company to:
    - Place the first three production scale batches on the stability program after approval
    - Submitting the minimum stability data requirements (as per variation transfer letter requirements: under real-time (minimum 6 months) and accelerated (minimum 3 months)) once completed mentioning the date of submission in the commitment.

- **N.B:**

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

Requirements for Inspection of Local Biological Products

A. Cover letter clarifying the purpose of submission.
B. Cover letter of the file contents.
C. Summary sheet (signed & stamped pdf).
D. 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).

- **Notice**: In case of performing the stability study in place rather than the manufacturer, attach the contract between the applicant and the place at which the stability was performed (authenticated by the legal counsel of EDA) and a copy of the license of the place at which the stability was performed.

E. Finished product specification (physical, chemical, impurities, related substances & microbiological), mentioning method of analysis and reference for each method.
F. Method of analysis. (detailed procedures)
G. Validation of analytical procedure of active ingredient assay and related substances along with HPLC chromatograms for each parameter (in case of HPLC analysis)
H. 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:**

- Required number of batches for each study:
  1- Long-term and accelerated studies on 3 (pilot or production) batches (in case of new) or one production batch (in case of renewal).
2- In-use :(after opening / after reconstitution / after dilution) stability study on at least two pilot scale batches (in case of new) or two production batches (in case of renewal).
   - (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. (in case of new only)
4- Long-term stability study of solvent on 3 (pilot or production) batches (in case of new) or one production batch (in case of renewal).

- 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 (in case of new) or one batch (in case of renewal) for each individual strength, container type or size, unless bracketing is applied.
- In case of more than one manufacturer, all stability studies must be submitted from each manufacturer (except photo-stability study).

- **Additional studies in case of biosimilar product:**

⇨ Side-by-side accelerated and stress studies 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:**

-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.