Regulatory Guideline on

Organizing the Rules and Procedures of the Re-registration of Human pharmaceutical Products in Accordance with the EDA Chairman Decree No. (150) of 2022

Code: GL.CAPP.030
Version No.: (5)
Issue Date: 30/11/ 2023
Effective date : 30/11/2023

First: General Rules:

- ❒ This guideline shall apply to reorganizing the rules and procedures of the Re-registration of Human pharmaceutical Products that are locally manufactured or imported for the purpose of local marketing or tenders.

- ❒ Human pharmaceutical products that are manufactured locally or imported shall be re-registered every ten years upon a request submitted by the company during the last year of the marketing authorization license's validity to the General Administration of Human Pharmaceuticals Registration at the Central Administration of Pharmaceutical Products, otherwise the product's marketing shall be suspended.

- ❒ The License holder shall apply for getting a preliminary approval to fulfill and complete the technical studies, requirements and approvals necessary for re-registration.

- ❒ In the case of exceeding the specified period for submitting the re-registration application (preliminary approval for re-registration procedures), the submitted applications shall be reviewed based on an integrated report including the reasons for exceeding the specified period and the significance of the product. These applications shall be processed on a case-by-case basis and be presented to the EDA Chairman through the General Administration of Human Pharmaceuticals Registration at the Central Administration of Pharmaceutical Products.

- ❒ The product that has a preliminary approval to proceed with the re-registration procedures shall be granted a grace period of a maximum of 4 years starting from the expiration date of the marketing authorization license's validity. The purpose of that grace period is to fulfill and complete the technical studies, requirements, and approvals required to get the re-registration marketing authorization license. During the mentioned period, the importation, manufacturing and marketing shall be permitted and authorized in accordance with the regulating rules, unless any contradicting regulations, updates or decisions have been issued.

- ❒ In the case of exceeding the specified period for re-registration, the submitted applications shall be reviewed based on an integrated report including the reasons for exceeding the specified period, the significance of the product, the degree of fulfilment of the technical studies and the requirements necessary to complete the re-registration procedures, in addition to the proofs demonstrating the company seriousness. These applications shall be processed on a case-by-case basis and be

presented to EDA Chairman through the General Administration of Human Pharmaceuticals Registration at the Central Administration of Pharmaceutical Products.

❒ **<u>Criteria for accepting the petitions of extending the grace period of re-registration prior to their submission</u>:**

1- The product shall be included in the valid list of drug shortages issued by EDA.
2- The product shall have other concentrations of the same box in the local market.
3- Other cases approved by the Technical Committee for Drug Control.

❒ The company shall submit the final re-registration dossier which includes all regulatory documents issued for the product, which guarantee the quality, efficacy and safety of the products and active ingredients.

❒ In the case of approval, the product shall be re-registered for another ten years starting from the date of approval of the Technical Committee for Drug Control. The company may submit a petition for reconsidering the final decision of the Technical Committee for Drug Control within 60 working days starting from the decision issuance date, provided that the petition shall include all the technical justifications and shall be supported by the documents and information on which the company relies. The petition shall be adjudicated within 60 working days from the date of its submission.

❒ The applicant shall submit a report on safety, quality and efficacy of the registered product within the last three months of the fifth year from the date of marketing authorization license. In case of non-compliance, the marketing of the product will be suspended based on a report from the relevant Central Administrations.

❒ All license holders under re-registration in the period prior to the effective date of the EDA Chairman Decree No. (150) of 2022, shall be obligated to complete the procedures and fulfill the requirements, approvals, technical studies and attachments necessary for re-registration in accordance with the following grace periods:

- Products under re-registration in accordance with Ministerial Decree No. (425) of 2015: They shall have a period of (4) years from the expiry date of the marketing authorization license's validity, or preliminary approval, or the approval of Scientific Committees or approval of the Technical Committee for Drug Control, whichever is the later.
- Products under re-registration in accordance with Ministerial Decree No. (296) of

2009: They shall have a period of (4) years starting from the effective date of this Decree on April 27th, 2022.

- Products under re-registration in accordance with the decision of the Sub-Committee and the Ministerial Decree No. (645) of 2012 or No. (370) of 2006: They shall have a period of two years from the effective date of this Decree on April 27th, 2022.

The company shall submit an application to the General Administration of Human Pharmaceuticals Registration at the Central Administration of Pharmaceutical Products after paying the service consideration for submitting the application for each product as from the effective date of this Decree on April 27th, 2022 for 6 months without prejudice to the payment -or completing the payment- of the specified re-registration service consideration as per the type of the product (locally manufactured products - imported or locally packaged products). In the case of exceeding the specified grace period granted to update the preliminary approval of proceeding with re-registration procedures, the companies may submit a request for being granted an additional grace period in order to submit the update application and provide the fulfilled required documents to update the preliminary approval of proceeding with re-registration procedures after paying the prescribed service consideration for being granted an additional grace period to submit the fulfilled and complete documents required for every month of delay.

- ❒ All relevant regulatory administrations in the Egyptian Drug Authority, within their respective areas of competence, shall be committed to announce on the submission links: all the attachments required to receive the applications and the studies necessary to complete and submit the final re-registration dossier.

- ❒ Without prejudice to the original grace period specified for re-registration, each head of a competent central administration shall, within their respective areas of competence, determine the grace periods required for the procedures of receiving and evaluation as well as presentation to the various committees and the grace periods granted to the company to fulfill the requirements and complete required documents in accordance with the nature of the procedure, provided that the granted grace period shall not be less than 30 days and not more than 120 days. Each relevant administration shall issue a checklist including the method of applying for getting the requested service, the required documents, paperwork, procedures, specified dates, grace periods, the submission links and the prescribed service consideration, whenever necessary.

- ❒ The production grace period of the locally manufactured products intended for local marketing as well as the importation grace period of the imported products that have a re-registration marketing authorization license shall be calculated based on the expiry date of the last batch produced. These grace periods shall not be applied to the registered products for export only or tender and export.

- ❒ In the case of a variation of quantity or quality of any of the active ingredients that aligns with reference products or scientific references or scientific committees' recommendations, all the specified procedures for registration as a new product shall be applied while keeping its place in the box. The marketing of the product shall be permitted after being presented to the Technical Committee for Drug Control until fulfilling the registration procedures of the new composition in accordance with the rules.

Second: Applying for getting preliminary approval for re-registration procedures

The preliminary approval for re-registration procedures shall be issued after license holder submits an application that shall include - at least- the following documents:

- ❒ Re-registration application form;
- ❒ A copy of the marketing authorization license;
- ❒ A copy of the latest scientific reference for the pharmaceutical form and the composition form;
- ❒ A valid Certificate of Pharmaceutical Product of the product in the country of origin "CPP" for imported finished products, products locally packed and locally manufactured products under license from a foreign company;
- ❒ Documents demonstrating the continuity of manufacturing and marketing of locally manufactured products for local marketing or documents demonstrating the importation of the products imported for local marketing;
- ❒ Documents stating the payment of the re-registration service consideration.

Third: Documents, approvals and technical studies required after issuing preliminary approval for re-registration procedures as per the relevant administrations.

(1) Central Administration of Pharmaceutical Care

(A) General Administration of Pharmaceutical Vigilance

- ❒ The company shall be committed to submit the pharmacovigilance file including all required documents in accordance with the principles of good pharmacovigilance practices and the governing rules and regulations within 6 months from the issuance date of the preliminary approval for re-registration procedures.

- ❒ In the case that pharmacovigilance file is not approved or the documents are not fulfilled, the General Administration of Human Pharmaceuticals Registration shall be addressed to present the pharmacovigilance file to the Technical Committee for Drug Control to take a reasoned decision thereon.

(B) General Administration of Pharmaceutical References and Medical inserts

- ❒ The company shall be committed to apply for approving and updating the medical leaflet that shall be attached to the re-registration dossier in the case that more than 5 years have passed since the last approved medical leaflet or in the case that warnings or updates that require approving and updating medical leaflets are issued.

(2) Central Administration of Drug Policies and Market Access

(A) General Administration of drug information centers – Pricing Policies and Pharmacoeconomics Administration

The company shall be obligated to provide any of the following documents regarding the products submitted for re-registration:

a. A valid pricing certificate.
b. An expired pricing certificate: It shall be along with the documents indicating submission of an application for renewing the validity of the pricing certificate and accompanied by a commitment made by the company's legal representative on the company's header, notarized by a valid bank signature, stating the approval of issuing the re-registration marketing authorization license in accordance with the current price and demonstrating the company's commitment to submit the updated pricing certificate immediately upon getting it unless a re-registration marketing authorization license is issued prior to the issuance of the updated pricing certificate.
c. A pricing certificate that has an unspecified validity: It shall be along with the documents indicating submission of an application for renewing the validity of the pricing certificate and accompanied by a commitment made by the company's legal representative on company's header, notarized by a valid bank signature, stating the

approval of issuing the re-registration marketing authorization license in accordance with the current price and demonstrating the company's commitment to submit the updated pricing certificate immediately upon getting it unless a re-registration marketing authorization license is issued prior to the issuance of the updated pricing certificate.

- ❒ For the cases that require renewal, the company shall be obligated to submit an application for renewing the pricing certificate validity in a period of 3 months before the expiry of the pricing certificate. The company shall be also obligated to price all packages prepared for local marketing which are intended to be stated with their prices in the re-registration marketing authorization license.

- ❒ The locally manufactured products intended to be marketed for tender and export as well as the packages prepared for tender and export shall not be subjected to the requirement of submitting a pricing certificate.

(B) General Administration for Importation and Custom Release

- ❒ It is permissible to allow importation and sealed medical customs release of
  - Pharmaceutical active ingredients/ packing and packaging materials used in the manufacturing of locally manufactured products.
  - Imported products (finished products/ packaging importation)

  that are concerned with the products registered and submitted for re-registration in accordance with registration / re-registration marketing authorization license or valid preliminary approval for re-registration, or the documents indicating the status of the product regarding re-registration based on the statement issued by the Central Administration of Pharmaceutical Products.

- ❒ The company shall be obligated to submit the documents required for the issuance of the approval/importation plan and the sealed medical customs release letter made in accordance with the regulatory guideline for the rules and procedures regulating import and medical customs release of medical products, their ingredients and packing and packaging requirements.

(3) Central Administration of Operations
General Administration of Factories Inspection

- ❒ Production lines of products imported from non-reference countries and not marketed in a reference country are inspected in accordance with the Risk based Inspection planning issued by the General Administration for Factories Inspection.

(4) Central Administration for Drug Control

- The license holder under re-registration shall be obligated to submit an application to update the analysis file to the Administration of Human Pharmaceutical Variation at the General Administration of Human Pharmaceuticals Registration at the Central Administration of Pharmaceutical Products, in order to issue the necessary transfer letter.

- The status of the product shall be studied by the Central Administration of Drug Control to issue a certificate of updating the analysis file of a registered human pharmaceutical product. The final analysis report of the product and the final composition approved by the Central Administration of Drug Control as well as the finished product specifications shall be attached to the certificate.

- In the cases requiring re-analysis at the Administration of Evaluation and Approval before issuance of the re-registration marketing authorization license: sealed samples of the product shall be provided to be analyzed at the Central Administration of Drug Control, the Administration of Evaluation and Approval via the Central Administration of Operations, without stopping the release of the production batch from which the sample has been taken based on a written commitment made by the company's legal representative on the company's header, notarized by a valid bank signature, and stating the company's full responsibility. That procedure shall be followed up by the Central Administration of Operations.

- In the case that the company wants to apply for fulfilling re-registration requirements at the Central Administration of Pharmaceutical Products utilizing a final report issued by the Administration of Evaluation and Approval within a year from the date of the approval of the final report at the Central Administration for Drug Control, the license holder may apply to get a statement from the Central Administration for Drug Control indicating that the product final report issued by the Administration of Evaluation and Approval has been updated as part of the procedures for reviewing the product file before analysis.

(5) Central Administration of Pharmaceutical Products

(A) General Administration of Stability

❒ The previously issued stability approval shall be considered as fulfilling all the required data to complete the product re-registration dossier, provided that the applicable rules shall be adhered to in the case of any variation in the product, based on the following:

A. The product shall have a previous re-registration marketing authorization license.

B. The full name of the product, the names of the active ingredients along with their concentrations and the amount of the equivalent salt, if any, the pharmaceutical form, the license holder, the applicant for re-registration and the name of the manufacturer.

C. The physical properties and the package with its detailed form and various sizes, if any, that indicates all the manufacturing materials of the primary and secondary packaging, the decision of the General Committee to assess Stability Studies, demonstrating the shelf life and complete storage conditions as per the pharmaceutical form in conformity with the provisions prescribed in the applicable rules of stability studies, provided that the purpose of the study is re-registration.
(In use shelf, Diluent, Solvent and its volume, storage conditions, dilution or reconstitution, shelf life after opening…etc.).

❒ In the event of non-fulfillment of the above-mentioned data, the General Administration of Stability shall be addressed for fulfilling the required data.

D. **The composition attached to the approval of stability**

❒ In the event of non-fulfillment of the above-mentioned data, the General Administration of Stability shall be addressed for fulfilling the required data.

E. The composition on which the stability study was conducted, indicating the "specifications" for each of the active and inactive ingredients starting from 2018 only, and the certificate of "Finished Product Specifications" for the approvals issued starting from 2018.

❒ In the event of non-fulfillment of the above-mentioned data regarding approvals issued starting from 2018, the General Administration of Stability shall be addressed to fulfill the required data.

❒ The company shall undertake the responsibility of ensuring that the stability approval issued for the purpose of re-registration indicates all fulfilled required data,

as mentioned above, before submitting the final re-registration dossier to the General Administration of Human Pharmaceuticals Registration.

(B) Evaluation Unit of Bioavailability and Bioequivalence Studies of Human Pharmaceuticals

- ❒ Evaluation Unit of Bioavailability and Bioequivalence Studies of Human Pharmaceuticals may exempt a product from re-conducting the bioequivalence study or in-vitro dissolution based on the type of the product and the variations it undergoes in the case that the conducted studies fulfill all the requirements, rules, and updated decisions regulating conducting these studies at the time of evaluation.

Fourth: Submitting the final and complete re-registration dossier

- ❒ The license holder shall submit the final re-registration dossier to the Administration of Regulatory Affairs, fulfilling all the requirements, approvals, technical studies and attachments necessary for re-registration to get the registration marketing authorization license.

- ❒ With regard to the imported finished products and packaged locally, it shall be permitted to state the previous API manufacturer that was used as a supplier to Egypt based on a commitment from the company along with submitting the quality file (Module 3) which shall be complete in accordance with the rules of the Administration of Regulatory Affairs.

- ❒ The Administration of Regulatory Affairs and its affiliated units review the dossier and notifies the company with the status of the dossier within 60 working days from the date of receiving the complete re-registration dossier, and in case of documents were required to be submitted by the company, the company shall be granted a grace period of 120 working days as a maximum from the date of notifying the company with the requirements to be evaluated within 30 working days as a maximum from the date of submitting the required documents. In the event that the deadline for completing the fulfilled required documents is exceeded, the company may apply to the General Administration of Human Pharmaceuticals Registration for extending the deadline of completing the fulfilled required documents after paying the service consideration.

- ❒ The matter shall be presented to the Technical Committee for Drug Control within 30 working days from the date when the company fulfills the complete dossier, so that the

Technical Committee shall take the appropriate decision whether to re-register the product or not.

The final re-registration dossier shall include the following:

1. The preliminary approval for re-registration procedures.
2. The Pharmacovigilance approval including all requirements based on the principles of good pharmacovigilance practices.
3. Factory license, toll manufacturing register.
4. Various forms and commitments announced on the submission links.
5. The valid Certificate of Pharmaceutical Product that indicates marketing of the pharmaceutical product in the country of origin for products imported or manufactured under license from a foreign company.
6. Documents indicating the continuity of marketing, of the production and import of the product.
7. Approval of the stability study or documents indicating the exemption of fulfilling some requirements as follows:

- The products under re- registration are exempted of submitting the required stability study approval for re-registration, provided that the product have a previous reregistration marketing authorization license and the stability study that was conducted on the production batches of the product for re-registration was previously evaluated by General Committee to assess Stability Studies.
- In the event that the name of the supplier of the active ingredient is not stated, the company shall address the Administration of Regulatory Affairs at the General Administration of Human Pharmaceuticals Registration so that the company shall submit written commitment on the company's header, made by its legal representative, notarized by a valid bank signature and indicating the name of the manufacturer of the active ingredient used in the manufacturing of the production batches on which the stability study of re-registration is conducted and the company shall submit the documents demonstrating that this source is used in the manufacturing of the product, such as an inspection report.
- Composition on which the stability study was conducted stating the specifications of each active and inactive ingredient in the issued approvals and the finished product specifications certificate.
- In the event of non-fulfillment of the above-mentioned data regarding approvals issued starting from 2018, the company shall address the Administration of Regulatory Affairs at the General Administration of Human Pharmaceuticals Registration so that the company shall submit a written commitment on the company's header, made by its legal representative, notarized by a valid bank signature, indicating the required data in detail and enclosing a certificate of

updating the analysis file of a human pharmaceutical product, the final analysis report of the product, and the final composition approved by the Central Administration for Drug Control at the Egyptian Drug Authority.

8. Bioequivalence study, in-vitro dissolution Approval of or the documents indicating the exemption as previously mentioned.

9. **<u>Updating the Analysis file by the Central Administration for Drug Control:</u>**
   - ❒ **The following documents shall be attached in the re-registration dossier for the products under re-registration:**
     - A transfer letter to update the analysis file,
     - A certificate of updating the analysis file of a registered human pharmaceutical product, and
     - The final analysis report of the product and the final composition approved by the Central Administration for Drug Control at the Egyptian Drug Authority.
   - ❒ **If the company desires, the following documents may be attached to the re-registration dossier for the products under re-registration:**
     - A transfer letter to update the analysis file,
     - The final analysis report of the product and the approved final composition.

   Upon the issuance of the re-registration marketing authorization license, the company shall be committed to apply to the Central Administration for Drug Control to update the analysis file after the marketing authorization license is issued as a condition for releasing the first batch/ shipment.

10. **Quality file evaluation**

- The quality file is evaluated in accordance with the cases requiring evaluation such as oncology products, immune-suppressants and all products that had been previously registered and that had included an evaluation of the quality file when registered. The products under re-registration before the issuance of this decree shall be allowed to submit the final re-registration dossier, which includes only the documents that indicate submitting and receiving the quality file for evaluation by the Administration of Technical Affairs if the re-registration grace period is about to end before getting the final approval for the quality file. Overall, the condition of evaluating quality file shall be applied to all the products that do not submit the final re-registration dossier before Jan. 1st, 2026.

11. **Copy of the latest scientific reference for composition and pharmaceutical form.**

- For the products that have lost their references, the company shall be obligated to apply to the Evaluation unit of Scientific data and drug Development for Human

Pharmaceuticals at the General Administration Human Pharmaceuticals Registration within (6) months from the date of issuing the preliminary approval for re-registration procedures. The mentioned unit may approve completing the procedures for the re-registration of these products, on the condition that the reasons for losing the product reference are not related to safety or efficacy and on the condition that this approval shall be based on the statement of the General Administration of Pharmaceutical vigilance regarding whether any indicators related to the product safety or efficacy are monitored or not. In the case of non-fulfillment of the aforementioned conditions, the General Administration of Pharmaceutical vigilance shall be addressed to evaluate the product safety taking into consideration the years during which the product has been marketed in the Egyptian market and to evaluate the pharmacovigilance files and the safety study of the product within the marketing period. In the case that the data related to the product safety are not sufficient, the company may be granted a grace period to fulfill the required data and documents in accordance with the grace periods stipulated for re-registration. The product files that fail to fulfill their required documents shall be presented to the Technical Committee for Drug Control to take a reasoned decision thereon.

12. A valid pricing certificate:

In the case of an expired pricing certificate: providing the documents indicating submission of an application for renewing the validity of the pricing certificate which shall be accompanied by a commitment made by the company's legal representative on the company's header, notarized by a valid bank signature, stating the approval of issuing the re-registration marketing authorization license in accordance with the current price and demonstrating the company's commitment to submit the updated pricing certificate immediately upon getting it unless a re-registration marketing authorization license is issued prior to the issuance of the updated pricing certificate.

13. Valid and approved medical leaflets

14. Update of the internal and external mockups.

- The Evaluation Unit of Trade Names and mockup of Human pharmaceuticals shall be responsible for approving the updated internal and external mockups after approving the updated stability study and medical leaflet whenever necessary.

Versions	Issue Date	Subjects of amendments
Version: 1.0	April 14th, 2022	
Version: 2.0	Jan. 5th, 2023	▪ Updating the preliminary approval for re-registration procedures. ▪ Central Administration for Drug Control
Version: 3.0	June 20th, 2023	▪ General rules ▪ Central Administration for Drug Control ▪ Submitting the final and complete re-registration dossier
Version: 4.0	September 20th, 2023	▪ General rules ▪ The applicant shall submit a report on safety, quality and efficacy of the registered product within the last three months of the fifth year from the date of marketing authorization license. In case of non-compliance, the marketing of the product will be suspended based on a report from the relevant Central Administrations.
Version:5.0	November 30th 2023	▪ General Administration of Factories Inspection ▪ Submitting the final and complete re-registration dossier