Emergency Use Approval Guideline

EGYPT

2020

Contents

I. Introduction & Legal Framework:

Based on the ministerial decrees for registration & marketing authorization of biological products & human pharmaceutical products, Egyptian Drug Authority EDA issues this guideline for emergency use application & approval (EUA) including details on regulatory requirements in public health emergency Cases. This guideline is intended to clarify these details for industry & other stakeholders as regulatory main tool for readiness & preparedness in such cases.

II. Scope:

- This guideline is applicable for public health emergency cases
- The EUA is a risk-based procedure for assessing unlicensed biological products and medicines for use during public health emergency cases. It is intended to provide a time-limited approval for unlicensed biological & medicinal products - 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.
- The goal of this guideline is to define & illustrate the steps & key considerations that satisfy the regulatory requirements to give an EUA for an unlicensed biological products & medicines.

III. Definitions:

Emergency: is a situation that poses an immediate risk to health, life, property or environment. An incident, to be an emergency, conforms to one or more of the following:

- Poses an immediate threat to life, health, property, environment.
- Has already caused loss of life, health detriments, property damage or environmental damage.
- Has a high probability of escalating to cause immediate danger to life, health, property or environment.

A pandemic: is an epidemic occurring worldwide, or over a very wide area, crossing international boundaries and usually affecting a large number of people. The classical definition includes nothing about population immunity, virology or disease severity.

An epidemic: is the rapid spread of disease to a large number of people in a given population within a short period of time.

Good clinical practice (GCP): A standard for clinical studies which encompasses the design, conduct, monitoring, termination, audit, analysis, reporting and documentation of the studies and which ensures that the studies are scientifically and ethically sound and that the clinical properties of the pharmaceutical product (diagnostic, therapeutic or prophylactic) under investigation are properly documented.

Good manufacturing practice (GMP): That part of quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization.

Adverse drug reaction (ADR): is an unwanted, undesirable effect of a medication that occurs during usual clinical use.

The Egyptian pharmaceutical vigilance center (EPVC): The center responsible for the collection, evaluation and assessment of information about the safety of pharmaceutical products and Medical Devices marketed in Egypt.

Periodic benefit risk evaluation report (PBRER): is an analysis of the safety, efficacy, and efficiency of a drug, once it is already in the market. The PBRER submission is intended to present a periodic, comprehensive, brief and critical evaluation of new or emerging information on the risks of the health product and the product's overall benefit-risk profile.

Pharmacovigilance system master file (PSMF): is a comprehensive document containing the detailed description of a Marketing Authorization Holders' (MAH's) pharmacovigilance (PV) system ensuring the safety of their products.

Risk assessment: A systematic process of organizing information to support a risk decision to be made within a risk management process. It consists of the identification of hazards and the evaluation of risk associated with exposure to those hazards.

Risk management plan (RMP): a document submitted as part of the marketing authorization dossier that is evaluated by regulatory authorities before a medicine can be authorized and which is regularly updated as new information becomes available. RMPs include information on a medicine's safety profile and explain the measures that are taken in order to prevent or minimize the medicine's risks in patients.

IV. Body of Data:

1. Eligibility of candidate products

The two product streams (biological & medicines) each have specific requirements for products to be eligible for evaluation under the EUA procedure. In order to qualify for assessment under this procedure, the following criteria must be met:

a. The disease for which the product is intended is serious or immediately life threatening, has the potential of causing an outbreak, epidemic or pandemic and it is reasonable to consider the product for an EUA assessment, e.g., there are no licensed products for the indication or for a critical subpopulation (e.g., children).
b. Existing products have not been successful or effective in eradicating the disease or preventing outbreaks (in the case of vaccines and medicines).
c. The product is manufactured in compliance with current GMP.
d. The applicant undertakes to complete the development of the product and apply for marketing authorization once the product is approved for emergency use. For that purpose, the remaining clinical trials and other testing needed to complete the

development of the product must already be underway at the time of the application for an EUA.

e. In case of imported products, the product must have been granted an EUA and/or is in market of the country of origin or the product is listed by the WHO for emergency use.
f. 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.
g. In case of EUA for generic medicinal product, it should 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.

2. <u>EUA for biological products:</u>

According to the Egyptian regulations in registration & marketing authorization of biological products stating the following;

(In emergency cases, any product can be freely sold with exceptions from some of the conditions mentioned in the decree (297/2009) according to a recommendation from EDA chairman deputy & EDA chairman's endorsement to this recommendation on condition that EDA withdraws samples to be analyzed in its control laboratories & the relevant person (applicant) submits a Registration File within 2 months from EDA

chairman's endorsement). This guidance introduces details on different phases of the emergency use procedure.

2.1 Roles & Responsibilities prior to EU application

- Before submission of EU application, early engagement between applicant with EDA is preferred.
- Based on the submitted data to EDA technical experts& the answers to their questions, EU approval procedure moves forwards.

2.1.1 Recommendations for included data

2.1.1.1 Chemistry, Manufacture & Control:

- For imported products, complete CTD file should be submitted (considering ongoing development & stability parts), while for local products, CMC may be accepted.
- The EUA request should include information on CMC; a detailed description of the manufacturing process and controls should be provided.
- Any manufacturing and process control data that will not be available at the time of submission of an EUA request should be clearly discussed with EDA well in advance of the submission of the EUA request and identified in the submission with sufficient justification, and a plan must be presented to address the data gaps with commitment to supply this information whenever its available.

a. Manufacturing:

- Complete details of the manufacturing process must be provided, including critical process parameters, critical quality attributes, batch records, defined hold times, and the in-process testing scheme. Justified specifications should be established for each critical parameter, starting material, intermediates, and final products should be established.
- Validation data from the manufacture including validation protocols and study reports for all critical process should be available.
- Process validation (based on quality risk assessment for the development stage) and demonstration of consistency of production at the production scale used for the lots to be distributed.
- Using of data on clinical batches with a commitment to complete validation on production batches and to submit the data as part of lot release review may be considered.
- Validation data from the manufacture of platform-related products may provide useful supportive information, particularly in the identification of critical parameters.
- Data for biological product storage, shipping and distribution at required temperatures should be available.
- After the emergency approval, any process changes &/or any intended changes for scale up, if any, should be submitted for evaluation of impact of these changes on the quality, efficacy and safety of the product.

b. Control of Drug Substance and Drug Product:

- Full characterization of cell banks, master and working seed organism(s), based on reference to the most appropriate WHO Technical Report Series 978 (TRS 978), and any subsequent updates.
- History and qualification of cell banks, history and qualification of virus banks, and identification of all human or animal derived materials used for cell culture and virus growth.
- An evaluation and mitigation plan for potential adventitious agents.
- Data to demonstrate that the drug substance (DS) is sufficiently characterized in order to identify and understand the critical properties that impact performance and stability.
- The manufacturing process and process controls should be adequately described. The manufacturing process typically starts with one or more vials of the cell bank and includes cell culture, harvest(s), purification, modification reactions and filling. A flow chart of all successive steps including relevant process parameters and in-process-testing should be given.
- Storage conditions, including the container-closure integrity, should be validated and this information should be provided for DS and drug product (DP).
- A stability plan including safety and stability-indicating tests and available stability data from all developmental, clinical, and commercial lots. Data to support short-term stability, reflecting storage conditions during transport and distribution and in clinics and covering the time from dose preparation to administration expected for DS and DP.

- The stability data should be submitted to cover the scale to be supplied in the field.
- The stability and expiry date of the biological's products in its final container, when maintained at the recommended storage temperature, should be demonstrated using final containers from at least three final lots made from different bulks.
- The DP must have been shown to maintain its quality especially the potency of biological products for a period equal to that from the date of release to the expiry date. Post marketing commitments to provide full shelf life data may be acceptable with appropriate justification.
- Analytical methods and qualification/validation data for all quality-indicating assays including key tests for vaccine purity, identity and potency, should be validated and shown to be suitable for the intended purpose.
- If novel test methods have been developed, full description of the test development and qualification must be presented. Validation data for assays used to evaluate critical vaccine qualities such as purity, identity, and potency shall be submitted.
- A tabular listing of all clinical studies and DP lot numbers used in each study including DS lot genealogy, manufacturing processes used, and the manufacturing site, as well as the certificates of analysis (COAs) for all clinical lots used in clinical studies and information on any lots that were initiated but not accepted for release.
- For imported Biological products:
- The manufacturer national regulatory authority's release certificates for the EUA lots should be submitted per batch.

- Report(s) from the responsible stringent regulatory authority (SRA) or WHO listed authority (Summary basis for the emergency use approval or equivalent), and the release certificates of the SRA for the phase 1, 2, 3 and EUA lots, if available, should be submitted.

c. Facilities and Inspections:

- Manufacturing data for drug substance and drug product should be submitted to support EDA regulatory decisions regarding compliance with GMP.
- Assessment of GMP compliance of facilities will be according to *WHO GMP Guidelines*, and any subsequent updates.
- Data as described below should be provided to support EDA regulatory decisions:

i. List of each site where the product (DS and DP), if authorized, is or would be manufactured.

ii. A Site Master file whose approval date was not more than one year ago including relevant layouts, premises & utilities information about each site and the current status of the manufacturing site(s) with respect to current GMP requirements should be submitted.

iii. List of all equipment used for manufacturing DS and DP should be submitted.

iv. Information about quality control unit and any outsourcing activities should be available.

-For foreign manufacturer, *desk assessment* of inspection information from national authorities, SRA/reference country & WHO will be done.

-The desk assessment process involves submission of *documentary evidence* by the applicant, usually a manufacturer or representative, to the NRA to demonstrate the conformity of all sites involved in DS & DP manufacturing, or of an outsourced quality control laboratory (QCL) to GMP & Good Laboratory Practice (GLP).

- **Essential submitted documentary evidence for desk assessment:**

I. Copy of the manufacturing authorization granted by national authorities (certified translation in English).

II. A site master file whose approval date was not more than one year ago, and any forecast modifications, together with:

1. List of each site where the product (DS & DP), if authorized, is or would be manufactured.
2. Facility layout & personnel & materials flowchart for production workshops are required.
3. Legible color printouts of water treatment and air-handling systems, including pipeline and instrumentation drawings in A3 or A2 format.
4. List of all equipment used for manufacturing DS and DP should be submitted.
5. Information about Quality control unit and any outsourcing activities should be available.

III. A list of all the products and dosage forms manufactured on-site.

IV. A copy of the last inspection report issued by the national regulatory authority (NRA) and GMP certificate (production-line specific); (a certified translated copy in English).

V. List of all regulatory inspections performed in the last 3 years and their outcomes.

VI. Most recent product quality reviews (PQRs) of the concerned product (if available).

VII. The completed batch manufacturing and packaging record(s), including the analytical part, for the most recently released batch of relevant product(s).

VIII. Master batch manufacturing and packaging record(s) of the product(s) of interest.

IX. A list of any recalls in the past three years related to products with quality defects.

X. Confirmation by the senior quality assurance representative that a full self-inspection or external audit dedicated to the product(s) has been performed and all matters dealt with (if applicable).

XI. Copy of any warning letter, or equivalent regulatory action, issued by any authority to which the site provides or has applied to provide the product.

- Based on risk-based approach, a decision will be taken based on reviewing submitted documents & evidence to perform a further on-site inspection or not.

- If onsite-inspections of manufacturing sites are considered for approval; In case of public health emergency, EDA will utilize all available tools, resources and sources of information to support regulatory decisions on applications that include sites impacted by EDA's ability to inspect due to emergency.

2.1.1.2 Non clinical data

a. All relevant in vitro and in vivo pharmacodynamics data, e.g., on microbiologic / virologic activity (including any modelling performed).

b. Data on efficacy and safety in in-vitro tests and in animal model(s) under well controlled and documented conditions. The preferred model depends on the disease and may vary according to the medicine's mechanism of action. The applicant must justify the choice of animal model.

b. 3-Evidence of efficacy should include improved survival and/or reduced morbidity of animals in the preferred model under relevant conditions. Surrogate markers, validated or reasonably expected to predict efficacy, would be supportive.

c. 4-All available evidence of the medicine's activity in vitro and in other animals, together with pharmacokinetics and efficacy in humans, also against other diseases should be submitted.

d. 5- A rationale should be provided for the proposed dosing in humans, with reference to drug exposures shown to be safe and effective in suitable models. Ideally, human pharmacokinetic data should be available, demonstrating similar levels of the drug following administration at the proposed dose, compared to blood levels found to be safe and efficacious in the relevant animal model.

e. 6- If human pharmacokinetic trials or studies in other indications at the exposure level proposed for treatment of the public health emergency disease have been conducted, assessment of safety using standard parameters (e.g., adverse events,

clinical laboratory monitoring, etc.) will be done. This safety evaluation may be supplemented by any other nonclinical and clinical data at different exposure levels.

Note: If the non-clinical package is not complete at the time of submission; the applicant must submit adequate justification for the lack of complete data and a plan and timeline for submitting those data.

2.1.1.3 Clinical data

Products- specific international guidelines are considered on case-by-case basis.

- In certain cases, we can approve by phase I and phase II, the applicant also submits the results of phase II study by time of the end-of-phase II, and also before initiation of the clinical trial(s) intended to serve as the primary basis for demonstration of efficacy; the applicant should submit phase III clinical study protocols with its evidence of ethical approval & GCP compliance.
- The approval may be granted if the EDA finds that all the following requirements are met:

I. The benefit-risk balance of the product is positive.
II. It is likely that the applicant will be able to provide comprehensive data.
III. Unmet medical needs will be fulfilled.
IV. The benefit to public health of the medicinal product's immediate availability on the market outweighs the risks due to need for further data.
V. Available safety and effectiveness information for the product.

VI. Reports of the on-site GCP inspections conducted by the other NRAs.

VII. Any advisory committee reports by other NRAs.

VIII. In all cases, preliminary clinical evidence demonstrating that the drug may represent a substantial improvement over available therapy should involve a sufficient number of patients to be considered credible.

IX. In the emergency situation, a sponsor should provide justification for why the endpoint or other findings should be considered clinically significant.

2.1.1.4 Pharmacovigilance requirements

Initial minimum requirements of the submitted file to be eligible for EU process

Locally manufactured product:

- The most updated “Risk Management Plan (RMP)" of the product.
- The most updated Pharmacovigilance System Master File (PSMF)/ PV system approval letter along with Summary PSMF of the MAH.

Imported product:

- The most updated "EU/Global/Core -Risk Management Plan (RMP)"
- The most updated Egyptian Display of RMP
- Periodic Benefit Risk Evaluation Report PBRER (If applicable)
- The most updated Pharmacovigilance System Master File (PSMF)/PV system approval letter along with Summary PSMF of the Global MAH

- The national Pharmacovigilance Sub-System File (PSSF) for local office/PV system approval letter or PSMF of the agent / PV system approval letter along with Summary of PSMF/ PSSF.
- If the applicant is an agent company, there should be a PV agreement between the global MAH and the local company including:
  - The responsibility of each party regarding all the PV activities (global & local).
  - The Signature of all involved parties
  - Authorized agreement regarding the local part and Embassy legalization regarding the global part(s) /or (official declaration to submit the legalized copy within specific timeline) with the signed agreement

2.1.2 Process flow:

EUA steps are illustrated as follows:

2.1.2.1 Pre-submission activities/ meetings

If considered necessary or desirable by the applicant and EDA, a discussion may be held before the actual evaluation process starts.

2.1.2.2 Submission of applications

The manufacturer must submit an application letter to EDA chairperson. The application letter should include details of country and sites of manufacture, the presentations proposed for the product.

2.1.2.3 Assessment of information received

- Once the product has been considered eligible for assessment under the EUA procedure, the product file is transferred to the concerned central administration in EDA where the head of this administration establishes a product evaluation team for the EUA assessment of a specific product.
- The product evaluation team will perform the screening of the submission to ensure that sufficient information is available to initiate the assessment based on the essential data requirements.
- Rolling submissions procedure is followed for evaluation of data & EDA requirements / reports are continuously sent to applicants as an outcome for each roll.
- Applicants should promptly submit any additional information on the development of the product to EDA particularly if it may affect the product's benefit/risk assessment.

2.1.2.4 Requirements for batch release:

- Each lot of biological products is subjected to lot release procedure before marketing in Egypt by EDA through applying risk based approach.

- The assessment and testing of biologicals is based on the degree of risk associated with the product.
- There are technical and logistic issues for pandemic emergency which could affect the EDA lot release policy for biologicals.
- Biological products received for batch release in Egypt should be produced in compliance with GMP and tested for quality and safety by the manufacturer.
- For emergency situations, first priority in lot release procedures should be given to review of the manufacturer's protocol and should always be part of the lot release by EDA.
- Protocol review: A summary protocol should be submitted to the EDA. It should be complying with the national and international regulations, as well as literature to support scientific consensus on aspects related to the specific type of product.
- Sample testing: In case of emergency, biological product could be released into the market after performing the minimum testing items that assure safety and quality of the product based on risk assessment in accordance to each product type and laboratories capabilities.

2.1.2.5 Assessment and issuance of the EUA

- EDA technical experts will prepare technical assessment report for submission to the emergency committee who will give the recommendation regarding issuing EUA for the product submitted.

- The head of the relevant central administration then displays to EDA chairman deputy who raises his recommendation to EDA chairman for endorsement followed by issuance of the conditional time-limited EUA from the relevant central administration.

2.2 Obligations after EUA

2.2.1 Pre-clinical data

A final study report, if available, for a developmental and reproductive toxicology (DART) study, or the timeline for study completion and submission of the final study report, should be provided in order to inform potential emergency use of the vaccine in pregnant women.

2.2.2. Clinical data

-The holder will be required to complete specific obligations (ongoing or new studies, and in some cases additional activities) with a view to providing comprehensive data confirming that the benefit-risk balance is positive.

- Post authorization efficacy study (phase 3) to ensure efficacy and safety of the product.

2.2.3. PV and post marketing data

- Allocation of reporting channels for ADRs, communicate it with HCPs and informing EPVC, and spread awareness for HCPs about these channels.

- Submission adverse events reports to EPVC in an expedited manner according to PV requirement whether they are classified as serious or not.
- Mandatory ICSR follow up using targeted follow up questionnaire.
- Reporting Pregnancy exposure and off-label use without an associated adverse event using Pregnancy exposure and Off label use reports.
- Submission of Global monthly safety report including: (narrative summary and analysis of ADR, newly identified safety concerns and actions taken for safety reasons during this interval, etc.).

*For local products, national monthly safety report will be requested.

- Submission of PBRER of periodicity determined by EPVC (e.g., 6 months for vaccines).

2.2.4 Post Approval Monitoring:

- After a product has been approved for emergency use, it will be put on the national market surveillance plan as a high risk product. Where, intense monitoring & sampling from the market and throughout the supply chain will be conducted.
- EDA reserves the right to restrict or revoke the emergency use approval under any dissatisfaction or non-conformity during post monitoring.

2.2.5 Lot Release

After EUA issuance for a vaccine, sampling from each imported or locally manufactured batch will be done by biological inspection department, to be sent for lot

release department for issuance of a batch release certificate according to risk based approach.

2.3 Road to granting licensing of EU approved vaccine:

According to the Egyptian regulations stated in cases of emergency, the approval holder should submit the MA file of the product within 2 months of the endorsement date for granting Marketing Authorization through normal procedure.

3 .Emergency Use Approval for medicines

- Emergency use approval for medicines (generic products);

3.1 Reviewing quality aspects to grant preliminary approval:

- The applicant should submit the following documents for evaluation by EDA to grant a preliminary quality approval to be able to proceed to the manufacturing process of the drug product within 3 month starting from the approval of the registration request:

- Specifications & certificate of analysis for the drug substance.
- Composition of the drug product.
- Specifications of the drug product.
- Container closure system of the drug product.

Notes:

1. Generic 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.

2. EDA has the right to request full data for drug substance and/or drug product in accordance with the most updated guidelines for assessing quality module 3 according to WHO or ICH guidelines.

3. The manufacturer will be allowed to produce commercial batches instead of primary batches to be able to perform Bioequivalence studies when applicable and accelerated stability testing for 6 months with a commitment to submit long term stability data when requested by EDA.

4. The drug substance and the commercial batches will be analyzed at EDA labs or at the manufacturing site by EDA labs analysts, the analysis results for the commercial batches will be considered a zero time for the stability study.

5. Results of accelerated stability study will be reviewed and assessed by EDA at 1st, 3rd and 6th month.

6. Excessive follow up for the accelerated stability study should be performed by the manufacturer at 2nd, 4th & 5th month, any out of specification results should be reported to EDA within 10 days.

3.2 Manufacturing process:

1. The manufacturer must have a valid preliminary quality approval on for the drug substance and drug product.
2. The manufacturer should comply with the current GMP regulations.
3. The commercial production batches must be produced under the responsibility of the manufacturer in the presence of EDA inspectors to attend and monitor all

manufacturing process to assure compliance with the requirements of the preliminary quality approval.

4. EDA inspector should confirm that required stability studies have been started.

5. The manufacturer must commit to continue the process validation study on the upcoming batches and the results of the validation should be submitted to EDA for assessment and evaluation.

3.3 Pharmacovigilance: As explained in biological products.

3.4 EU License for 8 months:

The applicant should submit the following essential documents to grant the EU License:

- Preliminary approval of quality aspects.
- EDA labs analysis report for the drug substance & drug product.
- Inspection report for the manufacturing process and compliance to the preliminary quality approval.
- Bioequivalence study approval. (if applicable)
- Preliminary stability approval.
- Preliminary pricing certificate. (if available)
- Medical Insert.
- Inner and outer artwork.
- Initial Pharmacovigilance report.

Notes:

1. After receiving the EU license, the commercial batches are allowed to be released gradually according to urgent necessity and consumption rates to the entities specified by the Egyptian governmental health authorities & the Egyptian Drug Authority according to a specific and restricted drug tracking and tracing system and monitoring**.**
2. If the time of release of the batches intersected by the 1st or 3rd or 6th month of the accelerated stability studies, the batches will not be released till EDA approves the stability data for the intersected time interval.

3.5 Final License:

The applicant should submit the following documents to have the Final License:

- Final Pricing Certificate.
- Results of accelerated stability study for 6 months.
- Results of long term stability study (when needed).
- Final Pharmacovigilance report.

Notes:

Full data concerning the drug substance and drug product (after production of 3 consecutive commercial batches) in accordance with the most updated guidelines WHO or ICH should be available upon request by EDA for assessing quality module 3.

V. Glossary

EUA: Emergency Use Approval

WHO: World Health Organization

ICH: International Conference of Harmonization

EDA: Egyptian Drug Authority

DS: Drug Substance

DP: Drug Product

GMP: Good Manufacturing Practice

NRA: National Regulatory Authority

GCP: Good Clinical Practice

SRA: Stringent Regulatory Authority

EMA: European Medicine Agency

FDA: Food & Drug Administration

ADRs: Adverse drug reactions

EPVC: The Egyptian Pharmaceutical Vigilance Center.

EU: European Union

HCP: Healthcare professional.

ICSR: Individual case safety report.

MAH: Marketing authorization holder

PBRER: Periodic benefit-risk evaluation report

PSMF: Pharmacovigilance system master file

PSSF: Pharmacovigilance sub-system files (on national level)

PV: Pharmacovigilance

RMP: Risk management plan

VI. Reference guidelines

- Development & Licensure of Vaccines to prevent COVID-19, FDA, June 2020
- WHO emergency use listing procedure, EUL, Jan. 2020