Guidance on Emergency Use Authorization

Document Number: **PE&R/GL/EU/010**
Document History: **1st Edition**
Effective Date: **16-June-2025**

DRUG REGULATORY AUTHORITY OF PAKISTAN
Prime Minister's National Health Complex, Park Road Chak Shahzad,
Islamabad 54000
www.dra.gov.pk

Table of Contents

1. Introduction

This guideline gives clarity on the regulatory requirements for an emergency use authorization of a medicinal product during a declared Public Health Emergency (PHE) involving (amongst others) a heightened risk of attack on the general public's life, health, safety or a significant potential to affect national security. This guideline should be read along with other guidance documents concerning information and application requirements published on the Drug Regulatory Authority of Pakistan (DRAP) website such as the Guidance documents for registration of pharmaceutical and biological drug products etc.,

The Emergency Use Authorization (EUA) is granted under the Drugs Act 1976 and Drug (Licensing, Registering & Advertising) Rules 1976. The EUA empowers the DRAP to permit the approval of an unregistered medicinal product in a PHE. This procedure takes into consideration whether the known and potential benefits outweigh the known and potential risks of the product when used to diagnose, treat, or prevent serious or life-threatening diseases or conditions, when there are no approved adequate, and available alternatives.

2. Purpose

This Guideline on Emergency Use Authorization (EUA) seeks to expedite access to quality, safe and efficacious medicinal products to the public during a PHE.

3. Scope

This document provides guidance to industries, government agencies, and the general public on the general recommendations and procedures on the issuance of EUA process for the use of a medicinal product during a PHE. This can be a repurposed medicinal product (approved product but unapproved use), a novel medicinal product (unapproved product) as well as a medicinal product that has been approved by designated Reference Regulatory Authorities.

The EUA is a special procedure for fast-track approvals of medicinal products in the event of a PHE when the public health authorities may be willing to tolerate less certainty about the efficacy and safety of products, given the morbidity and/or mortality of the disease and the lack or paucity of treatment, diagnosis/detection or prevention options.

To establish eligibility of unapproved medicinal products for assessment under this procedure, this guideline defines the steps that DRAP will follow, the essential information required, and the process to be used in conducting the assessment to determine whether an unapproved product can be approved on a time limited basis, while further data is being gathered and evaluated or for an unapproved indication for an approved product.

4. Legal Framework

The Rule 29 (8) of (Licensing, Registering & Advertising) Rules 1976 under the Drug Act 1976 empowers Registration Board of DRAP to grant market authorization/ registration to any medicinal product in public interest.

5. General requirements

5.1 Declaration of Emergency

The administrative ministry shall declare a national PHE by an order where there is a situation that poses an immediate risk to health or life. To meet the criteria for a national PHE, the incident should;

a. Immediately threaten life or health;
b. Have already caused loss of life or health detriments,
c. Have a high probability of escalating to cause immediate danger to life or health.

5.2 Eligibility for Emergency Use Authorization

This is when an unapproved medicinal product or an approved medicinal product with unapproved use can be authorized for use during a declared PHE involving a heightened risk of affliction or attack on the safety and security of the general public or a significant potential to affect national security. These products and their uses are not approved or registered as per standard registration procedure. The DRAP shall issue EUA if it concludes that:

i) The agent/pathogen/item specified in the declaration of emergency (in the following called "the agent") can cause a serious or life-threatening disease or condition.
ii) Based on the totality of scientific evidence available, including data from adequate and well-controlled clinical trials, if available, it is reasonable to believe that the product may be effective in diagnosing, treating, or preventing:

a. the serious or life-threatening disease or condition referred to in 1. above; or
b. a serious or life-threatening disease or condition caused by a product granted emergency use authorization for diagnosing, treating, or preventing the disease or condition referred to in 1. above.

iii) The known and potential benefits outweigh the known and potential risks of the product when used to diagnose, prevent, or treat the serious or life-threatening disease or condition that is the subject of the declaration.

iv) An approved alternative to the product for diagnosing, preventing, or treating such serious or life-threatening disease or condition is not available or not adequate.

v) The product is manufactured in compliance with current Good Manufacturing Practices (GMP).

vi) The applicant undertakes to complete the development of the product and apply for full approval. 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.

DRAP may consider reviewing a candidate product for an EUA that does not meet all the requirements as above. In such situations, the application letter and documentation provided to DRAP should justify the application of the product although it does not meet all eligibility requirements.

6. Instructions for the applicant

6.1 Request for consideration of EUA

Although an EUA may not be issued until after a PHE has been declared by the concerned ministry of Government of Pakistan, DRAP recognizes that during such exigent circumstances, the time available for the submission and review of an EUA request may be severely limited. Therefore, the DRAP strongly encourages an entity with a possible candidate product, particularly one at an advanced stage of development, to contact DRAP for the candidate product even before a determination of an actual or potential emergency. This guidance offers recommendations for both "pre-emergency" activities to be conducted prior to the determination of actual or potential emergency and "emergency" activities to be performed once the determination has been issued. In addition, this section of the guidance sets out the information for DRAP to allow an assessment of

safety and effectiveness and to make an adequate risk-benefit determination to support issuance of an EUA. Details about the format of submissions are specified in Annex I.

Pre-submission meeting

A pre-submission meeting is anticipated to facilitate the entire EUA process. For both pre-emergency and emergency activities, a pre-submission meeting is recommended. These meetings should be scheduled as early as possible. Applicants intending to make submissions for an EUA may face different challenges with respect to their applications. These may vary from complying with the administrative requirements in terms of the format and the availability of data. Therefore, DRAP encourages applicants to schedule a pre-submission meeting with the concerned division by email to obtain guidance in accordance with the requirements outlined in this guidance.

A presentation should be prepared detailing the product, the technology used, the data available, specific transport/storage and labelling information. Information on whether the medicinal product has been or is intended to be submitted to WHO, or other regulators for approval and the time frame for submissions should be shared. In advance to the meeting, the applicant should supply a list of questions addressed to the and propose a predefined agenda for an efficient meeting structure. Such meetings are important for discussing the availability of essential data required for specific products, expected timelines for submission and updates, monitoring of safety and effectiveness after deployment, and other relevant information. Additional meetings may be held during the assessment process, as requested.

Before the event of a PHE, the concerned division of DRAP shall be responsible to conduct the pre emergency and emergency activities; to evaluate the eligibility of an EUA. to participate in the pre-submission meetings, to communicate the essential data requirements, to communicate the timelines, to conduct the review in an expedited manner, e.g. as rolling review

Pre-Emergency Activities

Such activities may include discussions with DRAP about prospective EUA of a product and the appropriate procedure for submitting data on the product prior to an emergency declaration. The DRAP strongly recommends that an entity submitting data during a "pre-emergency" period, follows the recommendations for data submission outlined in the section *"Submission of a Request for Consideration"* below. If, prior to the declaration of an emergency, DRAP concludes that a

candidate product may meet the criteria for an EUA, the DRAP may share appropriate information on such product with the authority/body declaring the PHE.

Emergency Activities

Once a determination of an actual or potential emergency has been made, the concerned ministry may declare an emergency justifying the authorization to use an unregistered medicinal product for an unapproved use. The DRAP may coordinate with provincial governments and private entities (manufacturers & importers), where appropriate, to identify products that may be eligible for an EUA in light of the circumstances of the emergency and to facilitate timely submission of the EUA request by an appropriate entity.

6.2 Submission of a Request for Consideration

A request may be submitted based on the totality of scientific evidence available, to the DRAP (including data from adequate and well-controlled clinical trials, if available), it is reasonable to believe that the product may be effective in diagnosing, treating, or preventing the serious or life-threatening disease or condition. The exact type and amount of data needed to support an EUA may depend on the nature of the declared emergency and the nature of the candidate product. The request for consideration for an EUA shall include a well-organized summary of the available scientific evidence that evaluates the product's pharmaceutical quality, safety and efficacy.

6.2.1 Summary of required information

The information below summarizes the type of data required to support a request for consideration for EUA, the requirements specific for vaccines are described in detail in 6.2.2.

A description of the product and its intended use (e.g., identification of the serious or life-threatening disease or condition for which the product may be effective)

1. An identification and an explanation of what unmet medical need(s) would be addressed by issuance of the EUA.
2. A description of the product's international registration/Marketing Authorization (MA) status, including also, whether the product is WHO prequalified. In case of local manufacturing, the status of grant of approval of EUA in designated Reference Regulatory Authorities.

3. A list of each site where the product, if authorized, would be (or was) manufactured and the GMP status of the manufacturer.
4. An identification of any approved alternative products, including their availability and adequacy for the proposed use (if known).
5. Available safety and efficacy information for the product.
6. A discussion of risks and benefits.
7. A description of the information for health care providers or authorized dispensers and recipients of the product, (e.g., two separate "Condition of use" documents), and the feasibility of providing such information to health care providers or authorized dispensers and recipients in emergency situations.
8. Information on pharmaceutical quality (as per Module 3)
9. Medicinal product instructions for use as EUA product (e.g., if follow-up treatment is required)
10. Proposed labelling
11. Statements on whether the nonclinical laboratory studies were conducted in compliance with applicable Good Laboratory Practice (GLP) requirements and whether the clinical studies were conducted in compliance with applicable Good Clinical Practice (GCP) standards.

These data requirements are discussed in more detail in Annex II. Please note that the DRAP may also issue subsequent guidance providing greater detail on these recommendations and procedures for specific medicinal products and/or public health emergencies. DRAP can also ask the applicant to submit any data from any ongoing testing (e.g., longer term stability data) or other data or information that may change the evaluation of the product's safety or effectiveness that become available during the period of review.

6.2.2. Requirements specific for vaccines

A. Manufacturing and quality control Data:

Generally, should comply with CTD quality requirements as per ICH M4Q (R1) applicable to biotech. The following are additional relevant references/requirements for consideration:

i. Full characterization of cell banks according to WHO Technical Report Series (TRS) 978, and any subsequent updates or related guidelines.

ii. Full characterization of master and working seed organism(s), based on reference to the most appropriate WHO TRS or related guidelines.
iii. Process validation (based on quality risk assessment for the development stage of clinical batch) and demonstration of consistency of production at the production scale used for the lots to be distributed. If deemed appropriate, 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.
iv. Justified specifications for starting material, intermediates, and final products.
v. Stability data for the vaccine produced at the scale produced for the lots to be supplied. If available, accelerated stability data must be included.
vi. Inspection report(s) from the concerned NRA or WHO inspection team showing compliance with GMP requirements (if available) and;
vii. Process changes: by the time of submission, it is likely that the manufacturing process is not finalized and that numerous changes will have to be applied after the first listing. These changes should be submitted as updates.

B. Non-clinical and Clinical Data:

Non-clinical data demonstrating acceptable safety, immunogenicity, and efficacy (if available) in the most appropriate animal model. The applicant must justify the choice of animal model. 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.

Clinical data demonstrating the appropriate dose to be used and initial acceptable safety and immunogenicity in the population in which the vaccine will be used in the context of the public health emergency

Preliminary data showing some efficacy (if available). If preliminary human data showing some efficacy are not available for the vaccine under consideration and if not imminently available for other vaccines being concurrently developed, DRAP will consider whether the preponderance of evidence from the non-clinical, and early human studies justifies considering the immunogenicity data as a potential surrogate that is thought to be reasonably predictive of clinical efficacy. In such

cases, the emergency use listing can proceed, provided there are trials underway that will ultimately provide confirmation that immunogenicity is a surrogate.

Safety and immunogenicity data from other vaccines made by the manufacturer using the same product platform may be considered as supportive data for review if applicable.

C. Plan for monitoring and reporting of adverse events

Since the vaccines listed under the EUA procedure have not been licensed for use in routine immunization settings, post marketing data would not be available at the time of application. Therefore, the manufacturer should discuss with DRAP in pre-submission meetings, the plans to ensure the collection and analysis of information on the safety and effectiveness of the product during the period when the EUL listing would be in effect and for a reasonable time following such period.

DRAP encourages applicants to discuss proposals for active data collection and follow-up mechanisms to capture adverse event information under the EUA during the pre-submission meetings.

A Risk Management Plan (RMP) in line should be in place and submitted by applicant as part of EUA submission. The RMP may include Post Authorization Safety Study (PASS) and Post-Authorization Efficacy Study (PAES) and frequent submission of PSURs.

D. Labelling:

1. Summary of product characteristic (information for healthcare provider)
2. Patient information leaflet
3. Container labelling
4. Any other instructional materials provided to the user.
5. A plan to help assure that prospective recipients and healthcare providers are adequately informed about the uncertainties regarding both the potential benefits and risks.
6. The labelling should clearly indicate that that product is for **emergency use only**.

E. Environmental Risk Assessment (ERA)

If the product contains a Genetically Modified Organism, the applicant must submit a completed Environmental Risk Assessment report.

Ijaz Mustafa
Assistant Director-V (MIS)
Tuesday, 17 June, 2025, 1:7:27 PM

7. EUA Instructions for DRAP

7.1. Processing of an EUA

This section discusses DRAP's role in pre-emergency activities for an EUA of a medicinal product, as well as the procedures the DRAP will follow in processing a request for consideration for an EUA.

7.2. Pre-Emergency Submission

Before determination of actual or potential emergency, DRAP recommends that a pre-emergency submission be filed using existing processes to the extent feasible and appropriate. The extent of, and timelines for, evaluation of such submissions will be determined on a case-by-case basis and will depend on the nature of the emergency.

Subject to exigent circumstances beyond control, DRAP anticipates that pre-emergency submissions for high priority activities may be evaluated in a matter of weeks.

7.3 Prioritization of Requests for Consideration for an EUA

The DRAP intends to establish priorities for its evaluation of requests to consider an EUA prior as well as during a declared PHE. Such prioritization may be based on the circumstances, such as:

1. the seriousness of the clinical condition;
2. the incidence of the clinical condition;
3. the available information concerning the likelihood that the product may be safe and effective in preventing, treating, or diagnosing the condition;
4. the effect use of the product may have in ensuring national security;
5. whether the product is included in government strategic stockpiles, if applicable;
6. whether the product could be used by a large population or is limited to subpopulation(s) (unless such use may be critical in managing a public health threat or in protecting a subpopulation with no other suitable measures available);
7. request of another government agency;

8. the extent to which the product would serve a significant unmet medical need in a special population (e.g., pregnant women, infants and children, and immunocompromised persons);
9. the availability and, where known, safety and effectiveness of other countermeasures;
10. the urgency of the treatment need (i.e., the window of opportunity for treatment can vary between different medical conditions);
11. the adequacy of the supporting nonclinical and clinical information; and
12. the quantity of product available.
13. the feasibility of adhering to required storage conditions.
14. the security of the supply chain, if applicable.

7.4. Consideration for an EUA Request

The concerned Disvion shall be responsible for the overall disposition of the request and if required may interact directly with the entity submitting the request for consideration. The Registration Board of DRAP being competent forum for grant of EUA, may seek additional scientific and technical input from outside experts or may constitute a committee of experts for evaluation of submitted data on quality safety and efficacy and to make recommendation for grant of EUA.

7.5. Timelines for Evaluation of the Request

The timelines for evaluation and action on a request for consideration for an EUA will depend on the product's type; the nature of the emergency; and other relevant factors. Although the length of time required for action will vary, DRAP recognizes that it is likely that, in a PHE that is occurring or believed imminent, a request for consideration for an EUA will be acted upon with highest priority.

7.6. Validity, Revocation or Termination of an EUA

The validity of an Emergency Use Authorization (EUA) in the context of a PHE will generally be for 12 months. An EUA will be in effect for the duration of the declaration unless the EUA is

revoked because the criteria of issuance (as described in section 5.2 Eligibility for an Emergency Use Authorization) are no longer met or revocation is appropriate to protect public health or safety.

7.7. Publication

DRAP shall publish a notice of each EUA on the official website, including an explanation of the reasons for issuance, a description of the intended use, and any contraindications of the EUA product. DRAP also will promptly publish each termination or revocation of an EUA and an explanation of the reasons for the decision.

8. Post-Authorization Activities

Post EUA monitoring

After a product has been approved and used, DRAP shall take into consideration reports on safety surveillance, efficacy/effectiveness/performance monitoring, quality complaints and other relevant data that may impact the validity of the EUA

The sources of such information will inter alia be based on existing surveillance mechanisms in place in Pakistan and on post-approval surveillance commitments of the manufacturer, set as conditions for the EUA. The applicant must provide a Risk Management Plan considered necessary to identify, characterize and minimize the important risks of a medicinal product.

In case emergency use authorization holder is not responding to a post-approval quality/safety issue in a timely and/or scientifically sound manner and if post-approval quality/safety issues are identified and cannot be resolved, the DRAP reserves the right to restrict or revoke the EUA of the product.

Post EUA changes

The applicant must promptly inform DRAP of all changes regarding formulation, manufacturing process, testing methods, specifications, facilities and any other aspects that might result in a change of the safety and/or efficacy and/or performance of the product.

Glossary:

Active (Pharmaceutical) Ingredient (API)

An active ingredient is any component that provides pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or animals. Synonym is “active substance”.

Agent

Pathogen/item specified in the declaration of emergency causing a serious or life-threatening disease or condition.

Biological (product)

As defined in Schedule-I of DRAP Act 2012.

Dosage Form

The pharmaceutical form in which the active pharmaceutical ingredient, excipients and physical formulation of a medicinal product is presented e.g. tablet, capsule, solution for injection, cream, inhalation etc.

Finished Pharmaceutical Product (FPP)

Product that has undergone all stages of production, including packaging in its final container and labelling. An FPP may contain one or more active pharmaceutical ingredients.

Manufacturer (EUA)

Any person or entity with responsibility in manufacturing activities including implementation of oversight and controls over the manufacture of the medicinal product or active pharmaceutical ingredients or excipients to ensure quality.

Medicinal Product

Any substance or combination of substances prepared, sold or presented for use in the diagnosis, treatment, mitigation or prevention of disease, disorder of abnormal physical state or the

symptoms of it or restoring, correcting or modifying organic functions in human beings The term "medicinal products" in the context of guidelines includes finished pharmaceutical products (FPPs), bio therapeutics and vaccines. The medical devices, in-vitro diagnostics, blood products and animal products are not included.

Not Available

If there are insufficient supplies to meet fully the emergency need.

Not Adequate

- If there are data contraindicating the use of any available alternative for special circumstances or populations (e.g., immunocompromised individuals or individuals with a medicinal product allergy) or
- if the agent is or may be resistant to available alternative products

Risks

Any known and potential risks relating to the quality, safety or efficacy of the medicinal product as regards patients' health or public health.

Risk-benefit analysis

Evaluation of the known and potential benefits of the product, when used to diagnose, prevent, or treat the identified disease or condition, in relation to known and potential risks as defined above.

References

1. USFDA Guidance on Emergency Use Authorization of Medical Products and Related Authorities, Guidance for Industry and Other Stakeholders. January 2017.
2. WHO Emergency Use Listing Procedure (EUL) December 2020, Version 13 December 2020.
3. WHO Guidelines on regulatory preparedness for the oversight of pandemic or other emergency use vaccines in importing countries, April 2024

Annex I: Format of Submissions

1. The DRAP expects material to be provided in a reviewable form in Common Technical Document (CTD) format and sufficiently complete to permit substantive evaluation.

2. Submissions shall be made online through DRAP E-Application System It is recommended that the submission begins with a section that describes the contents and organization of the included materials. The applicant or anyone with a right of reference may refer to data or other information previously submitted to the <NMRA> in a registration and/or marketing authorization application.
3. DRAP expects that material to be provided in a reviewable form and sufficiently complete to permit substantive evaluation. Nevertheless, in rapidly developing or unexpected emergency circumstances, or when previously unanticipated or unavailable medicinal countermeasures are being considered, it may not be possible for an entity to provide all of the requested data or to provide it in the format suggested in a timely manner. In such circumstances, the DRAP will accept and evaluate the request for consideration for an EUA based on data in the form an entity is able to submit. Missing data and poor documentation may lead to a request for additional information and thus, may cause a delay in the decision-making process or even the decision not to authorize emergency use of the medicinal product.

Annex II: Details on required information for submission

It is recommended that the request for consideration include the following types of data, as appropriate and to the extent feasible given the exigencies of the circumstances:

1. Well-organized study reports that provide a complete assessment and analysis of available safety and effectiveness data and an interpretation of the findings. If final study reports are not yet available, any available interim study reports should be provided and clearly identified as such
2. Any relevant statistical analyses and source data for clinical studies, nonclinical laboratory studies, and any animal studies demonstrating safety and efficacy of the product in the treatment of the underlying disease or condition or a closely related disease or condition, such as case report tabulations for key studies; case report forms for all patients who died during the clinical studies and for all persons who did not complete the study due to an adverse event, regardless of causality; relevant reports in the published literature; and notarized translations of source materials in a language other than English.

Recommended safety data

The amount and type(s) of safety data that is recommended to be submitted as part of a request for consideration for an EUA will differ depending upon a number of factors, including whether the product is approved for another indication and, in the case of an unapproved product, the product's stage of development. DRAP will interpret safety information in light of the seriousness of the clinical condition, alternative therapies (if any), and the specific circumstances of the emergency. DRAP strongly encourages any person or entity with an EUA medicinal product to discuss with the DRAP at the earliest possible time (even before a determination of actual or potential emergency) the nature and type of safety data that might be appropriate to submit to DRAP

Ijaz Mustafa
Assistant Director-V (MIS)
Tuesday, 17 June, 2025, 1:7:27 PM

a) Unapproved uses of approved products

If the new indication uses a similar dose, duration, route of administration, and/or mechanism of action (as appropriate given the nature of the product), and the intended patient population is similar to that for which the product is approved, DRAP recommends

references of the approved application if the requester submitted the approved application or has a right of reference. If the new use poses a different risk to the patient population (e.g., suggesting the possibility of increased toxicity), the DRAP recommends that information from relevant in vitro studies, animal toxicology studies, and (if available) human clinical data and experience be provided to support such a use.

b) Unapproved products

The range of available data for such products will differ widely. DRAP recommends that any request for consideration for an EUA include available preclinical testing data, such as in vitro and animal toxicology data. The DRAP also strongly encourages that safety information in humans from clinical trials and individual patient experience should be provided, if available. DRAP further recommends that data submitted in the request attempt to link the likely patient exposure to any relevant existing preclinical data. Similarly, where animal data are used, sufficient information should be provided to link the results of these data to expected exposures related to the proposed use in humans. Any information on safety associated with use in humans of this or related compounds or devices of a similar design should be also submitted.

c) Approved products by another NMRA or reference institution

For data requirements for this approach reference is made to the "Guideline on Good Reliance Practices".

Recommended Effectiveness data

In general, for approved medicinal products with unapproved use as well as unapproved medicinal products:

DRAP recognizes that comprehensive effectiveness data are unlikely to be available for every EUA medicinal product, and the information necessary to authorize emergency use of a product will depend on the circumstances of the declared emergency, as well as available knowledge about the product's safety profile. DRAP plans to assess the sufficiency of the effectiveness data and the risk-benefit profile of each candidate product on a case-by-case basis.

DRAP recommends that requests for consideration for EUA include any available relevant scientific evidence regarding the following:

i. The mechanism(s) of the product's action to diagnose, treat, or prevent the disease or condition underlying the request.

ii. Preclinical testing data, such as in vitro evidence of effect of the product in preventing or reducing the toxicity of the specified agent.

iii. Data to demonstrate effectiveness in diagnosing, treating, or preventing the subject disease or condition in at least one animal species expected to react with a response predictive for humans, where the animal study endpoint is clearly related to the desired benefit in humans (e.g., enhancement of survival or prevention of major morbidity).

iv. Evidence of effectiveness in humans (e.g., in published case reports, uncontrolled trials, controlled trials, if available, and any other relevant human use experience)

v. Data to support the proposed dosage (including pharmacokinetics and pharmacodynamic data) for the intended use.

Ijaz Mustafa
Assistant Director-V (MIS)
Tuesday, 17 June, 2025, 1:7:27 PM