Central Administration of Pharmaceutical Products
General Administration of Human pharmaceuticals registration

Central Administration of Pharmaceutical Care
General Administration of Pharmaceutical Vigilance

Guideline

GUIDELINES ON
Assessment of safety and efficacy that impact withdrawal, suspension or revocation of registration procedures or marketing authorization license

Year 2023

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Introduction

EDA grants marketing authorization license (MA license) for medical products after evaluating quality, efficacy, and safety and when there is sufficient evidence that the product has a favorable benefit- risk balance. If a new safety information that affects the benefit- risk balance of the products in the market is discovered after approval, where the drug is used in larger populations for longer duration or for unapproved indications, previously unidentified adverse drug events often occur, several courses of action can be taken by EDA regulator and/or manufacturer, for instance adding a new product label with specific warnings , adding a new contraindication , issuing a direct healthcare professional communication , and in the most serious cases a decision of suspension, withdrawal or revocation of registration procedures or a MA license may be issued.

EDA examines the features of the adverse events that are relevant in making the decision, for instance: the benefit-risk balance, the time- course, dose relation of the adverse effect, the possibility of monitoring, and the availability of protective strategies.

Drug suspension or withdrawal in this document occurs whenever a pharmaceutical drug affects the benefit-risk balance negatively and should be removed from the market where the drug has events which are serious (for instance but not limited to event that required medical intervention, congenital malformation, disability, hospitalization, life- threatening event and death) and frequent enough or have altered the benefit- risk balance enough to result in the drug's removal from the market. Market restriction or removal may occur also when consumers use the drug improperly and that unauthorized use causes serious injury or death.

Legal Basis

- Pharmacy Profession Practice Law no. 127 for year 1955 article number (64), authorizing the competent health authority to suspend, and/or withdraw or revoke an MA in case there is/are finding(s) on quality, safety or efficacy issues based on technical committee for drug control decision.

- EDA establishment law no.151 for year 2019 and its executive regulations No.777 for year 2020; EDA's objective is to regulate, implement and supervise the quality, efficacy, and safety of medical products. EDA regulates and supervises the production and marketing of medical products and raw materials stipulated under this law, and verifies its quality, efficacy, and safety inside and outside the republic in the context of regulating Egyptian products and its representation abroad. EDA sets the rules and procedures that regulate the processes of importation, exportation, registration, pricing, marketing, supervision and inspection of medical products subject to this law and raw materials used in its manufacture, through coordination with relevant entities and in accordance with international standards. EDA sets regulations that guarantee the safety of medical products subjected to the provisions of this law, and their monitoring and following-up through all stages of marketing and applying these regulations to the producers and manufacturers of these products and taking the necessary decisions to withdraw the product, whose marketing may cause harm to public health, after the approval of EDA chairman.

- EDA Chairman Decree no. 786/2022 regarding the suspension or cancellation of procedures for registering human medical products or the marketing license based on the evaluation of safety and efficacy where EDA chairman has the right to suspend or cancel the registration procedures or the marketing authorization license of any human pharmaceutical product whose marketing is proven to cause harm to the public health, on the basis of a technical memorandum supported by scientific evidences and studies for each case individually.

- EDA Chairman Decree no. 150/2022, regarding the re-registration procedures, article 8, states that EDA Chairman has the right, based on a technical memorandum supported by scientific evidence and market studies and for each case on its own, to suspend or revoke the re-registration procedures for any human medical product, where its use would harm the public health.

Scope

This guideline is applied on all human pharmaceutical products raising concerns regarding quality, safety or efficacy issues locally or globally that requiring EDA to withhold, suspend, withdraw or revoke registration procedures or an MA.

Abbreviations

RA: Regulatory Authority
MA: Marketing Authorization
SRA: Stringent Regulatory Authority
EDA: Egyptian Drug Authority
PVGA: Pharmaceutical Vigilance General Administration

Definitions

- **EDA**: The organization responsible for granting MA License for medical products, cancelling, revoking and withdrawing any human medical product, where its use would harm the public health and other regulatory activities and functions concerning medical products.
- **Medical product:** Any product of formula containing a substance or a group of substances used for the purpose of treatment or prevention or diagnosis in humans or animals or which can be described as having another medical effect or which aims to restore, correct or modify physiological functions through having a pharmacological, immunological, or metabolic effect on general health in accordance to the applicable references and standards, as well as, any formula or substances that may be invented through advances in science and/or international references and standards.

- **Marketing authorization:** Product license or registration certificate. A legal document issued by the regulatory authority that authorizes the marketing or free distribution of a medical product in the country after evaluation of safety, efficacy & quality.
- **Non-reference product:** A medical product that has no reference product with the same dosage form, dose, indication or route of administration.
- **Reference countries: A regulatory authority which is:**
  A member of the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH), being the European Commission, the US Food and Drug Administration and Ministry of Health, Labour and Welfare of Japan also represented by the Pharmaceuticals and Medical Devices Agency.
  Or An ICH observer, being the European Free Trade association, as represented by Swiss medic, and Health Canada
  Or A regulatory authority associated with an ICH member through a legally-binding, mutual recognition agreement, including Australia, Iceland, Liechtenstein and Norway.
- **List of reference countries**: List of countries approved by the EDA technical committee for drug control dated on 16/9/2021, and its updates.
- **Pharmaceutical equivalents:** Products contain the same amount of the same molar amount of the same APIs in the same dosage form, if they meet comparable standards and if they are intended to be administered by the same route.
- **Therapeutic substitute:** Product replaces the originally-prescribed drug with an alternative molecule with assumed equivalent therapeutic effect. The alternative drug may be within the same class or from another class with assumed therapeutic equivalence.
- **Committee Members:** Experts from whom EDA may obtain their technical guidance and support within a particular subject, either by correspondence or at meetings to which the experts may be invited.
- **Expert Committees:**
  Scientific evaluation committee: Committee consists of expertise from a pool of scientific advisors of various specialties, provide scientific advice and information regarding the active substances for which new evidence has been issued in terms of safety, study therapeutic substitutes to the submitted products and the need of these products in the market.

Pharmacovigilance committee: an independent committee, it consists of an odd number of members and any expert (not affect voting) can be invited for additional scientific support. All external professionals of the committee are academic professors in different sciences to give the required support and recommendations for PV activities and requirements, it is held when there is a requirement for a scientific opinion, practical experience, and technical support on the evaluation of the risk-benefit balance for the pharmaceutical products, regarding the evaluation results according to the management of the product risks including the product status, monitoring of adverse events, and additional activities necessary to ensure its safety; evaluation of post authorization safety studies; evaluating the safety signals of the pharmaceutical and biological products and assessment of any updates related to the product safety issues, and adopt recommendations to take suitable actions when needed.

- **Adverse event**: An adverse event is any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment.
- **Adverse reaction**: All noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions.
- **Serious Adverse Event or Reaction**: Any untoward medical occurrence that:
  - Results in death
  - Is life-threatening
  - Requires inpatient hospitalization or prolongation of existing hospitalization
  - Results in persistent or significant disability/incapacity
  - Results in congenital anomaly
  - Other Serious (Important Medical Events) in accordance to Inclusion/exclusion criteria for the “Important Medical Events” list
    Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require medical or surgical intervention (treatment) to prevent one of the other outcomes.
- **Evidence-based:** A good review is evidence-based and reflects both the scientific and regulatory state of the art. It integrates legislative, regulatory and policy frameworks with emerging science.
- **Risk-based:** The combination of the probability of occurrence of harm and the severity of that harm.

Reporting

- In the event of receiving information from:
  a- Marketing authorization holder,
  b- Literature screening,
  c- Other regulatory authorities or international organization such as World Health Organization (WHO),
  d- Local sources; for example, locally received cases and local safety signals.
- Withdrawal or revocation actions for a safety emerging issue.
- Studying restriction on certain active pharmaceutical ingredients, formulations, dosage forms, and/or patient sub-population.
- Assessment of non-reference product submitted for registration or re-registration.
- Reviewing any updates concerning safety and efficacy globally raised.

Review strategy

Validation shall be a prerequisite for medical product files submitted for scientific assessment to ensure that it is well-organized and all relevant documents have been in a predictable and clear process in order to facilitate the subsequent scientific review and evaluation.

These applications are submitted according to current laws, decrees, guidelines, requirements, time frames, templates and checklists.

Review Strategy in the scientific assessment of the safety and efficacy of the medical product should take into account the following:

- Public health priority of the medical product.
- Understanding other RA's action on the application, especially stringent regulatory authorities (SRAs)

EDA shall follow evidence-based and risk-based review approaches based on risk level and reliance approaches, taking into account national laws, regulations, regional, international guidelines, monograph and standards.

The Acceptability of benefits and risks will depend on public health priorities, presence of available therapeutic substitutes, size and certainty of the treatment effect versus that of the adverse reactions and possible risk mitigation or benefit enhancement that can be implemented. The findings and conclusions of the review must be described in a well-documented review report.

Pharmacovigilance and Scientific Evaluation activities

In case there is a safety or efficacy concern that may need a regulatory action that results in the withdrawal, or suspension, or revocation of the product. The pharmaceutical vigilance general administration (PVGA) prepares a safety assessment reports representing all available information needed to evaluate the risk-benefit balance of the product in addition to, searching scientific references according to the approved list of reference countries (Annex 1) for safety concerns and actions taken by other regulatory authorities related to safety reasons, and review information obtained from other authorities to know the reasons of suspension, withdrawal or revocation. When needed, the safety assessment report presented to the Pharmacovigilance committee to recommend the suitable action.

The General Administration of Human Pharmaceutical Registration reviews and validates the scientific data and information. In addition to studying and evaluating pharmaceutical equivalents and therapeutic substitutes in the Egyptian market and assess the gathered information with the aid of scientific committee members to recommend the need to take a regulatory action and study alternative decisions, if required. This will improve public confidence; provide additional perspectives for the initial recommendation report to consider and provide expertise that otherwise may be lacking.

Finalization of the regulatory action

The initial recommendation reports from the General administration of human pharmaceutical registration & the Pharmacovigilance Administration are presented to the Technical Committee for Drugs Control within 2 weeks to decide the proper regulatory action.

- In case of revocation or suspension of registration procedures is recommended by the technical committee, a memorandum is raised to the head of Central Administration of Pharmaceutical Product by the General Administration of human pharmaceutical registration to be approved and then raised to the EDA Chairman to inform him with the decision.
- In case of a regulatory action of revocation, suspension or withdrawal of an MA is recommended by the Technical committee, a memorandum is raised to EDA Chairman by Central Administration of Pharmaceutical Product and EDA chairman either approve the aforementioned decision or recommend further study and evaluation.
- General administration of human pharmaceutical registration should publish the decision on EDA website.
- The marketing authorization holders may submit an appeal on the aforementioned decision, in accordance with the norms and procedures stipulated in EDA's law executive regulation, within 60 days from the decision announcement.

References

- EDA establishment Law No. 151 for Year 2019.
- Executive Regulations for EDA establishment Law No. 777 for year 2020
- The Pharmacy Practice Law 127/1955
- EDA chairman decree no. 786/2022
- EDA chairman decree no. 150/2022
- Technical committee decision 16/09/2021
- https://www.fda.gov/safety/reporting-serious-problems-fda/what-serious-adverse-event

Annex

- Annex 1: List of reference countries

Annex I

List of Reference Countries

SN	Reference Country
1	Australia
2	Austria
3	Belgium
4	Canada
5	Denmark
6	Finland
7	France
8	Germany
9	Iceland
10	Ireland
11	Italy
12	Japan
13	Luxembourg
14	Netherland
15	New Zealand
16	Norway
17	Portugal
18	Spain
19	Sweden
20	Switzerland
21	United Kingdom
22	United States of America