GUIDELINES ON
Reliance Practices During Registration of Medicinal Products

Year 2024

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Contents

I. Introduction

Egyptian Drug Authority follows WHO guidelines of GRelP in the context of WHO's approach of regulatory system strengthening and as a cornerstone for effective, efficient and smart regulatory activities of medicinal products.

In view of the extent and complexity of the regulatory challenges, establishing and maintaining a mature regulatory system will require adequate resources, including skilled, capable human resources and a significant financial investment. Thus, EDA promotes considering enhanced, innovative and more effective forms of collaboration to make the best use of the available resources and expertise, avoid duplication and placing greater focus at national level on value-added regulatory activities that cannot be undertaken by other authorities, such as, but not limited to vigilance, market surveillance, local manufacturing and distribution.

EDA believes that reliance pathways bring benefits to patients, industry and government, by facilitating and accelerating access to quality assured, effective and safe medicinal products while saving resources and decreasing burden on assessors and regulators at EDA.

II. Purpose

The purpose of this document is to promote a more efficient approach to regulation thereby improving access to quality-assured, effective and safe medical products. It provides guidance, definitions, key concepts and illustrative reliance mechanisms and activities that are adopted and implemented by EDA in assessment and evaluation of medicinal products.

III. Scope

This document covers activities and procedures that are conducted in EDA to implement reliance concepts in the field of regulation of medicinal products during registration, renewals and life-cycle maintenance. EDA considers reliance approaches in particular for certain categories of medicinal products, these include, but are not limited to, medicinal products for priority diseases for which there are unmet medical needs, medicinal products to be used in public health emergencies or during shortages and also for innovator medicinal products.

IV. Definitions and Concepts

- **Reliance:**

  The act whereby the regulatory authority in one jurisdiction takes into account and gives significant weight to assessments performed by another regulatory authority or trusted institution, or to any other authoritative information, in reaching its own decision. The relying authority remains independent, responsible and accountable for the decisions taken, even when it relies on the decisions, assessments and information of others. EDA adopts a unilateral approach.

- **Abridged Registration:**

  A limited assessment - assessing specific parts of the Common Technical Document (CTD) - of suitability of use under local conditions and regulatory requirements, while relying on prior assessment from Stringent regulatory authorities or WHO prequalification.

- **Verification:**

  An Administration process not a scientific assessment to reach a regulatory decision, based on registration or authorization by Stringent Regulatory Authority or WHO prequalification.

- **Sameness of Product:**

  Ensuring similarity of products (or that where differences exist, these are clearly stated) which are submitted to Egyptian Drug Authority compared to the reference Stringent Regulatory Authority (SRAs), regardless of the approaches or assessment activities conducted by the SRAs. The same pharmaceutical product is defined as characterized by:

  - The same qualitative and quantitative formulation.
  - The same manufacturing site(s) for the drug substance and finished product, including specific block(s)/unit(s), manufacturing chain, processes, control of materials and finished product.
  - The same specifications for the excipient(s), drug substance and finished product.
  - The same essential elements of product information for pharmaceutical products.

- **Full sameness of product:**

  The product for local marketing is equal or similar to that approved by the stringent regulatory authority or WHO prequalified including CMC.

- **Sameness letter:**

  It is an authorized document issued by the License Holder to assure the same quality of the product and to provide transparency about any potential differences compared to the reference Stringent Regulatory Authority (SRAs).

- **Stringent Regulatory Authority (SRA):**

  A regulatory authority which is:

  (a) 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 the Ministry of Health, Labour and Welfare of Japan also represented by the Pharmaceuticals and Medical Devices Agency;

  (b) or an ICH observer, being the European Free Trade Association, as represented by Swissmedic, and Health Canada;

  (c) or a regulatory authority associated with an ICH member through a legally-binding, mutual recognition agreement including Australia, Iceland, Liechtenstein and Norway.

- **WHO Listed Authority (WLA):**

  A regulatory authority (RA) or a regional regulatory system (RRS) that complies with all the relevant indicators and requirements specified by WHO for regulatory capability as defined by an established benchmarking and performance evaluation process. A regulatory authority provides the framework that supports the WHO recommended regulatory functions. This is the authority and affiliated institutions that are responsible for regulatory oversight of medical products in a given country or region and in charge of assuring the quality, safety and efficacy of medical products as well as ensuring the relevance and accuracy of product information.

  To be designated as WLA, a regulatory authority should undergo:

  i) a formal assessment with the WHO-Global Benchmarking Tool (GBT) to demonstrate adequate maturity (ML3 as entry point) and
  ii) a performance evaluation (PE) process that complements the results of benchmarking, confirming consistency of advanced performance against

international standards and best practices. Some transitional arrangements are in place for previously designated stringent regulatory authorities and regulatory authorities which had been previously assessed by WHO.

RAs that have reached a high-level regulatory capability and performance (WLA) may be used as a reference and to be relied on by other authorities, to avoid duplicating activities, foster better use of human and economic resources, increase oversight of the pharmaceutical products along the whole supply chain to ultimately enhance global access to high quality, efficacious and safe medicines.

V. Reliance based -review pathways:

EDA applies Good Reliance Practice to assess the safety, efficacy, and quality of human pharmaceutical products, encompassing both Verification and abridged evaluation routes that have specific eligibility criteria for each:

- **Verification:**
  To be eligible,
  - The product must be approved by at least two stringent regulatory authorities or one reference and WHO prequalification.
  - Full Sameness of product (where EDA ensures that the product for local marketing is equal or similar to that approved by the stringent regulatory authority or WHO prequalified including CMC).

- **Abridged:**
  To be eligible,
  - The product must be approved by at least one stringent regulatory authority or WHO prequalification.
  - Sameness of product.

VI. Submission Requirements for each pathway:

No.	Required Document
	For Verification Pathway
1.	EDA documents (Registration request approval, Naming Approval, proof for Pricing submission, proof for pharmacovigilance submission)
2.	Valid Certificate of Pharmaceutical Product
3.	Good Manufacturing Practice (GMP)
4.	Proof of approval from at least two stringent regulatory authorities or one reference and WHO prequalification
5.	Verification of Full Sameness (for example sameness letter)
6.	Unredacted Assessment report (otherwise justified with evidence)
7.	Q & A documents (if applicable)
8.	CTD dossier should be the same as that submitted to the reference drug regulatory agency for modules 2-5.
	For Abridged Pathway
1.	EDA documents (Registration request approval, Naming Approval, proof for Pricing submission, proof for pharmacovigilance submission)
2.	Valid Certificate of Pharmaceutical Product
3.	Good Manufacturing Practice (GMP)
4.	Proof of approval from least one stringent regulatory authority or WHO prequalification
5.	Verification of Sameness (for example sameness letter)
6.	Unredacted Assessment report (otherwise justified with evidence)
7.	Q & A documents (if applicable)
8.	CTD dossier should be the same as that submitted to the reference drug regulatory agency for modules 2-5.

VII. EDA's approved reliance list:

EDA relies on Stringent Regulatory Authorities (SRAs) included in the list of reference countries approved by the Technical Committee of Drug Control and also gives significant strength to WHO prequalified products in registration of imported products that are registered and marketed in any of SRAs included in the list of reference countries approved by the Technical Committee of Drug Control.

EDA's list of reference countries is approved by the Technical Committee of Drug Control on 31/12/2009, 16/9/2021 and 18/1/2024 chosen according to the WHO criteria and its definition to the SRAs.

The current list consists of 24 countries that EDA can rely on their regulatory authorities includes:

- Therapeutic Goods Administration (TGA), **Australia**
- Federal Office for Safety in Health Care (Austrian Medicines & Medical Devices Agency), **Austria**
- Federal Agency for Medicines and Health Products, **Belgium**
- Health Canada, **Canada**
- Danish Health & Medicines Authority, **Denmark**
- Finnish Medicines Agency, **Finland**
- National Agency for the Safety of Medicines and Health Products (ANSM), **France**
- Federal institute for drugs and medical devices, **Germany**
- Icelandic Medicines Agency, **Iceland**
- Health Products Regulatory Authority (HPRA), **Ireland**
- The Italian Medicines Agency (Agenzia italiana del farmaco, AIFA), **Italy**
- Pharmaceuticals and Medical Devices Agency (PMDA), **Japan**
- Luxembourg Agency for Medicines and Health Products (ALMPS), **Luxembourg**
- Medicines Evaluation Board, **Netherland**
- New Zealand Medicines & Medical Devices safety authority (Medsafe), **New Zealand**
- Norwegian Medical Products Agency, **Norway**
- INFARMED - National Authority of Medicines and Health Products, **Portugal**
- Spanish Agency for Medicines and Health Products (AEMPS), **Spain**
- Swedish Medical Products Agency, **Sweden**
- Swiss Institute of Therapeutic Products (Swissmedic), **Switzerland**
- Medicines and Healthcare products Regulatory Agency (MHRA), **United Kingdom**
- U.S Food and Drug Administration (FDA) **United States of America**
- Health Sciences Authority (HSA), **Singapore**
- Ministry of Food and Drug Safety of the Republic of Korea (MFDS), **South Korea**

VIII. Body of Data

Regulatory reliance can take many forms and encompasses a wide range of regulatory practices. It may be limited to certain regulatory process or function or comprise the full scope of regulatory functions throughout the life cycle of medicinal product.

The examples below illustrate the currently used reliance mechanisms in different regulatory functions at EDA.

1 Detailed Examples of Reliance Practices

1.1 Evaluation of Quality of the product

- Active Pharmaceutical Ingredients (APIs):

  EDA recognizes the Certificate of Suitability (CEP) for monographs in The European Pharmacopoeia for APIs as a validation of the quality of a certain API or the Confirmation of API prequalification by the WHO Prequalification programme for APIs and the review process may include:

  - Review of specific characteristics of the API in the elucidation techniques data.
  - Review of impurities characterization and limits including organic, inorganic, residual solvents and genotoxic impurities and any risk assessment for carryover impurities.
  - Review of specification tests and acceptance criteria of API.
  - Review of container closure system specification of API.

- Finished Pharmaceutical Products:

The review process may include

- Review of impurities characterization and limits including organic, inorganic, residual solvents and genotoxic impurities and any risk assessment for carryover impurities.
- Review of process validation reports performed on the current batches of the finished product.
- Review of specification tests and acceptance criteria of finished product.
- Review of container closure system specification of finished product.

1.2 Evaluation of Bioavailability and Bioequivalence Data

Imported generic medicinal products are waived from conducting bioavailability and bioequivalence studies. Instead, the Egyptian Drug Authority (EDA) reviews the data from studies conducted in the country of origin.

1.3 Evaluation of Stability Data

Imported medicinal products are waived from conduction of stability study in Egypt (i.e. EDA only review the resulting data of studies that were formerly conducted at country of origin) provided that study conditions (e.g. Stability Zone) are in accordance with EDA.

1.4 Evaluation of Clinical and Non-clinical Data

The following categories of medicinal products are waived from conduction, or evaluation of clinical and non-clinical data:

- Innovator medicinal products that are approved by an SRA included in the approved list of reference countries.
- Multi-source generics having a reference similar product that is approved by an SRA included in the approved list of reference countries or a WHO-PQ product.

1.5 Evaluation of Inserts Data

- Insert from any of SRA included in the approved list of reference countries can be used as a reference (the product must adhere to the reference).
- EDA relies on and takes into consideration information received regarding safety issues of medicinal products from Stringent Regulatory Authorities (SRAs).
- Warnings/contraindications and any other safety concerns rose by those SRAs, and confirmed by relevant EDA committees are to be generalized in inserts of relevant products.

1.6 On-site Factory Inspection

EDA might rely on other's NRAs inspections as follows:

- Imported medicinal products from reference countries are waived from EDA on-site inspection as a prerequisite for approving the manufacturing site. Whereas EDA shall only review the site valid GMP certificate.

1.7 Evaluation of Post-approval Changes

In accordance with the same reliance principles and mechanisms adopted in the initial marketing authorization, EDA may also broadly apply those mechanisms (declared in Guidelines on Human Pharmaceuticals Variations, version 5-2024) in assessing post-approval changes that are already approved by another reference countries.

1.8 Withdrawal and cancellation of medicinal products due to safety and efficacy issues

- EDA relies on and takes into consideration the information received concerning safety and efficacy issues of medicinal products from the global authorities' especially international organization as WHO and SRAs included in the approved list of reference countries.
- EDA shall review information obtained from communication with international authorities to know the reasons of withdrawal or cancellation understanding other RA's action on the application.
- EDA shall follow evidence-based and risk-based review approaches based on risk level and reliance approaches, considering national laws, regulations, regional, international guidelines, monograph and standards.

1.9 Public health emergency

The EUA is a risk-based procedure for assessing unlicensed medicinal products for use during public health emergency cases in an emergency context when limited data are available and the products are not yet ready for application for licensure through the normal marketing authorization pathways.

- In case of imported products, the product must have been granted an EUA and is in market of the country of origin or the product is listed under WHO EUL or approved by SRAs for emergency use.
- The product should be included in the treatment protocols for such pandemic or epidemic situation which is approved by the WHO or the Egyptian governmental health authorities.
- In case of EUA for generic medicinal product, EDA rely on an innovator product which has been at least granted an EUA approval or has a well-established approved indication for treating such epidemic or pandemic situation, for instance by the WHO, EMA, FDA, or Japan. Medicinal products subjected to EUA must have the same pharmaceutical form, composition, specifications of the drug substance and drug product, and container closure system of the innovator product.

IX. Abbreviations:

EDA: Egyptian Drug Authority

WHO: World Health Organization

WHO-PQ: World Health Organization prequalification

WLA: WHO Listed Authority

FDA: Food and Drug Administration

EMA: European Medicine Agency

GMP: Good Manufacturing Practice

ICH: International Conference of Harmonization

NRA: National Regulatory Authority

RA: Regulatory Authority

SRA: Stringent Regulatory Authority

EUA: Emergency Use Approval

WHO- EUL: World Health Organization Emergency Use Listing

CPP: Certificate of Pharmaceutical Product

CEP: Certificate of Suitability

API: Active Pharmaceutical Ingredient

GRelP: Good Reliance Practice

CMC: Chemistry, manufacturing and controls

X. References:

- Good reliance practices in the regulation of medical products: high level principles and considerations (Annex 10, WHO Technical Report Series, No.1033, 2021).

- Good practices of national regulatory authorities in implementing the collaborative registration procedures for medical products. (Annex 6, WHO Technical Report Series, No. 1019, 2019).

- EDA Chairman Decree 450 for the year 2023 and its regulatory guide, Version 3-2024

- EDA Chairman Decree 780 for the year 2022

- EDA Chairman Decree 786 for the year 2022

- Guidelines on Assessment of safety & efficacy that impact withdrawal, suspension or revocation of registration procedures or marketing authorization license, version 2 - 2023

- Guidelines on Emergency Use Approval, version 4-2023

- Guidelines on Human Pharmaceuticals Variations, version 5-2024

- Guidelines on Reliance Practices for Pharmacovigilance in Egypt, Version 1-2023

- Technical committee for drug control decision on 31/12/2009,16/09/2021 and 18/01/2024.

XI. Document History:

Version Number	Issue Date	Summary of Change
1	6/12/2022	New Issue
2	7/5/2023	• Updating EDA's approved reliance list to include WHO scope. • Clarification of reliance approach implementation in each division • Updating References
3	10/7/2023	• Updating References
4	11/8/2024	• Updating Definitions • Addition of Reliance based - review pathways and its eligibility criteria • Addition of submission requirements for each pathway • Updating list of reference countries to include Singapore and South Korea • Updating References