Botswana Medicines Regulatory Authority

Approved By: _____

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Date of approval (DD/MM/YY)

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Revision status sheet

Page	Changes Made	Issue No.	Process owner's name	Date
4	Update of scope; deletion of statement on voluntary participation	**2.0**	Manager Human Medicines- N. Kago	18-08-2023
4	Definitions updated; deletion of the definition of Market Authorization and addition of the definition for Emergency Authorization Listing (E.U.L)	**2.0**	Manager Human Medicines- N. Kago	18-08-2023
9	Addition information on validity of the EUL and transition from EUL to Registration	**2.0**	Manager Human Medicines- N. Kago	18-08-2023
N/A	Header- Changed the document from a policy to guideline	**1.0**	Manager Human Medicines- N. Kago	08-06-2022

1 Purpose

The purpose of this guideline is to guide applicants who are willing to submit applications with the goal of obtaining listing of their product(s) for use during public health emergencies.

2 Scope

This guideline is applicable to all products considered for EUL (vaccines and therapeutics/medicines). It defines eligibility of unregistered products for assessment, the essential information required, and the process to be used in conducting the assessment to determine whether an unregistered product can be listed on a time limited basis, while further data is being gathered and evaluated.

3 Definitions and Abbreviations

3.1 Definitions

3.1.1 Non-routine – refers to deviation from set requirements to cater for products needed in public health emergency situations.

3.1.2 Emergency Use Listing (EUL)- is a special procedure for unregistered vaccines and therapeutics in the event of a Public Health Emergency when the community/public health authorities may be willing to tolerate less certainty about the efficacy and safety of products, given the morbidity and/or mortality of the disease and the lack or paucity of treatment, diagnosis/detection, or prevention options.

3.1.3 Public health emergency - an extraordinary event which is determined as

i. Constituting a public health risk to other States through the international spread of disease; and

ii. Potentially requiring a coordinated international response.

3.2 Abbreviations

The following abbreviations shall apply;

3.2.1 BOMRA - Botswana Medicines Regulatory Authority

3.2.2 CTD - Common Technical Document

3.2.3 EUAL- Emergency Use Assessment and Listing

3.2.4 EUL - Emergency Use Listing

3.2.5 GMP - Good Manufacturing Practices

3.2.6 ICH- International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

3.2.7 PHE - Public Health Emergency

3.2.8 PHEIC - Public Health Emergency of International Concern

3.2.9 PIC/s - Pharmaceutical Inspection Cooperation Scheme

3.2.10 WHO - World Health Organization

4 Introduction

4.1 This guideline was adapted from the World Health Organization (WHO) Emergency Use Assessment and Listing (EUAL) procedure. This is a risk-based procedure for assessing and listing unregistered vaccines and therapeutics for use primarily during public health emergencies of international concern (PHEIC) but also in other public health emergencies if appropriate. For the purpose of this document, a PHEIC or other public health emergency for which the use of this procedure is authorized are referred to as a "PHE". BOMRA shall ensure that the use of an unregistered product under the EUL procedure is based on a pre-determined rationale and predetermined criteria.

4.2 It is imperative to note that the EUL is not equivalent or an alternative to product registration and should not be thought of as such. The EUL is a special procedure for unregistered vaccines and therapeutics in the event of a PHE when the community/public health authorities may be willing to tolerate less certainty about the efficacy and safety of products, given the morbidity and/or mortality of the disease and the lack or paucity of treatment, diagnosis/detection, or prevention options. It is intended to provide a time-limited listing for unregistered products in an emergency context when limited data are available and the products are not yet ready for application for registration.

4.3 This process has been developed to expedite the availability of unregistered medical products needed in public health emergency situations, to assist government/non-government agencies in procuring and determining the acceptability of using specific products in the context of a public health emergency, based on an essential set of available quality, safety, and efficacy/immunogenicity/ performance data.

4.4 The EUL is not intended to interfere with ongoing clinical trials. This means that the clinical development should proceed as planned after the initial submission and subsequent updates.

5. Eligibility of candidate products

Vaccines and therapeutics each have specific requirements to be eligible for evaluation under the EUL procedure. In order to qualify for assessment under this procedure, the following criteria must be met:

a. The disease for which the product is intended is serious or immediately life threatening, has the potential of causing an outbreak, epidemic or pandemic and it is reasonable to consider the product for an EUL assessment, e.g., there are no licensed products for the indication or for a critical subpopulation (e.g., children);
b. Existing products have not been successful in eradicating the disease or preventing outbreaks (in the case of vaccines and medicines);
c. The product is manufactured in compliance with current Good Manufacturing Practices (GMP).

6. Essential data requirements for EUL

The submission for EUL of medicines and vaccines should follow the ICH 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.

6.1 Vaccines

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

A. Manufacturing and Quality Control Data:

i. Full characterization of cell banks according to ICH Q5D Derivation and characterisation of cell substrates used for production of biotechnological/biological products.
ii. Full characterization of master and working seed organism(s), based on reference to the most appropriate ICH Q5 guideline.
iii. 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.

N.B., if full characterization 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. If novel test methods have been developed, full description of the test development and qualification must be presented.

1. Justified specifications for starting material, intermediates, and final products.
    a. Stability data for the vaccine produced at the scale produced for the lots to be supplied. If available, accelerated stability data must be included. The submitted stability data must support the proposed shelf life.
    b. If a multi-dose vaccine is 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.

2. Evidence of GMP compliance issued by ICH member or affiliated countries prior to 23 October 2015, regulatory authorities that participate in the Pharmaceutical Inspection Cooperation Scheme (PIC/s) or WHO or ZAZIBONA.

3. Process changes: by the time of submission, it is likely that the manufacturing process is not finalized and that numerous changes will have to be applied after the first listing. These changes should be submitted as updates.

B. Non-clinical and Clinical Data:

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. If the non-clinical package is not complete at the time of submission, the applicant must submit adequate justification for the lack of complete data and a plan and timeline for submitting those data.
2. 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.
3. 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, BOMRA will consider whether the preponderance of evidence from the non-clinical, and early human studies justifies considering the immunogenicity data as a potential surrogate that is thought to be reasonably predictive of clinical efficacy. In such cases, the emergency use listing can proceed, provided there are trials underway that will ultimately provide confirmation that immunogenicity is a surrogate. Safety and immunogenicity data from other vaccines made by the manufacturer using the same product platform may be considered as supportive data for review if applicable.

   Note: products developed under the animal rule will also be considered for review.

C. Plan for monitoring and reporting of adverse events:

Since the vaccines listed under the EUL procedure have not been registered for use in routine immunization settings, post marketing data would not be available at the time of application, Therefore, the manufacturer should submit the plans to ensure the collection and analysis of information on the safety and effectiveness of the product during the period when the EUL listing would be in effect and for a reasonable time following such period. BOMRA encourages applicants to discuss proposals for active data collection and follow-up mechanisms to capture adverse event information under the EUL.

D. Labelling:

1. Summary of product characteristic (information for healthcare provider).
2. Patient information leaflet.
3. Container labelling.
4. Any other instructional materials provided to the user.

E. Environmental Risk Assessment

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

6.2 Medicines

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

A. Manufacturing and Quality Data:

1. Information on the active ingredient(s) and finished product, including characterization (including known and potential impurities), composition, preparation, controls (specifications, analytical methods and their validation).

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 the medicine produced at the scale produced for the lots to be supplied. If available, accelerated stability data must be included. The submitted stability data must support the proposed shelf life.

4. Evidence of GMP compliance issued by ICH member or affiliated countries prior to 23 October 2015, regulatory authorities that participate in the Pharmaceutical Inspection Cooperation Scheme (PIC/s) or WHO or ZAZIBONA.

B. 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).

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

   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 nonclinical 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.

C. Labelling

1. Summary of product characteristics (information for health care provider)
2. Patient information leaflet
3. Primary and secondary labelling
4. Any other instructional materials provided to the user.

7. Timeline

The Authority shall finalise review of the information received within 3 months**.**

8. Validity

An emergency use listing will be valid for a period not exceeding 5 years. The EUL shall be subject to renewal at the end of five years post listing. BoMRA in consultation with the Ministry of Health will periodically review the circumstances and appropriateness of an EUL, including circumstances that might warrant revocation of the EUL.

9. Transition from EUL to Registration

The applicants of products under EUL shall be encouraged to transition them to the marketing authorization status i.e., registration. The applications for market authorizations shall be submitted in line with Guideline on submission of applications, BoMRA timelines and other relevant guidelines. Once the submitted data has been considered satisfactory, the Authority will grant a full market authorization.

10. General Notes

1. The medical products included in the EUL have not been granted a marketing authorization by BOMRA. This list is exclusively intended to assist procurement agencies in determining the acceptability of using a specific unlicensed product in the context of a public health emergency (PHE). The products included in this list have been evaluated based on a minimum set of available quality, safety, and efficacy data or performance and an agreed plan for their further development. This list is updated regularly. BOMRA may suspend or remove products from the list based on information that may subsequently become available to it.

2. The list is not an exhaustive list of products that may be used in a PHE. It reflects those unregistered products which have been submitted to BOMRA for evaluation by interested parties.

3. The fact that certain unregistered products and suppliers are not included in the list does not mean that if evaluated, they would not be found to meet the above-mentioned requirements.

4. This list may not be used by manufacturers and suppliers for commercial or promotional purposes.