Framework for

Emergency Use Authorisation

For the National Medicines Regulatory Authorities

of the Southern African Development Community

SADC-EUA-F

October 31, 2022

Federal Institute for Drugs and Medical Devices

PharmTrain-CoronaGlobal Project

GHP Programme

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Acronyms and Abbreviations

CG	Corona Global
CTD	Common Technical Document
EMA	European Medicines Agency
EUA	Emergency Use Authorisation
EUL	Emergency Use Listing
GBT	Global Benchmarking Tool
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practices
ICH	The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
LOQ	List of Questions
NMRA	National Medicines Regulatory Authority
PEG	Product Evaluation Group
PHE	Public Health Emergency
PQS	Pharmaceutical Quality System
QMS	Quality Management System
RMP	Risk-Management Plan
SADC	Southern African Development Community
SADC-EUA-F	Southern African Development Community-Emergency Use Authorisation-Framework
TAG	Technical Advisory Group
TOR	Terms of Reference
TRS	Technical Report Series
TWG	Technical Working Group
WHO	World Health Organisation
ZaZiBoNa	Collaborative procedure for the joint assessment of medicinal products in the SADC region meaning “Look to the future” in Nyanja (a local Zambian language)

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Executive Summary

Recent infectious disease outbreaks such as the Monkeypox virus, SARS-CoV-2 pandemic, Zika, and Ebola show that public health emergencies (PHEs) become increasingly common in a globalised world. Pathogens do not respect borders and pose a serious risk to public health worldwide impacting human well-being and causing social and economic damages. One of the key elements in emergency management represents emergency preparedness. This requires national medicines regulatory authorities (NMRAs) to build up and strengthen sound and effective systems. A part of it relies on a stable and well-functioning national medicines regulatory system which is central for building and sustaining a robust health care system to deal with PHEs. NMRAs underpin the high quality, safety, and efficacy of medicinal products and undertake a crucial role in timely approval and use of product candidates during PHEs.

In the face of the COVID-19 pandemic, many NMRAs around the world invested in their regulatory systems to develop procedures for a prompt review of COVID-19 vaccines and other potential treatments concerning the quality, safety and efficacy. In the Southern African Development Community (SADC), regulatory systems are differently equipped, especially for regulatory processes during emergencies.

In this regard, this framework:

- Was developed based on the World Health Organisation (WHO) Emergency Use Listing (EUL) Procedure to shorten timelines for a rapid approval and use of medicinal products during a PHE;
- Is designed as a tool for NMRAs in the SADC region to implement, adopt and manage emergency use authorisation (EUA) procedures with the following aims:
    - To build and/or strengthen structures; and
    - To promote harmonisation and reliance;
- Emphasises the importance of emergency preparedness.

This guidance includes considerations for an EUA guideline development and identifies core activities associated with enhanced emergency preparedness and accelerated authorisation mechanisms.

1 Introduction

Mandates of national medicines regulatory authorities (NMRAs) encompass a stable supply and a safe, quality-assured access to essential medicines and vaccines to ensure people's health which is also represented in the Sustainable Development Goal 3.8 (1-3). A NMRA plays a key part in a country's health system and presents a core component for a resilient health system (4).

In recent years, public health emergencies (PHEs) have caught more and more attention due to recurrent threats of infectious disease outbreaks and other emergencies. As a result, health systems including NMRAs around the world have been increasingly under pressure. Depending on the cause, PHEs can involve emerging and re-emerging infectious disease outbreaks, natural disasters, social unrests and conflicts, food contaminations, or industrial accidents including chemical or radioactive nuclear spills, among other hazards and risks (5). Following the onset of the COVID-19 pandemic, international organisations watched carefully the global trend of rapidly evolving pathogens contributing to a rise of health crises of international concern (6). The largest Monkeypox outbreak outside endemic areas in the first half of 2022 shows clearly that emergencies can occur any time with the ability to affect the international community regardless of borders. Therefore, it is of great importance to develop regulatory strategies to overcome the issue of being unprepared.

In the wake of this worldwide challenge, there is a need for preparedness to respond effectively to emergencies (7, 8). In this context regulatory preparedness and the role NMRAs undertake is critical to manage PHEs (9). Resilient systems with well-functioning and stable structures, regulatory capacity, as well as harmonised standards and procedures in place are essential for enhanced emergency preparedness and response (2, 3, 10).

International awareness led to the call for accelerated procedures concerning the regulatory review and approval process. In the face of the COVID-19 pandemic, NMRAs around the world put enormous efforts into the development of procedures aiming to expedite the availability of medicinal products during PHEs and providing guidance for applicants during the submission process for products to be used in health emergencies. As such, the World Health Organisation (WHO) published the updated document on the "Emergency Use Listing (EUL) Procedure" (11) which is a special procedure for listing of unauthorised medicines, vaccines and *in vitro* diagnostics in the event of a PHE by NMRAs. Several NMRAs around the world have adopted and implemented various different guidelines or procedures with regards to expedited approval pathways for COVID-19 health products (12). For strengthening the

regulatory emergency preparedness in Southern Africa, particularly in the South African Development Community (SADC), a framework was developed to provide guidance on adopting, implementing and managing an EUA procedure with the emphasis on harmonisation amongst NMRAs in the SADC region.

2 Purpose and Objectives of the Framework

The purpose of this document is to provide practical guidance to the NMRAs in the SADC region on how to expedite the approval/marketing authorisation/registration/licensing[1] process of medicinal products in emergencies. The framework for the SADC region, adopted by the NMRAs and endorsed by the Heads of Agencies, outlines steps required for the assessment of unauthorised medicinal products in a PHE. It provides a comprehensive action plan for the authorisation of medicinal products, i.e. medicines and vaccines, based on accepted international standards and guidelines from WHO and SADC. The document is targeted towards the NMRAs in the SADC region, and may apply also to other regional economic communities, initiatives promoting reliance and harmonisation concepts as well as relevant stakeholders engaged in the regulatory field.

The framework builds mainly on the WHO EUL Procedure, which delineates the approach to determine whether an unauthorised product can be listed by WHO on a time-limited basis, while further data is being gathered and evaluated (11). Recently published EUA frameworks were also taken into consideration for the development of this framework (12, 13). The overall goal of the Framework for Emergency Use Authorisation in the SADC region (SADC-EUA-F) is to facilitate building regulatory structures for an EUA at the national level, foster harmonisation and promote work-sharing with the aim of reducing gaps in regulatory emergency preparedness and response to PHEs as well as ensuring an accelerated assessment of medicinal product candidates in emergencies.

The main objectives of the SADC-EUA-F are:

- To support the NMRAs of SADC in strengthening their preparedness for PHEs;
- To support the NMRAs of SADC in building structures and capacity for a drug regulatory system that ensures its functionality, as well as a critical benefit-risk assessment of regulated medicinal products during a health crisis;
- To help establish standardised emergency authorisation procedures at the NMRAs in SADC;
- To promote harmonisation and reliance among the NMRAs in SADC.

[1] The term “authorisation” and related terms, such as “(un)authorised” will be used in the remainder of the document as placeholder for the different terminologies used at the national level.

2.1 Context of the Framework

The framework is a tool to assist regulatory authorities to develop a new EUA guideline or strengthen existing emergency use guidelines in compliance with good review practices in line with WHO guidance (14, 15). It also lays emphasis on the concept of reliance and harmonisation in the SADC region as an instrument to increase efficiency, i.e. saving resources and reducing time required for the authorisation of medicinal products. While strongly promoting harmonisation in the SADC region, a common legislation is currently not available and national legal provisions have to be considered. Therefore, a joint EUA guideline for the entire SADC region cannot be realised under the current circumstances. This framework is meant to serve as the basis for domestication and national implementation. This document should be used together with national PHE guidelines.

This framework illustrates three phases of the EUA process: (1) pre-emergency phase, (2) emergency phase and (3) post EUA phase. These key areas are significant for the NMRA in the EUA process of authorisation of medicinal products with focus on enhancing emergency preparedness of regulatory authorities. Considering the crucial role of regulatory systems in access to safe and effective medicinal products strengthening the NMRA enables an efficient response to emergencies. The WHO Global Benchmarking Tool (GBT), a standardised instrument for evaluating strengths and areas for improvement of NMRAs, contains indicators relevant to PHEs (9). The implementation of, and compliance with these indicators play a key role for the maturity of regulatory authorities and contribute to improved preparedness and functionality in PHEs.

2.2 Development Process

In September 2021, a joint technical working group (TWG) of representatives from the SADC NMRAs and the team of the PharmTrain-Project, funded by the German Federal Ministry of Health within the Global Health Protection Programme and located at the Federal Institute for Drugs and Medical Devices, was established. The TWG comprised members from eleven countries in the SADC region including Angola, Botswana, Comoros, Lesotho, Madagascar, Mozambique, Namibia, South Africa, Tanzania, Zambia, and Zimbabwe. The PharmTrain team acted as a facilitator.

First, a desk review was carried out to identify potential emergency use procedures in the respective countries. The documents were screened and evaluated based on the GBT. Second, a gap analysis was conducted to identify related needs and areas for improvement of the NMRAs in the SADC region. The TWG followed a schedule with regular online meetings in the first year to share experiences with the EUA processes and regulatory preparedness. In the course of those meetings, key areas necessary for

the SADC-EUA-F and emergency preparedness were identified. This framework is based on the contributions of the members of the TWG. It builds mainly upon the WHO EUL procedure and incorporates relevant aspects of emergency use guidelines shared by some of the TWG member states and those of other authorities and institutions considered appropriate as a reference by the working group.

3 Definitions

The definitions given below are applicable to this framework. The terms used in this document may have different meanings in other contexts.

Applicant

A person or entity who has applied for regulatory approval of a product or a change thereof. In some jurisdictions this term is used in a wider sense (see “Marketing authorisation holder”).

Assessment

For the purpose of this document, the term “assessment” covers the process of the evaluation and its outcome conducted for a regulatory function (e.g. evaluation of a clinical trial application, evaluation of an initial authorisation for a medicinal product or any subsequent post-authorisation changes, evaluation of safety data, evaluation as part of an inspection, etc.).

Synonym: review

Batch

A defined quantity of material produced in a process or series of processes so that it is expected to be homogeneous within specified limits.

Synonym: lot

Effectiveness

The performance of a medicinal product under 'real-world' conditions.

Efficacy

The ability of a drug to produce the intended effect as determined by scientific methods, for example in pre-clinical research or clinical research studies.

Finished (Pharmaceutical) Product (FPP)

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

Good Manufacturing Practices (GMP)

A standard concerning the production, processing, packing, release, and holding of a medicine which ensures that medicines are consistently produced and controlled according to quality standards appropriate to their intended use and as required by marketing authorisation.

Lot Release

The process of NMRA/National Control Laboratory of an individual lot of an authorised vaccine before giving approval for its release on to the market.

Manufacturer

Any person or entity with responsibility in manufacturing activities including implementation of oversight and controls over the manufacture of the active pharmaceutical ingredient(s) and/or finished pharmaceutical product to ensure quality.

(Marketing) Authorisation (MA)

Approval to market a medicinal product in the NMRA's country. MA is issued by the NMRA with a legal document for the purpose of marketing or free distribution of a product in one or more countries after evaluation for safety, efficacy and quality in the marketing authorisation assessment process.
Synonyms: licencing, registration, approval

Marketing Authorisation Certificate

An official document issued by a NMRA for the purpose of marketing or free distribution of a product after evaluation for safety, efficacy and quality.
Synonyms: registration certificate, license

Marketing Authorisation Holder

A person or entity whose product has been authorised by a NMRA to be on the market.
Synonyms: holder of certificate of registration/ applicant

Market Surveillance and Control

Market surveillance and control function plays a crucial role in assuring medicinal products consumer safety since its objective is to ensure compliance of the products placed on the market with pre-set criteria for quality, safety and efficacy (i.e., verify compliance with marketing authorisation and good practices guidelines). Market surveillance and control function activities are primarily concerned with four themes: (1) control of import activities, (2) prevention and detection of and response to

substandard and falsified medicinal products, (3) market surveillance program for monitoring the quality of medicinal products throughout the supply chain, and (4) control of promotional, marketing and advertising activities. The aforementioned activities may or may not be undertaken by a single entity (e.g., organisation, division, or department).

Medicines

See medicinal product including biological and biotechnological products except for vaccines.

Medicinal Product

A substance or combination of substances that is intended to treat, prevent or diagnose a disease, or restore, correct or modify physiological functions by exerting a pharmacological, immunological or metabolic action.

In this framework, vaccines and medicines account for medicinal products.

National Medicines Regulatory Authority (NMRA)

A national body that has the legal mandate to set objectives and administer the full spectrum of medicines regulatory activities. NMRAs are responsible for ensuring that products released for public distribution (normally pharmaceuticals and biological products, such as vaccines and medical devices including test kits or related products) are evaluated properly and meet international standards of quality, safety, and efficacy.

Patient Information Leaflet

A leaflet in every pack of medicine containing information on the medicine for the user, such as patients.

Public Health Emergency

(see Chapter 4.1)

Post-marketing Monitoring

Includes activities referring to vigilance and market control and surveillance after MA granting.

Recognition

The acceptance of the regulatory decision of another regulator or trusted institution. Recognition should be based on evidence of conformity that the regulatory requirements of the reference regulatory authority are sufficient to meet the regulatory requirements of the relying authority.

Recognition may be unilateral or mutual and may, in the latter case, be the subject of a mutual recognition agreement.

Reference Regulatory Authority

An authority or institution which assessment and its outcome serve as basis for regulatory reliance. As per WHO guidance (https://www.who.int/news/item/29-04-2021-who-publishes-new-guidance-to-promote-strong-efficient-and-sustainable-regulatory-systems) this encompasses different levels of reliance.

In this document this term relates to a list of authorities/institutions determined by the NMRA including the transitional WHO listed authorities referred to as group B+C (https://www.who.int/publications/m/item/list-of-transitional-wlas) and WHO Prequalification Programme.

Reliance

The act whereby the NMRA in one jurisdiction may take into account and give significant weight to assessments performed by another NMRA or trusted institution, or any other authoritative information in reaching its own decision. The relying authority remains independent, responsible and accountable regarding the decisions taken, even when it relies on the decisions and information of others.

https://www.who.int/news/item/29-04-2021-who-publishes-new-guidance-to-promote-strong-efficient-and-sustainable-regulatory-systems

Repurposed Product

A medicinal product that is used for a purpose other than its original intended (authorised) use.

Risk Management Plan (RMP)

The aim of a risk management plan is to document the risk management system considered necessary to identify, characterise and minimise a medicinal product's important risks. To this end, the RMP contains:

1. The identification or characterisation of the safety profile of the medicinal product, with emphasis on important identified and important potential risks and missing information, and also on which safety concerns need to be managed proactively or further studied (the 'safety specification');
2. The planning of pharmacovigilance activities to characterise and quantify clinically relevant risks, and to identify new adverse reactions (the 'pharmacovigilance plan');

3. The planning and implementation of risk minimisation measures, including the evaluation of the effectiveness of these activities (the 'risk minimisation plan').

Rolling Review

A rolling review is a regulatory tool that is used to speed up the assessment of a promising medicine or vaccine during a public health emergency. Normally, all data on a medicine's or vaccine's quality, efficacy and safety as well as all required documents must be ready at the start of the evaluation in a formal application for marketing authorisation. In the case of a rolling review, the NMRA reviews data as they become available from ongoing studies.

Summary of Product Characteristic (SmPC)

A document describing the properties and the officially approved conditions of use of a medicine. The SmPC forms the basis of information for health care professionals on how to use the medicine safely and effectively.

Unauthorised Medicinal Product

A medicinal product for human use in respect of which no marketing authorisation has been granted by a relevant NMRA.

Synonym: unregistered product, unapproved product

Vaccines

A heterogeneous class of medicinal products containing immunogenic substances capable of inducing specific, active and protective host immunity against an infectious disease. Of note, hyperimmunoglobulines/monoclonal antibodies used for so-called passive immunisation are not part of this definition

Vigilance

Medicinal products' vigilance, defined as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicinal product-related problems, is extremely important for guaranteeing that safe and effective medicinal products of high quality are used within the country.

ZaZiBoNa

The regional collaborative medicines registration initiative in Southern Africa focusing on dossier assessments and good manufacturing practice (cGMP) inspections. It was founded in October 2013 by four countries Zambia, Zimbabwe, Botswana and Namibia with the support of WHO prequalification and the Southern Africa Regional Program on Access to Medicines. The name ZaZiBoNa is a combination of the first two letters of the name of the founding countries and coincidentally means 'to look to the future' in a local Zambian language, Nyanja. Out of 16 SADC member countries, 14 are either active or non-active participants, based on their internal capacity to conduct assessments and inspections.

https://zazibona.com/

4 General Requirements for an EUA

4.1 Declaration of a Public Health Emergency

Before a NMRA may issue an EUA, a declaration of exceptional circumstances by the responsible government body is required to justify this kind of authorisation. These circumstances are related to an immediate risk to health, life, property, or the environment and can be of national and/or international concern. Such extraordinary events are determined as those that:

- Immediately threaten life, health, national security, property or the environment;
- Have already caused loss of life, health detriments, property damage or environmental damage; or
- Have a high probability of escalating to cause immediate danger to life, health, property or the environment.

In case of an emergency declaration, it is important to differentiate between the emergency declaration allowing for an EUA procedure and the emergency declarations issued by other governmental authorities to manage a PHE. For example, a government may put in place a “national state of disaster” to implement protecting mechanism for the management of a crisis. This “state of disaster” does not automatically allow for an EUA procedure but other measures to combat it.

4.2 Termination of a Public Health Emergency

When a PHE is officially declared over by the responsible governmental body, then any EUA(s) issued based on that PHE will no longer remain in effect. The NMRA will inform the stakeholders that the circumstances that precipitated the EUA have ceased. Nationally, legal provisions other than EUA may be in place for continued use.

4.3 Eligibility Criteria of EUA Candidate Products

In the context of this framework EUA candidates are medicinal products. Categories of products that may be considered for an EUA include unauthorised products, repurposed products as well as products authorised by acknowledged reference regulatory authorities. Each product stream has specific requirements to be eligible for an EUA.

To qualify for assessment under this procedure, the following criteria must be met:

- 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 is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating such serious or life-threatening disease or condition. This can apply to the whole population or to a critical subpopulation (e.g. children);
- Existing products have not been successful in eradicating the disease or preventing outbreaks;
- The product is manufactured in compliance with current Good Manufacturing Practices (GMP);
- The applicant undertakes to complete the development of the product. 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.

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

4.4 Criteria for Issuance of an EUA

Legal provisions, regulations and policies for an EUA should underpin the criteria for issuing EUAs. In addition to the eligibility criteria for an EUA application, stated in section 4.3, the following criteria for issuance of an EUA should be met:

a) 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 disease or condition caused by an agent;
b) 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;
c) The product is manufactured in compliance with current GMP, and
d) The applicant undertakes to complete the development including monitoring and reporting of the product and apply for full authorisation.

5 EUA Procedure

This chapter provides an overview of practical considerations for NMRAs in the SADC region to develop and implement an EUA procedure. In this context, the EUA applies to medicinal products (medicines and vaccines) during a PHE declared by WHO or the relevant government body. The procedure constitutes three steps:

1. Pre-Emergency Phase
2. Emergency Phase
3. Post-EUA Phase

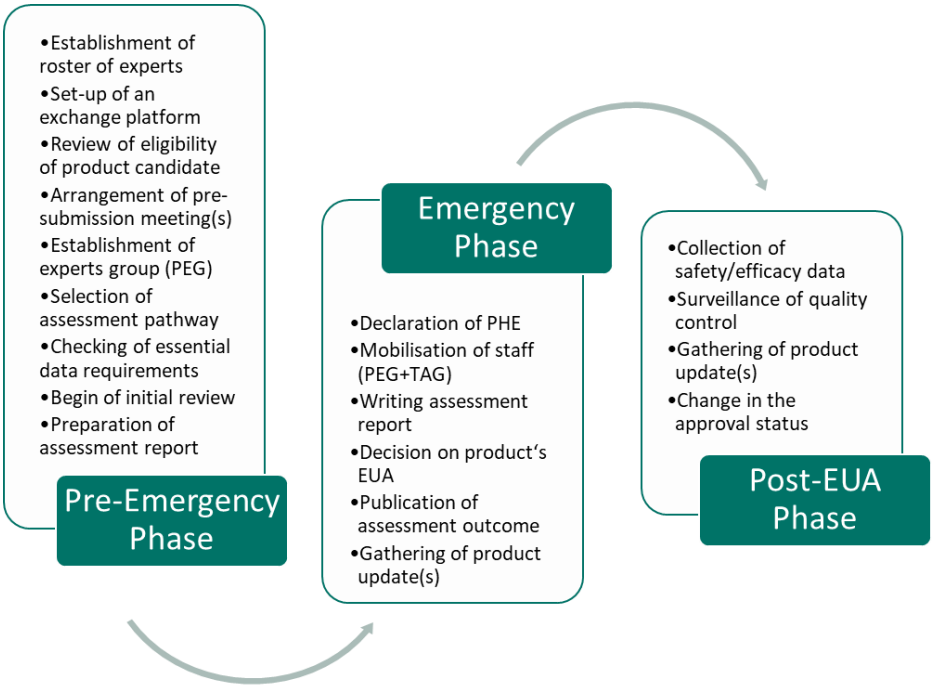

Fig.1. Three step EUA procedure.

The three phases of the EUA procedure are envisioned as a series, with one phase leading into another. These steps build upon each other and explain as to what constitutes emergency preparedness and response with respect to an EUA. Each step contains several activities which may occur concurrently depending on the circumstances.

5.1 Pre-Emergency Phase

The pre-emergency phase describes the time prior to the determination of a PHE by the national government body. In this time, potential risks may be assessed and appropriate response plans developed. The process of planning to outline roles and responsibilities as well as understanding organisational structures and functions is critical (16). This phase represents the key to emergency preparedness and contributes to strengthening the regulatory preparedness of agencies. Preparedness refers to a set of complex, multidimensional processes (17) that enables an effective, rapid response and recovery to promote resilience of the systems (16). The concept of emergency preparedness is based on the adaptability to local conditions which in turn plays an important role to secure sustainability. This section focuses on the activities that can be done in advance, thus minimising the time required for a decision about an EUA of a product, once the PHE is declared.

There are several key actions that can be undertaken and executed during the pre-emergency phase. Areas of preparation include setting timelines, selecting potential products for the assessment process and determining required resources. Resources in this context include staffing in terms of numbers and capacities as well as technical tools, such as IT tools and capacities.
The scope and types of regulatory activities during the pre-emergency phase shall be defined individually at country-level.

This definition can depend on aspects such as (1) the assessment of the likelihood of an emergency occurring in the country taking into account the location of the outbreak and its extent (international concern or nationally-/regionally-limited) and (2) the interests and resources of the respective NMRA. In this framework, a few scenarios are presented as to what the pre-emergency phase can encompass (see table 1 below). Ultimately, the decision lies with the national government/NMRA.

Table 1. Definitions of scenarios for the Pre-emergency Phase.

Pre-Emergency Scenarios	Acceptance of EUA Application
Scenario 1 Pre-emergency phase refers to the time when an immediate threat to the public's health is anticipated and a PHE is officially declared by the WHO but not (yet) by the governmental body.	Yes
Scenario 2 Pre-emergency phase refers to the time when an immediate threat to the public's health is anticipated. The PHE is officially declared by neighbouring countries or countries whose NMRAs serve as reference authorities for regulatory decision-making. There is no official PHE declaration by WHO or national governmental body as yet.	Individual decision of each NMRA whether to accept EUA application of candidate medicinal product or to apply an alternative marketing authorisation process.
Scenario 3 Pre-emergency phase refers to the time in-between emergencies, i.e. one PHE has ended but the causative circumstance has the potential of causing another outbreak in the future. There is no official PHE declaration by WHO or national governmental body as yet.	Individual decision of each NMRA whether to accept EUA application of candidate medicinal product or to apply an alternative marketing authorisation process.

There are three types of pre-emergency activities according to the objectives and the stakeholders involved: (1) Establishment of expert groups; (2) Arrangement of pre-submission meetings and (3) Definition of data requirements for the EUA procedure (Fig.2). It is strongly advised to initiate activities as early as possible and to concentrate on those that can be done in advance. All three activities are closely connected and cannot be separated from each other. They may run in parts concurrently to accelerate the decision-making process. If regulatory preparedness does not include pre-emergency activities for EUA, these would be implemented during the emergency phase. In this situation, timelines for the process will be impacted.

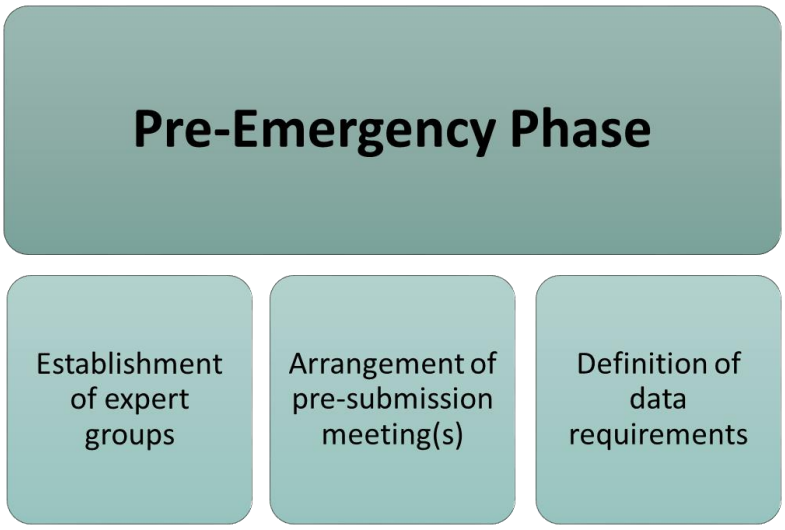

Fig. 2. Overview of Pre-Emergency Phase activities.

5.1.1 Prioritisation of Pre-Emergency Activities

Prior to a determination of an actual or potential emergency, it may be beneficial for the NMRA to establish priorities for the activities it intends to undertake. Such prioritisation may be based on a variety of factors. These include:

- The seriousness and incidence of the clinical disease or condition;
- The public health need for the product and, when known, the safety and effectiveness of other potential medical countermeasures;
- The urgency of the treatment need (i.e., the window of opportunity for treatment can vary for different medical conditions);
- Availability and adequacy of the information concerning the likelihood that the product may be safe and effective in preventing, treating or diagnosing the condition;
- The potential role that the use of the product may have in ensuring national security;
- Whether the product is included in government strategic stockpiles e.g. for infectious diseases such as tuberculosis, malaria and HIV;
- The extent to which the product would serve a significant unmet medical need including in:
    - A subpopulation (e.g. pregnant women, infants, children, or immunocompromised persons)

- The stage of the emergency response (e.g. evolving understanding of the disease or condition);
- Whether request is from a government agency/stakeholder;
- The availability of the product (e.g., the quantity and manufacturing capacity); and
- Whether other authorisation mechanisms might be more appropriate for allowing emergency access to products under development (when there are little or no safety or efficacy data available).

5.1.2 Pre-Emergency Activities

This section elaborates in more detail on the three areas for pre-emergency activities and its related procedures. It shall give the NMRA support in its planning and preparedness for a PHE. The extent of implementation will depend on available resources of the health and regulatory system in the individual country.

5.1.2.1 Activity 1: Establishment of Expert Groups

Activities include establishment of a roster of experts to be called upon to set up the necessary expert and advisory groups at the different stages of the procedure, consultations, strategic planning, and oversight of systems/procedures to support the implementation of the EUA. A collaborative network ensures the information sharing process and brings together various skill sets from different backgrounds leading to improved emergency preparedness. There are two types of groups that will be set up on an (ad hoc) basis from the established roster of experts:

A. For the ZaZiBoNa process only: Product Evaluation Group based on the ZaZiBoNa procedure (ZaZiBoNa-PEG),
B. Technical Advisory Group for EUA (TAG-EUA) at national level (NMRA-TAG)[2]

1. Roster of Experts

A roster of experts may be selected and formed among suitably qualified staff, other professionals or members of standing advisory groups through a selection process by identifying the necessary qualification based on the nature of the product to be assessed and tabled for discussion. These shall be representatives from NMRAs, NMRAs responsible for the regulatory oversight of products, NMRAs of potentially affected countries, academia, and other relevant institutions. The pool of expertise should cover all technical and scientific areas to be considered during the pre-emergency, emergency

[2] Currently, there exists no legal provision for the establishment of a supra-national advisory group.

and post-EUA phase, so that the required assessment teams, expert and advisory groups can be rapidly established when required for assessment and recommendations relevant to specific products.
External experts (not belonging to the NMRAs) will be assessed for conflicts of interest and be required to enter into a confidentiality undertaking.

2. Joint Product Evaluation Group for EUA

Depending on the requested type of submission, a PEG may be set up as part of the ZaZiBoNa process (ZaZiBoNa-PEG). For an EUA process at national level, selection of staff and external experts for the assessment of a product candidate will follow the usual procedure for dossier assessment and are hence not specifically outlined in this framework.

The ZaZiBoNa-PEG will be called during the pre-emergency phase of the procedure to:

- Determine the sets of guidelines, requirements and scientific consensus guidelines -when available- to be used to assess a product;
- Evaluate applications of products that have met the EUA eligibility criteria and have passed the initial screening;
- Perform a risk-based assessment of the scientific data for a product, including quality, safety/efficacy/performance, and programmatic aspects;
- Prepare and submit a report with the ZaZiBoNa-PEG's recommendations to the NMRA-TAG-EUA (see below) for consideration when a PHE is declared.

Should a submission only be received once the PHE had been declared, the ZaZiBoNa-PEG will be convened in the emergency phase. Timelines for review and report will in this case be impacted and the process nonetheless expedited as much as possible.

3. National Technical Advisory Group for EUA (NMRA-TAG-EUA)

In addition to the agency's board taking the decisions on regular marketing authorisation, the NMRA may establish a TAG either while the PHE declaration is still pending or upon declaration of a PHE. Additional experts from academia or other areas may be co-opted onto the roster, should the necessary expertise not be already available or contracted with the NMRA. If a TAG is implemented, provisions shall be made at the NMRA for establishing communication routes to and within the NMRA-TAG-EUA.
For the ZaZiBoNa-pathway, the ZaZiBoNa focal point will provide the TAG-EUA members with the report prepared by the ZaZiBoNa-PEG and any other information considered critical for the deliberations and decisions to:

- Provide a recommendation on whether or not an unauthorised medicinal product should be authorised for an emergency.

This decision will be primarily based on the assessment report prepared by the ZaZiBoNa-PEG supplemented with further data from the submission as required**.**

5.1.2.2 Activity 2: Establishment of Pre-submission Meeting

The provision of a meeting platform for an exchange of information and interaction between the agency and the applicant represents another key element in the pre-emergency phase. This activity includes pre-submission meetings/activities, selection of products for assessment according to established eligibility criteria, assignment of the evaluation pathway, and assessment of submitted data (initial data and updates), with reports thereon. The applicant and representatives of the NMRA such as project coordinator/manager and assessors, as needed, are involved in the pre-submission meeting. For the ZaZiBoNa process, pre-submission meetings are also encouraged.

I. Function of the Meeting Platform

This platform enables pre-submission meetings as an opportunity for the applicant to receive guidance on the required documentation, structure of the application, relevant guidelines, review pathway, and review timeframe. Such consultations 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 required.

II. Function of the Pre-submission Meeting

The pre-submission meeting aims at enabling an applicant to submit a dossier that may proceed more quickly through the screening and subsequent stages of assessment. If considered necessary or desirable by the applicant and SADC member state(s) where the applicant wishes to submit their application, a discussion may be held between the applicant and the respective NMRA(s) before the actual evaluation process starts. The applicant may express interest for a product assessment by the ZaZiBoNa joint review process, and discuss further details during a pre-submission meeting. More information on the organisation of the meeting as well as a template of a meeting request form are included as Annex 2.

III. Evaluation Pathways and Guidelines

There are several assessment pathways listed below for the assessment of a medicinal product under EUA depending on the available data, existing collaborations amongst NMRAs and the individual

decision of the NMRA assigning the most appropriate pathway (Fig.3). Annex 3 assists in the decision-making on pathway assignments.

For the assessment, SADC guidelines and country specific guidelines should be used. Alternatively, when SADC and country specific guidelines are inadequate, recognised international guidelines or those from recognised reference authorities will be utilised.

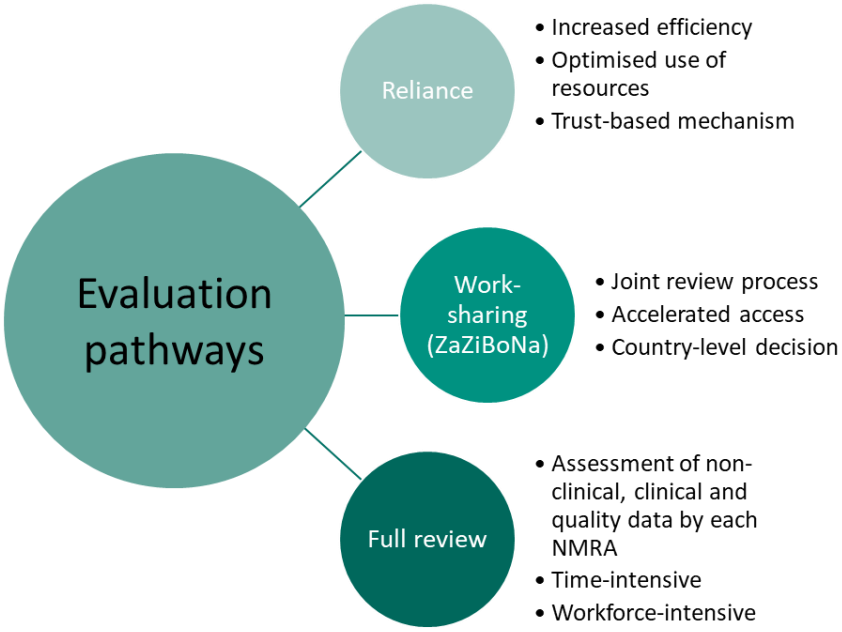

Fig. 3. Overview of evaluation pathways.

1. Reliance

   The reliance pathway should be utilised where the applied product is either listed by the WHO-Prequalification Programme or approved by a reference authority. The reliance pathway in the form of an abridged review or verification is applied to assess the assessment reports and decisions made by a supporting NMRA or WHO. Findings and results of the review may be shared with the NMRA of the SADC region for use/consideration, depending on country-specific processes. Reliance increases efficiency of NMRAs, helps strengthen regulatory systems and optimises the use of resources. Note that the NMRA ensures that the medicinal product which is approved in-country is the exact same version as that which received approval by the reference authority.

2. Work-sharing: ZaZiBoNa regional pathway

   This pathway allows for a joint review process with all the participating countries. Prerequisite for this approach is the expressed interest of the applicant in the joint review. A recommendation is made to the countries and the decision-making process lies with each authority.

3. Full review

   Full review requires the assessment of quality, non-clinical and clinical data as well as the relevance of missing information by the NMRA to conclude on the benefit-risk profile of the product.

For the pre-emergency phase, the following timelines are recommended:

Table 2[3]**.** Recommended timelines for evaluation pathways during pre-emergency phase.

Screening	Reliance	Work-sharing (ZaZiBoNa)	Full Assessment
5 days	45	90 days	90 days

5.1.2.3 Activity 3: Definition of Data Requirements/Information for an EUA Procedure

This section outlines critical information including general, technical and formal data requirements to be provided for medicinal products such as medicines and vaccines to support an EUA. This activity is closely connected with the pre-submission meeting activities since recommended information and required data will be discussed case-by-case with the applicant. It is recommended that a request for an EUA includes a well-organised summary of the available scientific evidence regarding the product's safety and efficacy, risks and benefits, as well as any available approved alternatives to the product. In general, the exact type and amount of data needed to support an EUA may vary depending on the nature of the declared emergency or threat of emergency and the nature of the candidate product.

The three categories of medicinal products that may be considered for an EUA include (1) unauthorised medicinal products (novel products), (2) repurposed medicinal products and (3) products approved by a reference authority. It is of advantage to provide comprehensive data as early as possible.
Importantly, the submission of data cannot be limited to a certain phase of the EUA procedure and therefore, the provision of data may be possible in all three emergency phases. However, a minimum

[3] Note: The recommended timelines refer solely to working days, clock stops are excluded.

set of clinical and non-clinical data is required for an EUA. Recommendations cannot be made for the use of the product if the safety is not yet established. Applicants must ensure that submissions meet the minimum requirements as set by the NMRA and provide a written commitment to submit outstanding documents necessary for granting EUA.

The following aspects for stipulating data requirements in the EUA process should be considered:

- Severity of the disease;
- Specific circumstances of the emergency;
- Candidate product has been approved for another indication (similarity to dose, duration, route of administration, and/or mechanism of action, intended patient population should be considered);
- Candidate product is an unapproved product;
- Candidate product's stage of development;
- Available data on safety at submission.

Annex 4.1 comprises a detailed overview of information and data required for an EUA and on the stages at which they should be made available to the respective NMRA.

I. General Requirements

General aspects on what is required:

- The EUA procedure is applicable to applications which are submitted for use in addressing, treating or preventing PHE situations, where the relevant country has declared a PHE or based on the WHO declaration.
- Applications should be submitted in each country, for which the applicant seeks an EUA.
- Where available, comprehensive data should be provided, which refer to a complete application with all quality, safety and efficacy information. Comprehensive data may only be available for some applications; such as for products which are used for other indications and have been repurposed for use in the PHE, therefore these will be determined on a case-by-case basis.
- For novel products, only limited information may be available at early stages of submission. Comprehensive data will become available at a later stage and should be submitted once available. Data that are not available at the time of application and EUA should be discussed and agreed on by the applicant and the NMRA in pre-submission meetings.
- For products which are approved by other regulatory authorities, reliance approaches may be used for EUA, however, all data which is currently available and was submitted to the relied upon authority, should be submitted with the application. A submission of a declaration of

sameness from the applicant is recommended. For reliance processes to be used, full scientific assessment reports may be required and additional data may be requested from the applicant, based on country-specific requirements for reliance. Reference authorities allowing for this approach are defined by the NMRA.

II. Formal Requirements

The submission for an EUA application for medicines and vaccines should follow the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Common Technical Document (CTD) format. In the CTD dossier, sections for which no information is available at the time of the initial submission should be indicated as "data or information not available", "study ongoing" or "not applicable" as the case may be. An indication should be given by the applicant on the timeline for submission of the missing data.

III. Summary of Recommended Information and/or Data

For the NMRA to evaluate a request for consideration for an EUA, the following information should be submitted:

1. A description of the product and its intended use:
    a) Identification of the serious or life-threatening disease or condition for which the product may be effective;
    b) Where/when/how product is anticipated to be used;
    c) Target population for which the product may be used;
2. A description of the product's international marketing authorisation status:
    a) Unauthorised product;
    b) Repurposed product;
    c) Product authorised for the same condition/target population by a reference authority;
3. The need for the product including any approved alternative product(s) and their availability and adequacy for the proposed use, and the unmet medical need(s) the EUA addresses;
4. Available safety and efficacy information for the product depending on the category of the product (unauthorised or repurposed) and the product's stage of development;
5. A discussion of risk and benefits;
6. Information on chemistry, manufacturing and controls (see Annex 4.4);
7. A list of each site where the product, if authorised, would be (or was) manufactured and the GMP status of the manufacturer(s);
8. Information about the quantity on hand and the surge capabilities of the manufacturing site(s);
9. Information comparable to an approved product information or instruction of use:

Drafts of the "information sheet" to be furnished to health care professionals or authorised dispensers and recipients of the product and discussion of the feasibility of providing such information in an emergency;

10. Proposed labelling of primary package:

    As a minimum this should include the following information: Name of medicinal product, name of the active ingredient, dosage form and strength, total volume (if applicable), batch number and expiry date;

11. Proposed labelling of secondary package (if applicable):

    As a minimum this should include the following information: Name of the active ingredient and excipients, dosage form and strength, name and address of the manufacturer, special storage conditions if applicable, batch number, manufacturing date and expiry date, legal status and limitations of use;

12. Product samples may be required.

IV. Benefit-Risk Balance

The benefit-risk balance is determined at each stage of the process, i.e. after submission of initial and additional data. This assessment is based on the data available at the time. A favourable benefit-risk profile is required in order to be considered for an EUA. To determine the known and potential benefits and risks, the NMRA evaluates the totality of scientific evidence. The quality and adequacy of the available evidence should also be assessed by the NMRA, given the current state of scientific knowledge. The benefit-risk assessment will be adjusted as new information is submitted for review.
Based on the outcome of a risk-based analysis concerning the quality, efficacy and safety of the medicinal product in question, an EUA may be granted, with conditions that require the submission of outstanding information within a timeframe stipulated by the authority.

V. Risk Management Plan

The applicant is required to submit a risk management plan (RMP) when applying for an EUA to ensure that safety monitoring is in place (see Annex 4.3). In general, the RMP should contain at minimum the following information:

- A medicinal product's safety profile;
- How its risks will be prevented or minimised in patients;
- Plans for studies and other activities to gain more knowledge about the safety and efficacy of the medicinal product;
- Measuring the effectiveness of risk minimisation measures.

As new information becomes available with time, the RMP will continuously be modified and updated throughout the life cycle of the product(s). Hence, only limited information may be available at early stages in the application process as the medicinal product authorised under the EUA procedure has not been licensed for use in routine settings. In some application processes, post-marketing data gained from other countries may be already available due to delays in global distribution. Therefore, the manufacturer should discuss with the NMRA 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 EUA would be in effect and for a reasonable time following such period. A complete RMP may only be available after further data have been generated.

VI. Conditions for EUA

To ensure ongoing evaluation of safety and efficacy, conditions on the product's EUA should be imposed by the NMRA. A wide range of conditions exists and the NMRA will determine these conditions.

Conditions on medicinal products relating to the following areas should be considered (12):

- Conditions to ensure that health care providers administering the product are aware of the product emergency use status, its significant known benefits and risks, and any alternatives;
- Conditions to ensure that patients are made aware of the product's emergency use status, known significant benefits and risks, and any alternatives, and option to accept or refuse the product;
- Conditions for monitoring, analysing, and reporting adverse events;
- Conditions for the manufacturer regarding recordkeeping and reporting;
- Conditions on distribution of the product regarding who may distribute the product and means of distribution;
- Conditions on collecting and analysing safety and effectiveness data;
- Conditions relating to advertising the product during the period of emergency use;
- Condition requiring the applicant to submit an application for full approval once adequate data is available and/or within a certain period after the medicinal product has obtained full authorisation from a reference authority.

5.2 Emergency Phase

The emergency phase begins with the official declaration by the responsible governmental body once a determination of an actual or potential emergency has been made. The phase will be terminated by the same body when the circumstances causing this decision have changed. Detailed information on the termination of an EUA is provided in the respective chapters of this framework (see chapter 4.2 and 5.2.1.3).

Subsequent to the pre-emergency phase, the emergency phase continues seamlessly. This phase concentrates on the management and the response procedures to an emergency. The NMRA undertakes activities such as (1) the mobilisation of staff (expert groups), (2) the review and decision-making concerning the EUA and (3) the publication of the assessment outcome.

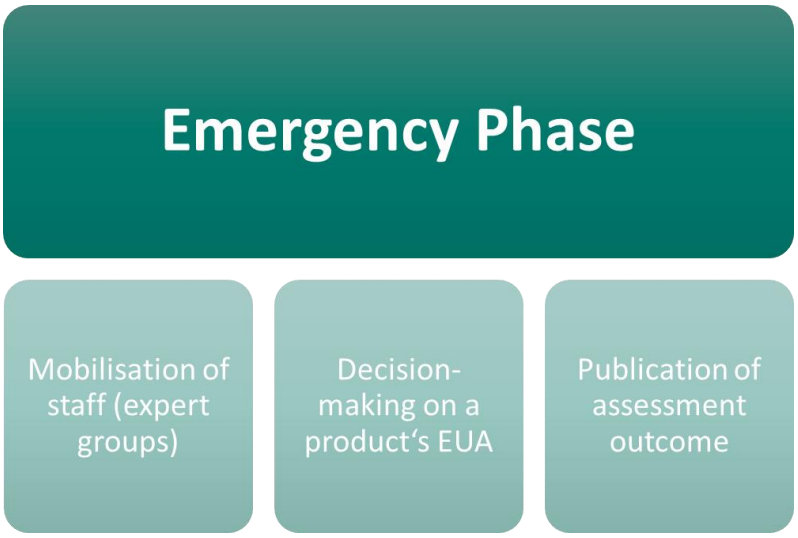

Fig. 4 Overview of Emergency-Phase activities.

5.2.1 Emergency Phase Activities

This section explains the responsibilities and activities of the NMRA to ensure an appropriate response to the emergency and to allow for an EUA process.

Recommended timelines for each evaluation pathway in the emergency phase are provided in the table below.

Table 3[4]**.** Recommended timelines of each evaluation pathway during the emergency phase.

Screening	Reliance	Work-sharing (ZaZiBoNa)	Full Assessment
1 day	10 days	To be determined at time of dossier submission	30 days

5.2.1.1 Activity 1: Preparation of the Assessment Report

For NMRA-specific application: The assessment team evaluates the product dossier according to the established in-house procedures.

For the ZaZiBoNa pathway, the ZaZiBoNa-PEG prepares an assessment report and ensures that newly available information will be continuously included in this document. The report will be submitted by the ZaZiBoNa focal point to the NMRA-TAG team. In case the ZaZiBoNa-PEG has not been established in the pre-emergency phase and no assessment of the product candidate was conducted in this period, the ZaZiBoNa-PEG has to prepare the assessment report in the emergency phase and submit to the TAG.

5.2.1.2 Activity 2: Mobilisation of the NMRA-TAG-EUA

As previously described, if a TAG-EUA is established at the NMRA, this group is responsible for the evaluation of a specific product candidate under the EUA procedure. The TAG may be established by the NMRA either while the PHE declaration is still pending or upon a declaration of a PHE. The selection process for the members of the TAG-EUA will be undertaken by the NMRA based on the established roster (see chapter 5.1.2.1). The TAG-EUA appoints a Group Lead who may undertake a leading role in organising and managing the communication and the process (see also Annex 1). Provisions shall be made at the NMRA for establishing communication routes to and within the NMRA-TAG-EUA.

5.2.1.3 Activity 3: Decision-making on EUA

This procedure includes provisions to concentrate most of the activities related to the submission and assessment of available data during the pre-emergency phase. Therefore, optimally the NMRA-TAG-EUA will have all the necessary information to deliberate and issue a recommendation to the NMRA on whether or not the product should be authorised for emergency use. The NMRA-TAG-EUA may request further information from the applicant and the NMRA before making a recommendation. The recommendation will be used by the NMRA (its responsible committee) to decide whether or not the product can be granted an EUA. For products that underwent the ZaZiBoNa process conducted by the

[4] Note: The recommended timelines refer solely to working days, clock stops are excluded.

ZaZiBoNa-PEG, each NMRA makes an individual decision on the authorisation or rejection of a medicinal product.

The NMRA may consider as part of the conditions of an EUA, certain requirements for the applicant to fulfil within a predetermined timeframe in order to convert the EUA to a full authorisation. If the emergency has been declared over, before these requirements have been met, the EUA holder shall be encouraged to transition the product to the (full) marketing authorisation status.

I. Validity of an EUA

The validity of an EUA in the context of a PHE will generally be for 12 months, unless the EUA is revoked because the criteria of issuance (see section 4.4) are no longer met or revocation is appropriate to protect public health or patients' safety. The EUA of a product may be extended if deemed necessary by the NMRA.

II. Revocation and Revision

The NMRA will periodically, at minimum once, prior to expiration of the validity of the EUA, review the decision concerning the circumstances and appropriateness of the EUA, including circumstances that might warrant revocation of the EUA. The review will include regular assessments based on additional information provided by the EUA holder. The agency will revise or revoke an EUA if:

- Initial circumstances justifying the issuance no longer exist[5]; or
- Other circumstances require a revision or revocation to protect the public health or patients' safety.

Such circumstances may include:

  - Significant adverse inspectional findings (e.g., when an inspection of the manufacturing site and processes has raised significant questions regarding purity, potency, or safety of the EUA product that may affect the benefit-risk assessment);
  - Reports of adverse events linked to the EUA product;
  - Product failure in terms of pharmaceutical quality;
  - Product ineffectiveness (e.g. due to newly emerging data that may contribute to a revision of the NMRA's initial conclusion that the product "may be effective against a particular pathogen);
  - Request from the EUA holder to revoke EUA;

[5] If necessary, patients who began treatment when the declaration was in effect may complete their treatment course.

- A material change in the benefit-risk assessment based on evolving understanding of the disease or condition and/or availability of medical countermeasures; or
- A change in the approval status of the product (that may render an EUA unnecessary).

5.2.1.4 Activity 4: Publication of Assessment Outcome

Transparency, accountability and communication are important for ensuring good regulatory practice and should be part of the marketing authorisation process. This applies also to EUAs. Open and transparent communication is a trust-building approach among stakeholders. Hence, it is essential that the NMRA implements a comprehensive communication strategy to provide information to an audience from various backgrounds such as patients, health care providers or community leaders. Aspects to consider include language and disability access to ensure accessibility of information to the entire population (12).

If an EUA has been granted this information will be made publicly available by the NMRA. The NMRA will also promptly inform the public about each termination or revocation of an EUA. Also, any EUA revision impacting the conditions of use or the product's quality attributes, and hence of interest to the public, warrants publication of a notice by the NMRA.

5.3 Post-Emergency Use Authorisation Phase

This phase begins with the EUA of a medicinal product. Depending on the circumstances, the emergency declaration is still in force or has been already terminated. The post-EUA phase describes the responsibilities of the NMRA and the EUA holder in areas such as pharmacovigilance, market surveillance and control, applying for a full marketing authorisation, submitting product data to NMRA, and reporting product defects or recalls. This phase involves (1) post-market surveillance programmes, (2) updates on newly emerging data and (3) change in approval status (Fig. 5).

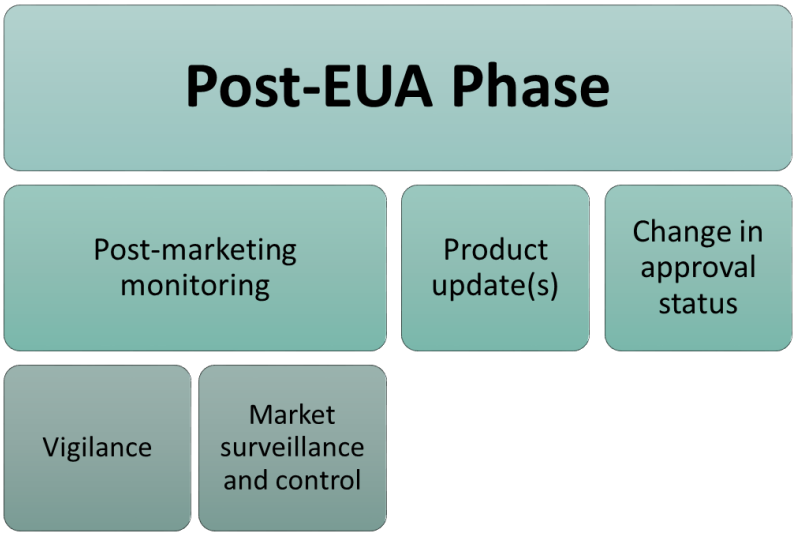

Fig. 5. Overview of Post-EUA Phase activities.

5.3.1 Post-EUA Activities

This section elaborates on the importance of safety monitoring and a RMP after the authorisation of a medicinal product to ensure its effectiveness, safety and quality. Additionally, any changes to the product and the handling of newly available data also fall under this phase.

5.3.1.1 Activity 1: Post-marketing Monitoring

After a product has been authorised for emergency use, the NMRA will take into consideration aspects related to safety surveillance, efficacy/effectiveness/performance monitoring and quality complaints. Vigilance, market surveillance and control are primary concerns for post-marketing monitoring.

In the post-EUA phase, new, potential risks of the product may be identified, followed by a NMRA's evaluation concerning their importance for patient safety and whether information should be added to the safety specification of the RMP. These activities are related to post-authorisation safety reporting, including the product's effectiveness and pharmaceutical quality.

General recommendations for post-marketing monitoring plans comprise:

- Submission of reports of specific adverse events of interest in an expedited manner beyond required routine reporting;
- Submission of adverse event report summaries at more frequent intervals than specified for routine required reporting;
- Submission of NMRA-specific requirements on post-authorisation plans;
- Further studies, e.g. a pharmacoepidemiologic study may be imposed to further evaluate important identified or potential risks or to study uncommon or delayed-onset adverse events of special interest;
- A pregnancy exposure registry that actively collects information on use of the medicinal product during pregnancy and associated pregnancy and infant outcomes.

5.3.1.2 Activity 2: Update on Changes to the Product

New information on the EUA product may lead to the extension of a product's use to other patient groups or may change the initial use as a therapeutic to a preventive product. The evaluation thereof is the responsibility of the NMRA. The NMRA should require from the EUA holder to report any changes to the product concerning:

1. Pharmaceutical quality, e.g. formulation, manufacturing process, testing methods, specifications, or facilities;
2. Efficacy and safety, e.g. preclinical information, pharmacokinetic, pharmacodynamic or clinical efficacy/safety data; and
3. Any other aspects that might (a) result in a change of the safety and/or efficacy and/or performance of the product or (b) change the basis for the EUA recommendation.

This information including a critical discussion of its relevance to the product use should be reported immediately, i.e. within 30 days, to the NMRA, when the EUA holder becomes aware of them.

The NMRA will establish a communication strategy in form of standard operating procedures for the organisation of newly emerging data and updates to the EUA product to ensure the information is received and processed efficiently and in a timely manner. Newly emerging information will be

submitted to the NMRA using specific processes. Specific EUA expert groups (see section 5.1.2.1) shall be involved as appropriate.

5.3.1.3 Activity 3: Change in Authorisation Status

In the post-EUA phase, the authorisation status of the EUA product may change depending on the circumstances and a full marketing authorisation as the ultimate goal might be obtained. There are different ways in order to receive a full marketing authorisation of the medicinal product:

1.) The NMRA requires the EUA holder to provide a plan for fulfilling conditions for a full marketing authorisation prior to the termination of the emergency declaration. If the emergency has been declared over before these requirements have been met, the EUA holder shall be encouraged to transition the product to the (full) marketing authorisation status.

2.) In case a reference authority has granted full marketing authorisation, reliance will be used in order to grant full authorisation before the emergency ends. This approach may be applied, especially when the EUA itself was also based on a reliance mechanism.

6 Summary of Key Activities

This table summarises the key activities recommended during the three phases of the EUA procedure.

Table 4. Overview of activities at each stage of the EUA management.

Activity	Acting	Pre-emergency phase	Emergency Phase	Post-EUA Phase
Procedures for the different processes (national, ZaZiBoNa) are put in place after consultation with stakeholders	NMRA, ZaZiBoNa, (future) applicants	✓		
Establishment of roster of experts for: • ZaZiBoNa-PEG • NMRA-TAG	NMRA, ZaZiBoNa	✓	✓	
Establishment of expert groups: • ZaZiBoNa-PEG • NMRA-TAG-EUA	NMRA, ZaZiBoNa	✓	✓	
Assessment of eligibility of applications	NMRA, ZaZiBoNa	✓	✓	
Pre-submission meetings of applicant and NMRA	NMRA, ZaZiBoNa	✓	✓	
Selection of assessment pathway (full national review, national reliance, full ZaZiBoNa review, ZaZiBoNa reliance)	Applicant	✓	✓	
Assessment of submission (dossier)	NMRA, ZaZiBoNa-PEG	✓	✓	✓
Evaluation of ZaZiBoNa-PEG/NMRA report	NMRA-TAG-EUA		✓	
Submission of updates	Applicant	✓	✓	✓
Decision on EUA approval	NMRA-TAG		✓	
Publication of outcomes	NMRA		✓	✓
Surveillance of Post-marketing monitoring plans	NMRA			✓
Decision on extension of EUA validity	NMRA		✓	✓
Change in approval status	NMRA			✓

Annex 1: Terms of Reference for Expert and Advisory Groups

1.1 Terms of Reference for the Product Evaluation Group (PEG-EUA)

I. Background

In the context of the procedure for an EUA of medicinal products under ZaZiBoNa, the NMRA(s) of the SADC member states will require advice from an evaluation group named ZaZiBoNa-PEG. This group is comprised of members drawn from different NMRAs participating in the ZaZiBoNa initiative. There will be two PEGs, one for each product stream under the EUA (vaccines and medicines):

- ZaZiBoNa-PEG-V: for evaluation of vaccines.
- ZaZiBoNa-PEG-M: for evaluation of medicines.

The experts will be selected from a pre-established roster, according to the requirements for evaluation of the EUA product candidate. Experts selected for the ZaZiBoNa-PEG from the pre-established roster will be required to make every effort to be available on a short notice to perform their PEG-related responsibilities. The PEG will have the functions described below.

Members must respect the impartiality and independence required of each NMRA in the SADC region. They must be free of real, potential or apparent conflicts of interest. Members represent the interest and norms of their NMRAs, not their personal views. To this end, proposed members may be required to complete a declaration of interest form and their appointment, or continuation of their appointment, will be subject to the evaluation of completed forms by the NMRA determining that their participation would not give rise to a real, potential or apparent conflict of interest.

Information and documentation to which members may gain access in performing PEG-related activities will be considered as confidential and proprietary to NMRAs and/or parties collaborating with NMRAs including in particular, but not limited to, the applicants. PEG members shall not purport to speak on behalf of, or represent, the PEG to any third party, and treat the deliberations of the PEG as strictly confidential.

II. Functions

The functions of the PEG are:

a. To assess what published guidelines, requirements/recommendations and international guidance documents are available from SADC and other regulatory agencies that are relevant for the evaluation of a product;
b. To conduct a search for relevant publications with evidence of scientific consensus with regards to, where applicable, safety, immunogenicity or clinical efficacy of a product;
c. To agree on a set of guidelines, requirements/recommendations and other parameters that will be used to evaluate a product or group of products;
d. To screen submissions for completeness of the information required;
e. To review the quality and clinical information of the unauthorised medicinal product (See Annex 4 for information required, after the product has been determined to be eligible for EUA assessment);
f. To make a recommendation to the NMRA-TAG on the benefit-risk balance (positive/negative) of the product. This recommendation should be based on a review of the available data and the applicant's response to the PEG List of Questions (LOQ).

The report and recommendation by the ZaZiBoNa-PEG will be based on the following:

a. Dossier as submitted by the applicant to the NMRAs
b. Responses from the applicant to the LOQ prepared after the initial review (if applicable)
c. Additional information or updates submitted by the applicant at any point and
d. Other information related to the product that the group deems important for the review

PEG members shall be selected to represent the broad range of disciplines relevant to the product under review.

III. Membership

The ZaZiBoNa-PEG is composed of regulatory officers of the NMRA and/or external assessors, involved in the EUA assessment. They shall be selected by the NMRA to represent the broad range of disciplines relevant to the product under review. External experts need to enter into the standard Memorandum of Agreement for Temporary Advisers with the respective NMRA(s).

ZaZiBoNa-PEG-V

The PEG-V should include the following areas of expertise:

- Production and quality control
- Quality systems, quality risk management and GMP
- Non-clinical and clinical assessment
- Pharmacovigilance
- Infectious disease specialists

Note: More than one expert may be selected for each area of expertise.

ZaZiBoNa-PEG-M

The PEG-M should include the following areas of expertise:

a) Regulators with the relevant expertise in the assessment of:

- Pharmaceutical quality data (production, quality control and GMP)
- Toxicological/pre-clinical data
- Pharmacokinetic and modelling/simulation data
- Clinical efficacy and safety data
- Pharmacovigilance measures

Note: More than one expert may be selected for each area of expertise.

b) Infectious disease specialists (clinician, non-regulator), paediatricians and, depending on the nature of the disease also other specialists e.g. virologists.

IV. Term

External ZaZiBoNa-PEG members will commit to serve on an ad hoc basis until the evaluation of the product in question has been completed, including post approval data. The NMRA may terminate a member's membership at any time prior to his/her term and the member will be replaced. However, for consistency and efficiency of the EUA process it is generally preferable to maintain the same group composition until the end of the procedure.

V. Structure

The PEG members shall agree on their roles in the group. A lead assessor who will serve as the Group Lead should be selected. The Group Lead will be responsible for:

- Chairing the meeting(s) of the ZaZiBoNa-PEG;
- Managing communications with the NMRAs in accordance with established communication lines in ZaZiBoNa
- Managing/coordinating the process of review, consolidation of any LOQs and reports;
- Ensuring compliance with timeframes.

VI. Operation

Schedule of the ZaZiBoNa-PEG Activities

The arrangement of PEG activities will be supported by the existing structures of the SADC Medicines Regulatory Harmonisation Project.

Timelines for review and preparation of the final report depend on the phase of the emergency as detailed in section 5.1.2 and 5.2.1 of this framework. In the pre-emergency phase, the experts will normally have a maximum of 90 days (active time) to review the information received and to prepare a report. In case the submission is received after a PHE has been declared, the timeline will be reduced (see chapter 5.2.1, table 3). If additional information is required for the assessment, each expert will prepare questions to be added to the LOQ and submit these to the Group Lead. The Group Lead may coordinate a discussion among ZaZiBoNa-PEG members as required. The Group Lead will consolidate the LOQ and will send it to the ZaZiBoNa focal point. Once the responses are received, each expert will report to the Group Lead if the answers are satisfactory or if there are inadequacies. There may be more than one round of LOQs, until no further information is required or forthcoming from the applicant. Based on the information available, the Group Lead will prepare a consolidated report and will circulate it to all PEG members for adoption. The ZaZiBoNa-PEG will adopt its reports and develop its recommendations by consensus. Any dissenting views will be noted in the report.

VII. Management of Communication

For assessment at national level as well as for ZaZiBoNa joint assessment, the focal person of the NMRA will be responsible for handling all communications with the applicant.

For each review the ZaZiBoNa focal person will:

a. Confirm sameness of the manufacturers for each submission received by the NMRA;

b. Facilitate the arrangements for teleconferences, face-to-face meetings and any other means of communication among members of the ZaZiBoNa-PEG;
c. Monitor progress with the Group Lead;
d. Submit LOQ to the Applicant;
e. Assist the ZaZiBoNa-PEG Group Lead in the preparation of draft agendas and reports, receive the final report with recommendations from the PEG Group Lead, and formally close the review. In case of a conclusion of the review in the pre-emergency phase: Should no additional data become available before a public health emergency occurs that justifies the use of the product, ZaZiBoNa-PEG focal point may submit the final report to the NMRA-TAG-EUA. If additional data are submitted (i.e. updates on clinical trial results, completion of validation of processes and tests, etc.), the PEG will be requested to update its final report and submit the updated final report to the NMRA, through the Group Lead. The report shall be prepared using a standardised format (Annex 6) that will include an executive summary, the assessment of the information reviewed, LOQs and responses as well as the final recommendation.

All ZaZiBoNa-PEG recommendations are advisory to the NMRA. The NMRA retains full control over any subsequent decisions and actions, including whether or not to publish the findings and recommendations of the ZaZiBoNa-PEG in a public report and whether or not to submit the report of the PEG to the NMRA-TAG-EUA.

1.2 Terms of Reference for the National Advisory Group for EUA (TAG-EUA)

I. Background

In the context of a procedure for EUA of medicinal products, the NMRAs may require advice from an evaluation group known as the TAG. The TAG should be established at national level referred to as NMRA-TAG. Alternatively, an agency's advisory board/technical board/committee may undertake this role depending on each NMRA.

There will be two NMRA-TAGs, one for each product stream under the EUA (vaccines and medicines):

- NMRA-TAG-EUA-V: for vaccines, and will be selected, convened and coordinated by the NMRA
- NMRA-TAG-EUA-M: for medicines and will be selected, convened and coordinated by the NMRA

The experts will be selected from a pre-established roster, according to the requirements for evaluation of the EUA product candidate.

Members must respect the impartiality and independence required of each NMRA in the SADC region. In performing their work, they may not seek or accept instructions from any Government or from any authority external to the agency. They must be free of real, potential or apparent conflict of interest. To this end, proposed members will be required to complete a declaration of interest form and their appointment, or continuation of their appointment, will be subject to the evaluation of completed forms by the NMRA determining that their participation would not give rise to a real, potential or apparent conflict of interest.

Information and documentation to which members may gain access in performing NMRA-TAG-EUA related activities will be considered as confidential and proprietary to NMRA and/or parties collaborating with NMRAs including in particular, but not limited to, the applicants. TAG members shall not purport to speak on behalf of, or represent, the NMRA-TAG-EUA to any third party, and treat the deliberations of the NMRA-TAG-EUA as strictly confidential. All proposed members will be required to commit to an appropriate confidentiality undertaking and agree to provisions on ownership. To this end, each member will be required to enter into a Memorandum of Agreement with the respective NMRA.

II. Functions

The function of the NMRA-TAG-EUA is to provide a recommendation on whether or not an unauthorised medicinal product should be approved for emergency use under the EUA procedure, and if so, under what conditions.

In formulating its recommendation, the NMRA-TAG-EUA will use any information deemed critical by the NMRA for consideration. This may include the report on quality, safety and efficacy or performance, prepared by the ZaZiBoNa-PEG or by the assessor team at national level, including the initial evaluation and any updates based on additional information submitted by the applicant.

The NMRA-TAG-EUA will furthermore consider any emergency program needs when applicable, as well as any additional information which the NMRA-TAG-EUA may request from the applicant.

The report prepared by the NMRA-TAG-EUA should follow the template in Annex 6 and will be submitted by the Group Lead to NMRA.

III. Membership

NMRA-TAG-EUA

The NMRA-TAG-EUA-V consists of members from the established roster of experts and should include:

- At least one member with expertise in the epidemiology of the disease that should be prevented with the vaccine in question;
- At least one member with regulatory expertise relating to vaccine evaluation and risk management plans;
- One or more members from the NMRA of the affected countries;
- One member with expertise in quality assessment;
- One member with expertise in clinical assessment;
- One or more members (non-expert) from the affected SADC region are informed and representatives of the local community viewpoint may be included at the discretion of the NMRA.

NMRA-TAG-EUA-M

The TAG-EUA-M consists of members from the established roster of experts and should include:

- At least one member with expertise in the epidemiology of the disease or condition of interest;
- At least one member with regulatory expertise relating to the product and potential risk management plans;
- One or more members from the NMRA of the affected countries;
- One member with expertise in quality assessment;

- One member with expertise in clinical assessment;
- One or more members (non-expert) from the affected SADC region are informed and representatives of the local community viewpoint may be included at the discretion of the NMRA.

IV. Term

All NMRA-TAG-EUA members will commit to serve on an ad hoc basis until the process of developing the required recommendation has been completed.

V. Structure

One member will be appointed to serve as the Group Lead. The Group Lead should be selected by the NMRA-TAG-EUA members and has the following responsibilities:

- Chairing the meeting (s) of the NMRA-TAG-EUA;
- Managing communications with the NMRA;
- Managing the process of review and preparation and approval of agendas, records and reports;
- Assuring compliance with timelines.

VI. Operation

The focal person of a NMRA will convene the members of the NMRA-TAG-EUA on short notice in a virtual or face-to-face meeting and provide them with the information deemed critical by the NMRA for consideration by the NMRA-TAG-EUA. This may include the consolidated report prepared by the ZaZiBoNa-PEG for the specific product and any other data considered relevant for the discussions.

The NMRA-TAG-EUA should in principle submit its recommendation to the NMRA within five working days after the virtual or face-to-face meeting. If additional information has been requested, a recommendation should in principle be issued within three days of receipt of this information.

The Group Lead will prepare a consolidated report (template in Annex 6) and will circulate this to all NMRA-TAG-EUA members for adoption. The NMRA-TAG-EUA will adopt its reports and develop its recommendations by consensus. Any dissenting views will be noted in the report.

VII. Management of Communication

A focal person, designated by the NMRA, will manage all communications between the NMRA-TAG-EUA and the applicant.

For each review the focal person will:

- Provide the NMRA-TAG-EUA Group Lead with the information deemed critical by the NMRA for consideration. This may include the consolidated report prepared by the ZaZiBoNa-PEG for the specific product and any other data considered relevant for the discussions;
- Keep the applicant informed of the procedure and status of the application;
- Facilitate the arrangements for teleconferences, face-to-face meetings and any means of communication among members of the NMRA-TAG-EUA;
- Manage communications with the applicant as required;
- Assist the NMRA-TAG-EUA Group Lead in the preparation of draft agendas and reports and receive the final report with the recommendations from the NMRA-TAG-EUA Group Lead and formally close the review. The report shall be prepared using a standardised format (Annex 6) that will include the recommendation (positive or negative) and a summary justification.

All NMRA-TAG-EUA recommendations are advisory to the NMRA, the respective NMRA retains full control over any subsequent decisions and actions. The NMRA also retains full control over the publication of the reports of the NMRA-TAG-EUA, including whether or not to publish to share them with other institutions, such as NMRAs.

1.3 Template for External Advisors: Memorandum of Agreement - Terms and Conditions for Temporary Advisors

I, the undersigned, in accepting to act as a Temporary Adviser to a NMRA < name of NMRA > agree to the following:

1. RELATIONSHIP BETWEEN THE PARTIES

The execution of the work as Temporary Adviser does not create any employer/employee relationship as between the < NMRA >, on the one hand, and me and/or persons claiming under me, on the other hand. Thus, the < NMRA > shall not be liable to me or any other person whatsoever for any damage, loss, accident, injury, illness and/or death sustained by me in connection with, or as a result of, my assignment as Temporary Adviser to the < NMRA >, including travel.

2. TRAVEL COSTS, PER DIEM AND INCIDENTALS

I understand that my travel, per diem and incidentals will be paid by the < NMRA >, in accordance with the rules described in Annex 1 attached hereto.

3. CONFLICT OF INTERESTS

I agree to truthfully complete the Declaration of Interests for < NMRA > Experts in the SADC region and disclose any circumstances that may give rise to a real, potential or apparent conflict of interest in relation to my work as Temporary Adviser. I will ensure that the disclosed information is correct and will truthfully declare that no other situation of real, potential or apparent conflict of interest is known to me. I undertake to promptly inform the < NMRA > of any change in these circumstances, including if an issue arises during the course of my work as Temporary Adviser. I understand and agree that this Memorandum of Agreement may be cancelled by the < NMRA > if the < NMRA > determines that the information disclosed by me in the Declaration of Interests requires modification or cancellation of the invitation extended to me to serve as Temporary Adviser to the NMRA in the SADC region.

4. INSURANCE

The provision of insurance for TAG members shall be made by the respective NMRA.

Annex 2: Pre-submission Meetings

2.1 Organisation of Pre-submission Meetings

1. To request a pre-submission meeting, the applicant must send the completed Pre-submission Meeting Request Form (see Annex 2.2) to the respective NMRA. The agency will reply to the applicant with a proposed date for the meeting as appropriate and the deadline to submit the information package. The applicant must send the list of proposed participants (up to a maximum of 10 participants per applicant) not later than 15 days before the meeting. The information package should be sent by the applicant not later than 10 business days before the proposed meeting date.
2. To request a pre-submission meeting with the intention of a ZaZiBoNa joint review process, the applicant must send the completed Pre-submission Meeting Request Form (Annex 2.2) to the relevant member states where the applicant wishes to submit their application. The focal person of the NMRA(s) will reply to the applicant with a proposed date for the meeting as appropriate and the deadline to submit the information package. The applicant must send the list of proposed participants (up to a maximum of 10 participants per applicant) not later than 15 days before the meeting. The information package should be sent not later than 10 working days before the proposed meeting date.
3. If the applicant has decided on a ZaZiBoNa process for the medicinal product, a request letter of consent for the ZaZiBoNa assessment by the applicant should be attached to the meeting request form to avoid delay in the process.
4. The focal person of the NMRA will be responsible for leading and organising pre-submission meeting(s). He/she ensures compliance with timelines, organises follow-up actions and keeps track of newly provided data by the applicant.
5. The meeting can be virtual and online, via a chosen method of communication, or face-to-face.
6. The meeting should at most be three hours with the manufacturer responsible for noting minutes. The minutes will be a summary of information presented, the questions raised and the responses, as well as follow-up actions if applicable. These will be sent to the NMRA(s) within seven days for final review and comments.
7. The pre-submission meeting should be made as early as possible, preferably 5 – 7 working days before the expected date of submission. For a successful and efficient meeting, the applicant is encouraged to provide as much comprehensive data as possible, as listed in the pre-submission checklist.

8. The applicant should ensure the agenda is shared with the NMRA(s) before the pre-submission meeting is held.
9. Senior officers from the NMRA, in case of ZaZiBoNa process also from more than one NMRA, where the application is to be submitted with relevant expertise should be involved in these meetings. Where necessary, external experts may be called upon on a case-by-case basis.

2.2 Pre-submission Meeting Request Form for EUA Procedure

Please complete each section of this application form and submit electronically as a Microsoft Word document to the NMRA as appropriate.

Vaccines: example@NMRA.com;
Medicines: example@NMRA.com.

Attachments in electronic format that are 8 MB or less in size can be sent by email with the completed pre-submission meeting request form, including a proposed agenda for the meeting. Attachments in electronic format that are larger than 8 MB should be submitted on CD/DVD, or else be printed and sent by courier or surface mail to the relevant NMRA.

Contact Details

Applicant (name of manufacturer)	
Contact person responsible for this application	
Contact's person job title/position	
Contact details (Including full postal address, phone, fax, email)	

Meeting Details

Type of meeting requested

Face-to-face ☐ Teleconference ☐

Product description

INN	
Strength	
Dosage	
Expected date for submission to NMRA for EUA	

Type of application

Country specific application ☐ ZaZiBoNa process ☐

ZaZiBoNa request form included

Yes ☐ No ☐

Specific objectives/outcomes expected from the meeting

Preliminary proposed agenda including estimated time needed for each agenda item (up to a maximum of 3 hours for the entire meeting) and designated speaker(s)

List of specific questions by technical area

List of all individuals (including titles) who will attend the proposed meeting from the applicant's organisation and/or consultants (up to a maximum of 10 proposed participants).

1.
2.
3.
4.
5.
6.
7.
8.
9.
10.

Proposed date(s) and time(s) for the meeting

Proposed dates	**Proposed times**

Additional information is attached: Yes ☐ No ☐

Additional information will be forwarded separately: Yes ☐ No ☐

Completed by (Name) Signature Date

For NMRA internal use only

Internal Reference	
Scheduled date of the meeting	
Location	

Annex 3: Checklist for Assignment of Pathway

Application Package Contents	Required by pathway			
	Work-sharing (ZaZiBoNa)	Verification	Abridged Assessment	Full review
EUA Application Form	Yes	Yes	Yes	Yes
ZaZiBoNa Request Letter	Yes	Yes	Yes, if applicable	No
Minutes from pre-submission meeting	Yes, if applicable	Yes	Yes	Yes
Proposed package insert	Yes	Yes	Yes	Yes
Proposed information sheet of medicinal product for health care professionals or authorised dispensers and recipients of the product	Yes	Yes	Yes	Yes
Proposed post-marketing surveillance plan	Yes	Yes	Yes	Yes
Certificate of the responsible NMRA's or WHO's decision	Yes	Yes	Yes	Yes
Assessment reports of the responsible NMRA or WHO	Yes	Yes	Yes	Yes, if available
Evidence of quality and good manufacturing practices compliance (GMP certificate)	Yes	Yes	Yes	Yes
Statement for complying with Good Clinical Practice and Good Laboratory Practice	Yes	Yes	Yes	Yes
CTD Module 2 quality, nonclinical and clinical overview	Yes	Yes	Yes	Yes
Full dossier as required by national law/or and regulations (e.g., CTD Modules 2-5)	Yes	Yes	Yes	Yes

Please, note that if required information is not available at time of submission indicate the missing documents and give an explanation in the cover letter. For information needed for an EUA issuance, provide a letter of commitment that missing information will be handed in as soon as possible. See also Annex 4 "data requirements".

3.1 Preliminary Benefit-Risk Assessment Tool for Pathway Assignment

Applicant Name	
Name of medicinal product	
Use of the medicinal product	
Application No.	
Application Receipt Date	
ZaZiBoNa-PEG members/authors	
NMRA-TAG members, if applicable	
Criteria	**Discussion of Risks and Benefits**
Prior Review decisions (e.g. review outcomes of approved products by reference authorities)	
Quality (e.g. GMP certificates, whether manufacturer has other WHO pre-qualified or approved products by reference authority)	
Safety (e.g., consider important identified or potential risk(s) from the clinical development programme, missing information or other uncommon or delayed-onset adverse events of special interest)	

Criteria	Discussion of Risks and Benefits
Need (e.g., ability of already approved products to meet short-, medium-, and long-term demand for different populations in the country, reported efficacy of the medicinal product relative to other products on the market)	
Access (e.g., the extent to which the country will be able to access the product if approved, which may be influenced by manufacturing capacity, access channels through international mechanisms, planned donations, cost)	
Deployment feasibility (e.g., special transportation and storage requirements such as cold chain, number of doses required)	

Annex 4: Data Requirements

4.1 Overview Data Requirements

Table 5. Overview of required data for an EUA at each emergency stage.

Data Package Contents	**Required data for each emergency phase**		
	(Pre-) Emergency Phase: Submission EUA	Emergency-Phase: Decision EUA	Post - EUA Phase
A description of the product and its intended use	✓		
A description of the product's international marketing authorisation (MA) status.	✓		
The need for the product including any approved alternative product(s) and their availability and adequacy for the proposed use, and the unmet medical need(s) the EUA address.	✓		
All available safety and efficacy information for the product	✓	✓	✓
A discussion of risks and benefits	✓	✓	✓
Information on chemistry, manufacturing, controls and stability	✓	✓	✓
A list of all sites where the product, if EUA is granted, will be (or was) manufactured and the GMP status of the manufacturer		✓	✓
Information about the quantity of finished product on hand and the surge capabilities of the manufacturing site(s)		✓	✓
Information comparable to summary of product characteristics and patient information leaflet (“Instructions for Use”-documents)	✓	✓	✓
Proposed labeling of primary and secondary package	✓	✓	✓
Product samples as per sampling schedule		✓	✓

4.2 Commitments of the Applicant

An EUA procedure often means that comprehensive data are not available at the time of the application submission. It is allowed to accept an application while further data are being gathered and evaluated. Thus, a letter of commitment provided by the applicant to assure the compliance with standards and regulations is expected when ultimate information and data are still missing for an EUA approval. In such cases, the applicant must be aware that some requirements may have to be met also prior to an EUA approval.

Commitments of the applicant:

1. The manufacturer must assume responsibility for the quality of the medicinal product to ensure that it is fit for its intended use, comply with the requirements of the emergency use authorisation and does not place patients at risk due to inadequate quality, efficacy or safety.
2. Senior management of the manufacturer has the ultimate responsibility to ensure an effective pharmaceutical quality system (PQS) is in place, is adequately resourced, and that roles, responsibilities, and authorities are defined, communicated and implemented throughout the organisation.
3. While the attainment of this quality objective is the responsibility of senior management it requires the participation and commitment of staff in many different departments and at all levels within the company, the company's suppliers and the distributors. To achieve this quality objective reliably, there must be a comprehensively designed and correctly implemented PQS incorporating GMP and quality risk management.
4. GMP applies to the life-cycle stages from the manufacture of investigational medicinal product, technology transfer, and commercial manufacturing, through to product discontinuation.
5. The PQS appropriate to the manufacture of medicinal products should ensure that:
    a. Product realisation is achieved by designing, qualifying, planning, implementing, maintaining, and continuously improving a system that allows the consistent delivery of products with appropriate quality attributes;
    b. Medicinal products are designed and developed in a way that takes account of the requirements of GMP and other associated codes such as those of good laboratory practice and good clinical practice;*
    c. All necessary controls on starting materials, intermediate products, and bulk products and other in-process controls, calibrations and validations are carried out;*
    d. The finished product is correctly processed and checked, according to the defined procedures.*

* Note that these marked commitments are critical for assessment and therefore, data must be provided prior the EUA.

4.3 Risk-Management Plan

A risk-management plan (RMP) to document the risk management system is considered necessary to identify, characterise and minimise the important risks of medicinal products. In general, the RMP should contain (18):

- The identification or characterisation of the safety profile of the medicinal product, with emphasis on important identified and important potential risks and missing information, and also on which safety concerns need to be managed proactively or further studied (the 'safety specification');
- The planning of pharmacovigilance activities to characterise and quantify clinically relevant risks and to identify new adverse reactions (the 'pharmacovigilance plan');
- The planning and implementation of risk minimisation measures, including the evaluation of the effectiveness of these activities (the 'risk minimisation plan').

Checklist for writing or assessing a RMP

Safety specification	
	Have all appropriate data been reviewed when compiling the safety specification, e.g. are there important (outstanding) issues which have not been discussed in the safety specification?
	If parts of the target population have not been studied, have appropriate safety concerns in relation to potential risks and missing information been included?
	Have limitations in the safety database (e.g. related to the size of the study population, study inclusion and exclusion criteria) been considered and what are the implications of such limitations on the safety profile of the medicinal product? Has reference been made to populations likely to be exposed during the intended or expected use of the medicinal product in the medical practice? Does the safety specification provide a true reflection of the safety concerns (e.g. important identified risks, important potential risks and/or missing information) with the medicinal product?
Pharmacovigilance Plan	
	Are all safety concerns from the safety specification covered in the pharmacovigilance plan?
	Are routine pharmacovigilance activities adequate or are additional pharmacovigilance activities necessary?
	Are the activities in the pharmacovigilance plan clearly defined, described and suitable for identifying or characterising risks or providing missing information?

	Are the safety studies that have been imposed by a competent authority as conditions clearly identified?
	If there are safety concerns derived from medication errors, does the RMP include appropriate proposals to monitor the correct use of the product?
	Are the proposed additional studies necessary, feasible, non-promotional and able to provide the required further characterisation of the risk(s) and address the scientific questions?
	Are timelines and milestones appropriate and feasible for the proposed actions, including those for the submission of results?
Plans for post-authorisation efficacy studies	
	Have all post-authorisation safety studies, either as conditions of the marketing authorisation or as specific obligations, been included?
Risk minimisation measures	
	Are routine risk minimisation measures sufficient or is there a need identified for additional risk minimisation activities?
	Have additional risk minimisation activities been suggested and, if so, are these sufficiently justified and risk-proportionate? Is implementation feasible in respective countries of the SADC region?
	Have criteria for effectiveness of additional risk minimisation activities been defined a priori?
	Are the methods for evaluating the effectiveness of risk minimisation activities well described and appropriate?
Summary of the Risk Management Plan	
	Is it a true representation of the RMP?
	Have the facts been presented appropriately without any elements of promotional nature?

4.4 Essential Data Requirements

Minimum available evidence for vaccines and medicines:

- Non-clinical and early clinical data that demonstrate promising evidence of safety and efficacy;
- Written confirmation that phase 2/3 trials have started and a sufficient number of subjects are or will be enrolled to determine the safety and efficacy within an appropriate and reasonable time; and
- A plan stipulating the proposed timelines for submitting the various components of the application. If not available at the time of submission the applicant should make a commitment to provide the plan as soon as possible.

4.4.1.1 Minimum Data Requirements of Medicines

Clarification of specific data requirements will require discussion between the applicant and the NMRA. Applicants are highly encouraged to contact the NMRA as early as possible to discuss specifics of the application.

I. <u>Chemistry, manufacturing and control data:</u>

1. Information on the active ingredient(s) and finished product, including characterisation (including known and potential impurities), composition, preparation, controls (specifications, analytical methods and their validation) as per any recognised guidelines.
2. A list of intended changes for scale up, if any, along with a discussion on impact of these changes on the quality and safety/efficacy profile of the product.
3. Stability data for a minimum of one month accelerated and three months long-term stability studies. Stability data obtained from the proposed container closure system and the final formulation.
4. Inspection report(s) from a reference authority or from the ZaZiBoNa initiative or a WHO prequalification inspection showing compliance with GMP requirements. Based on the acceptability of the reference authority's report, the NMRA may or may not need to perform its own assessment of GMP compliance. NMRAs may accept inspection reports or outcomes from other NMRAs in the SADC region.

II. Non-clinical and clinical data:

1. All relevant *in vitro* and *in vivo* pharmacodynamic data, e.g., on microbiologic/virologic activity (including any modelling performed); the relevance of the applied cell types/line(s) for the target disease should be justified.
2. Data on efficacy and safety from in-vitro tests and in animal model(s) under well-controlled and documented conditions. The preferred models depend on the disease and may vary according to the medicine's mechanism of action. The applicant must justify the choice of in-vitro and animal model.
    a. 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.
    b. 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.
3. 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.
4. If human pharmacokinetic trials or studies in other indications at the exposure level proposed for treatment of the PHE 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 non-clinical and clinical data at different exposure levels.
5. If available, clinical data demonstrating safety and efficacy at the proposed dose for PHE field use should be submitted.
6. For products that are repurposed, literature data on the safety of the product may be provided, however if dosage differs for the PHE disease, safety data for this dose should be provided.
7. For products authorised for other uses, data requirements will not be the same as new registration applications, as the product is known. Since the safety profile is known, additional non-clinical safety data may not be needed, however clinical data to support the new indication must be included.

III. Regional requirements for labelling

Specific labelling requirements:

1. At a minimum, basic labelling requirements should be met before authorisation. This can be revised as more data is provided.
2. Minimum requirements for the following to be in English/French/Portuguese or one official national language, depending on the end user:
    a. Information comparable to the summary of product characteristics/professional information (information for health care provider) or professional information, e.g. “Instructions for Use” document;
    b. Information comparable to the patient information leaflet, e.g. “Instructions for Use” document;
    c. Primary and secondary labelling;
    d. Any other instructional materials provided to the user; and
    e. A plan to help ensure that prospective recipients and health care providers are adequately informed about the uncertainties regarding both the potential benefits and risks.

Note: When a novel product is authorised, the labelling should clearly indicate that the product is for emergency use only. Exemption of labelling could be considered, such as acceptance of labelling in English for products that are meant for professional use, such as vaccines.

Additional clinical requirements/implications based on public health issues specific to the country should be met.

4.4.1.2 Minimum Data Requirements of Vaccines

I. Chemistry, manufacturing, and control data:

1. Full characterisation of cell banks according to WHO Technical Report Series (TRS) 978, and any subsequent updates and other authoritative guidelines.
2. Full characterisation of master and working seed organism(s), based on reference to the most appropriate WHO TRS and other authoritative guidelines.
3. 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. If deemed appropriate by the NMRA, data on clinical trial batches with a commitment to complete validation on production batches and to submit the data as part of lot release review may be considered.

   N.B., if full characterisation is not possible at the time of submission, adequate justification must be submitted as to why not, and a plan must be presented to address the data gaps. Validation of potency tests and other critical assays. If novel test methods have been developed, full description of the test development and qualification must be presented.
4. Justified specifications for starting material, intermediates, and final products.
5. Stability data for the vaccine produced at the scale produced for the lots to be supplied. If available, accelerated stability data must be included. For vaccines being assessed for emergency use, the relevant committee for each NMRA, will consider programmatic suitability and may consider candidate vaccines with characteristics that would not be accepted for registration or approval by the NMRA.
   a. Vaccines requiring storage at less than -20°C are generally not accepted for the emergency procedure. However, such vaccines can still be considered.
   b. Routinely, if a vaccine presented for approval requires storage below +2°C during its shelf-life period, it should have a minimum period of storage between +2°C and +8°C of 6 months. Under this emergency procedure, vaccines with a shelf life at +2 to +8°C of less than 6 months may be considered. The application should include stability data at +2 to +8°C to determine the minimum acceptable storage period at +2 to +8°C. Upon receipt of such an application, as mentioned above, the NMRA staff responsible for emergency response vaccine deployment will be informed by the applicant, if they (NMRA/country emergency response team and applicant) have infrastructure for vaccine storage and distribution at required temperatures. If the country does not have the ability/infrastructure to store at these temperatures, stability data to support the shelf life of the product at higher temperatures, should be submitted.

c. Overall, single dose vials are preferred. Routinely, multi-dose vaccines should contain adequate preservative, unless they are live attenuated vaccines (where the preservative may have an adverse effect on the viability of the microbe). However, if a multi-dose vaccine submitted under this emergency procedure does not contain a preservative, information/plans on how such a vaccine could be safely managed in the field should be submitted.

6. Inspection report(s) from a reference authority showing compliance with GMP requirements for other, but similar products. Based on the acceptability of the reference authority's report, NMRA may or may not need to perform its own assessment of GMP compliance. NMRAs may accept inspection reports or outcomes from other NMRAs in SADC region.
7. Process changes: by the time of submission, it is likely that the manufacturing process is not finalised and that numerous changes will have to be applied after the first emergency authorisation. These changes should be submitted as updates.

II. <u>Non-clinical and clinical data:</u>

1. 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.
2. 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.
3. 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.
4. 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, NMRA 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 EUA can proceed, provided there are trials underway that will ultimately provide confirmation that immunogenicity is a surrogate.
5. 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.

III. Regional requirements:

Specific labelling requirements:

1. At a minimum, basic labelling requirements should be met before authorisation. This can be revised as more data is provided.
2. Minimum requirements for the following to be in English/French/Portuguese or one official national language, depending on the end user:
    a. Information comparable to the summary of product characteristics/professional information (information for health care provider) or professional information, e.g. “Instructions for Use” document;
    b. Information comparable to the patient information leaflet, e.g. “Instructions for Use” document;
    c. Primary and secondary labelling;
    d. Any other instructional materials provided to the user; and
    e. A plan to help ensure that prospective recipients and health care providers are adequately informed about the uncertainties regarding both the potential benefits and risks.

Note: When a novel product is authorised, the labelling should clearly indicate that the product is for emergency use only. Exemption of labelling could be considered, such as acceptance of labelling in English for products that are meant for professional use, such as vaccines.

Additional clinical requirements/implications based on public health issues specific to the country should be met.

Annex 5: Communication

5.1 Website

Websites of NMRAs and ZaZiBoNa are suitable communication platforms to share information about regulatory processes of medicinal products for emergency use with the public. The webpages should provide information on approved EUA products by the NMRA as well as the termination and revocation of an EUA for a product. It is recommended to share additional information on the website as well including product's overview, authorisation details, product information, assessment history, frequently asked questions, and any safety updates. Furthermore, it would be beneficial if the public could also access latest updates, available treatments as well as information on current review processes and its timeframe.

5.2 Press release

Using press release to publish essential information of a product can be an important communication channel to reach the public with mass media, such as news websites, TV, and radio. A press release gives the opportunity for summarising key information provided from representatives of the NMRA(s).

5.3 Social Media

Sharing key information of a product online with the public using social media and other channels can be a useful tool to improve the outreach of people receiving important news and information. A social media post, for instance, may be created to link it to the official communication channel of a NMRA e.g. the NMRA's website.

5.4 Information for Health Care Professionals and Authorised Dispensers

The NMRA should establish a system to inform health care providers about the approved EUA product considering the following aspects:

- The approval of medicinal product for an EUA including the product name and an explanation of its intended use;
- Summary of the significant known and potential benefits and risks of the emergency use of the medicinal product, and the extent to which such benefits and risks are unknown; and
- Available alternatives and their benefits and risks.

Essential information of the product can be given in form of a "fact sheet" for professionals. Additional information can complement the Fact Sheets in the areas:

- A description of the disease/condition;
- Any contraindications or warnings;
- Dosing information including specific instructions for special populations; and
- Contact information for reporting adverse events and additional information about the product.

5.5 Information for Recipients

To support transparency and build trust recipients should also be informed about the authorisation of the medicinal product and its circumstances. Recommended information:

- The authorisation of the medicinal product for emergency use by the respective NMRA;
- Summary of the significant known and potential benefits and risks of the emergency use of the medicinal product, and the extent to which such benefits and risks are unknown;
- The recipient has the option to accept or refuse the EUA product;
- Informing on any available alternatives to the product and of the risks and benefits of available alternatives.

Essential information of the product can be given in form of a “fact sheet” for professionals. Additional information can complement the Fact Sheets in the areas:

- The product name and an explanation of its intended use;
- A description of the disease/condition;
- A description of items to discuss with a health care provider and adverse event information, including contact information for how to get more information and for reporting adverse reactions; and
- Dosing information including specific instructions for home use or preparation.

Annex 6: Assessment Report Template

6.1 Template for Vaccines:

A. Executive Summary
B. Background
    a. Outbreak background
    b. Available therapies
    c. Applicable regulatory requirements
C. Guidelines
    a. List of guidelines from reference authorities, WHO recommendations, international guidance that the PEG has agreed to use as a set of parameters to assess the information submitted for the product.
D. Vaccine Overview
    a. Vaccine Composition
    b. Dosing Regimen
    c. Proposed Use
E. Review of Clinical Safety and Effectiveness Data
    a. Overview of Clinical Studies
    b. Analysis of Specific Studies
        i. Design
        ii. Assessment of Follow-up Duration
        iii. Subject Disposition and Inclusion in Analysis Populations
        iv. Demographics and Other Baseline Characteristics
        v. Vaccine Efficacy
        vi. Safety
F. Review of Other Information Submitted in Support of Application
    a. Plan for Continuing Blinded, Placebo-Controlled Follow-up
    b. Pharmacovigilance Activities
    c. Non-Clinical Studies
    d. Chemistry, Manufacturing and Control Information
    e. Clinical Assay Information
    f. Inspections of Clinical Study Sites
    g. Prescribing Information and Fact Sheets
G. Benefit/Risk Assessment in the Context of Proposed Indication and Use Under EUA
    a. Known Benefits

   b. Unknown Benefits & Data Gaps
   c. Known Risks
   d. Unknown Risks & Data Gaps

H. Review Meeting Summary

I. Overall Summary and Recommendations including major objections, if applicable

J. References

6.2 Template for Medicines

A. Executive Summary

B. Background
    a. Outbreak background
    b. Available therapies
    c. Applicable regulatory requirements

C. Guidelines
    a. List of guidelines from reference authorities, WHO recommendations, international guidance that the PEG has agreed to use as a set of parameters to assess the information submitted for the product

D. Pharmaceutic Overview
    a. Drug product Composition
    b. Dosing Regimen
    c. Proposed Use

E. Review of Clinical Safety and Effectiveness Data
    a. Overview of Clinical Studies
    b. Analysis of Specific Studies
        i. Design
        ii. Assessment of Follow-up Duration
        iii. Subject Disposition and Inclusion in Analysis Populations
        iv. Demographics and Other Baseline Characteristics
        v. Pharmaceutic Efficacy
        vi. Safety

F. Review of Other Information Submitted in Support of Application
    a. Plan for Continuing Blinded, Placebo-Controlled Follow-up
    b. Pharmacovigilance Activities
    c. Non-Clinical Studies
    d. Chemistry, Manufacturing and Control Information
    e. Clinical Assay Information
    f. Inspections of Clinical Study Sites
    g. Prescribing Information and Fact Sheets

G. Benefit/Risk Assessment in the Context of Proposed Indication and Use Under EUA
    a. Known Benefits
    b. Unknown Benefits & Data Gaps
    c. Known Risks

   d. Unknown Risks & Data Gaps

H. Review Meeting Summary

I. Overall Summary and Recommendations including major objections if applicable

J. References

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