**African Vaccine Regulatory Forum (AVAREF)**

**Guidance and Considerations on Compassionate Use Access**

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# Definitions

* ***“Compassionate use”*** is the use of an investigational medicinal product (IMP) for patient(s) who cannot be treated satisfactorily with existing treatment options. The IMP, and situation must meet eligibility criteria designed to protect the patient.

*or*

***“Compassionate use”***is a treatment option that allows the use of an unauthorized medicine. Under strict conditions, products in development can be made available to individual patients or groups of patients who have a disease with no satisfactory authorized therapies and who cannot enter clinical trials.

* **“*Group of patients*”** is interpreted as any set (i.e. more than one) of individual patients that would benefit from a treatment for a specific condition.
* **“*Chronically or seriously debilitating disease or disease considered as life-***

***threatening*”**: The severity of the disease, i.e., its chronically or seriously debilitating, or life-threatening nature needs to be justified, based on objective and quantifiable medical or epidemiologic data. Whereas a life-threatening condition is relatively easily recognizable, definitions of what conditions are chronic and seriously debilitating should consider aspects of the condition associated with morbidity that has substantial impact on patients’ day-to-day functioning and will progress if left untreated. Typical examples are cancer, HIV/AIDS, neuro-degenerative disorders and auto-immune diseases.

* ***“Emergency Use List”***refers to the World Health Organization, Emergency Use List which is a list of investigational medicinal products which have completed pre-clinical studies and have gone into clinical trials. These investigational products show a positive benefit/risk advantage over existing available therapy and may be suitable for compassionate use in the context of a pandemic or epidemic situation*.*
* ***“life- threatening”,*** in the definition above refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe. The event described as ‘life-threatening’, requires inpatient hospitalization or prolongation of existing hospitalization, or results in persistent or significant disability/incapacity.
* **“*Patients who cannot be treated satisfactorily*”**, means patients without treatment options or patients whose disease does not respond or relapses to available treatments, or for whom the available treatments are contraindicated or inadequate.
* ***“off-label use***” “means any use not authorized as part of the marketing authorization (e.g. unapproved indication or in an unapproved age group, dosage, or route of administration)”
* ***“orphan medicine”****,* is a medicine intended for the treatment, prevention or diagnosis of a disease that is life-threatening or chronically debilitating;
* the prevalence of the condition must not be more than 5 in 10,000 (at national level/in the country) or it must be unlikely that marketing of the medicine would generate sufficient returns to justify the investment needed for its development;
* no satisfactory method of diagnosis, prevention or treatment of the condition concerned can be authorized, or, if such an option exists, the orphan medicine offers significant and documented therapeutic advantage to those affected by the condition.

# 2.0 Acronyms

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| CTD  | Common technical document |
| CUA | Compassionate Use Application  |
| DOI  | Declaration of Interest |
| EUL  | Emergency Use Listing |
| GCP  | Good clinical practice |
| GLP  | Good laboratory practice |
| GMP  | Good manufacturing practices |
| QMS  | Quality Management Systems |
| ICH  | International Council for Harmonization of Technical Requirements  |
| IVDs  | In vitro diagnostics |
| NRA  | National regulatory authority |
| PHE  | Public Health Emergency |
| PHEIC  | PHEIC Public Health Emergency of International Concern |
| PSUR  | Periodic safety updated report |
| R&D  | Research and Development |
| TORs  | Terms of Reference |
| WHO | World Health Organization  |

# 3.0 Background

 In situations where no proven effective treatment exists, offering individual patients experimental interventions on an emergency basis outside clinical trials can be ethically appropriate. Similarly, to address a public health emergency, a provision for access to an experimental intervention is ethically appropriate in situations where no proven effective treatment exists.

Experimental intervention in the situations described could be therapeutic or prophylactic depending on the specific public health emergency. Generally, compassionate use for an individual patient is limited to therapeutic interventions.

Several countries have recognized the need to have guidance in place, in the interest of individual patients or cohorts of patients to address situations that do not fit neatly into the existing system of marketing authorization.

Where possible and feasible for a treatment to be given as part of a clinical trial, this should be explored as a preferred option. Safety data may be collected during compassionate use of a therapeutic intervention, however, this cannot replace clinical trials for investigational purposes, and compassionate use is not a substitute for properly conducted randomized trials. Compassionate use should therefore not hinder or delay the implementation or continuation of clinical trials intended to provide essential information on the benefit/risk of an IMP.

A common approach regarding the conditions of use, the conditions for distribution and the patients targeted for the compassionate use of unauthorized new medicines will be beneficial for countries within the same continent, as there are similarities in epidemiology and public health concerns, especially in a pandemic situation. Within the continent, epidemics threaten all countries.

# 4.0 Scope

The provisions of this guideline should only be applied if the investigational medicine or investigational therapeutic intervention is expected to help an individual patient or a group of patients with life-threatening, long-lasting or seriously debilitating illnesses, which cannot be treated satisfactorily with any currently authorized, available medicine.

The investigational medicinal product (IMP) must be undergoing clinical trials, or the un-registered novel product must have entered the marketing-authorization application process. Pre-clinical studies should have been completed; however the product’s full safety and efficacy profile in humans and dosage guidelines may not be fully established.

Compassionate use provisions are not appropriate for a medicinal product which has already been authorized elsewhere, even if the proposed conditions of use and target population are different from those of the existing market authorization. Thus compassionate use of an investigational or unregistered novel product is to be clearly distinguished from “off-label use” of an existing approved and marketed product. A critical difference is that in compassionate use, an investigational medicinal product is used in advance of marketing authorization, while for off-label use the product has an existing marketing authorization for different indication(s).

In this guidance, “compassionate use” applies to both individual named-patient treatment, and treatment of a group of patients.

In all instances:

* The individual patient or group of patients is/are unable to, not eligible to, or unwilling to participate in a clinical trial of the IMP. Participation in a trial should be the first option for the patient/patients, and attempts to bypass trials are to be discouraged. **Patient safety is likely to be better assured in trials than in compassionate use situations.**
* The potential benefit must justify the potential risk to the patient or patients.
* The sponsor /manufacturer must agree to provide the compassionate use access of the IMP or therapeutic product to the patient.
* Although the medicine requested under the compassionate use provision may be investigational, its use should be for the primary purpose of diagnosing, monitoring, or treating a patient’s or patients’ disease or condition. (Clinical trials are the appropriate route for generation of scientific data on the safety and efficacy of the IMP.)
* In all cases the applicant (usually the prescribing physician or an appropriate public health professional) will assume ultimate responsibility for the use and outcomes of the IMP/un-registered novel medicinal product.

Generally, compassionate use applications (CUA) will fall into one of two categories:

* Individual (or named) patient CUA, including for emergency use
* Group of patients CUA, including for emergency use

Examples of situations that might necessitate submission of a CUA for a group of patients are epidemics, local or regional public health emergencies, and a public health emergency of international concern (PHEIC). The AVAREF Strategy and Guidance for Emergency Preparedness[[1]](#footnote-2) contains recommendations for national regulatory authority (NRA) and ethics committee (EC) preparedness that apply, where relevant, to CUAs and emergency CUAs for groups of patients.

# 5.0 Eligibility Criteria for the IMP /un-registered Novel Medicinal Product

In order for an IMP or un-registered medicinal product to be eligible for consideration for compassionate use approval to address a declared epidemic/pandemic/ public health emergency of international concern, ideally, the product would be included in the WHO Emergency Use List (EUL).

Public health emergency situations may occur, where the WHO EUL may not include the IMP or where the CUA is for an individual patient. In these instances, the WHO EUL may not include the IMP, in which case the following eligibility criteria apply:

* The disease for which the product is intended is serious or immediately life threatening, has the potential of causing/ has caused an outbreak, epidemic or pandemic and there are no licensed products for the indication or for a critical subpopulation (e.g., children);
* Existing products have not been successful in eradicating/ treating the disease or preventing outbreaks (in the case of vaccines and medicines);
* The product is manufactured in compliance with current Good Manufacturing Practices (GMP) in the case of medicines and vaccines and under a functional Quality Management System (QMS) in the case of IVDs, and;
* The manufacturer/sponsor undertakes to complete the development of the product (validation and verification of the product in the case of IVDs) and apply for marketing authorization. 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.
* The approval for compassionate use expires when the pandemic ends or 12 months from issue date, whichever occurs first.

Countries may consider reviewing a candidate product for CUA that does not meet all of the requirements, based on specific risk-benefit assessment.

# 6.0 Application Procedure for Compassionate Use of Medicine for an Individual Patient

For an individual patient, the physician submits a letter of intent to the NRA together with the CUA (Appendix 1) which should contain the following information:

* Name, designation and contact details of applicant
* Evidence that the sponsor is in agreement with the use of the IMP as being applied for
* Name (INN, study code if applicable), dosage form, manufacturer details and country of origin of the IMP/un-registered novel product
* Quality, Safety and Efficacy information
* Quantity to be imported and dose and duration to be administered
* Estimated date of import
* Patient’s description, gender, and other relevant details
* Diagnosis of the condition
* Justification for the application
* Evidence that the patient is aware of and has agreed to use the IMP/ un-registered novel product
* The applicant/physician responsible for administering the therapy to the patient, commits to inform the NRA and EC of the outcome of therapy

• Any other relevant information

The NRA should confirm that the quality, safety and efficacy information available justifies the use of the IMP for the individual named patient.

The CUA should include information required for EC assessment. The physician should provide a detailed patient history and treatment plan, usually including the following:

•The proposed daily dose, route, and frequency of administration, duration of planned treatment, criteria for discontinuation of treatment, and planned monitoring for adverse events;

•The key details of the patients’ individual history, including diagnosis and summary of prior therapy (including response to such therapy), as well as information regarding the patient’s relevant clinical characteristics (such as comorbid conditions and concomitant medications) that are necessary to assess the potential for increased risks of the drug;

•A summary of known risks of the IMP/ un-registered novel medicine

•For pediatric patients, evidence of age-appropriate assent from the child, and written permission from the parent or guardian should be submitted.

**Some of the above points are “practice of medicine” issues and may not be fully answerable in detail. However,** **it should be clear that a careful benefit/risk assessment of all options has been made in recommending compassionate access. The information provided should justify why compassionate access to the IMP/medicine is the only appropriate route in the case.**

The EC should confirm that the primary purpose of the CUA is to diagnose, monitor, or treat a patient’s disease or condition, rather than to generate scientific information on the safety and efficacy.

In approving the use of the IMP or unregistered novel product for use by an individual patient, NRAs and ECs should clearly state in the approval letter the conditions and context of the permission in accordance with national laws. Conditions should include but are not limited to the following:

* The approval is for the use of the IMP/un-registered novel product within the context requested for and for the individual patient only.
* The outcome of the use is the responsibility of the physician making the request.
* The physician should submit a safety report on the use of the IMP/un-registered medicine to the NRA and EC.
* If an import permit is issued it should be specified that the permit is for a single import of the stated quantity only. The import permit validity should also be stated, for example valid for 6 months from date of issue. In general, a reassessment of the patient’s need should occur at least every 6 months.

For emergency Compassionate Use, the physician is required to notify the NRA about intent to import and should receive an emergency import permit within 24 hours, if required by national legislature and import control regulations. The emergency compassionate use import permit should state the necessary details of the patient and IMP or un-registered novel product.

The quantity that may be imported should be limited to a quantity that can safely (based on existing data) and reasonably be administered to the patient for the stated diagnosis, during a period of 6 months.

The outcome of the use of the product is under the direct responsibility of the physician, and all relevant national laws on clinical practice apply.

# 7.0 Application for Compassionate Use of Medicine for a Group of Patients

This provision would apply to a public health emergency or a public health emergency of international concern/pandemic. A public health emergency may arise suddenly or unexpectedly and require urgent responses to minimize devastation. Such emergency scenarios tend to be time limited. In dealing with a public health emergency, authorities must respond with agile and decisive measures.

The key difference between a CUA for and individual patient and a group of patients is the focus of the benefit-risk analysis. In general, the review of a group compassionate use application considers the “high-level” view of potential risks and benefits for a population/group of patients, while remaining mindful that all groups are made up of individual persons with specific needs.

For group CUAs, the applicant is usually the Minister for Health and not a practicing physician, therefore section A of the CUA form (Appendix 1), should include the name and details of the responsible physician. To facilitate NRA and EC assessment of group CUAs, additional information on quality, safety and efficacy will be necessary. The NRA and EC will need to agree on the information to be submitted by the applicant.

Necessary information may differ depending on several factors including the severity of the public health emergency, patient prognosis, rate of spread, potential efficacy and side effects of the IMP, and any other information which will collectively inform a risk-benefit assessment and decision.

For a group CUA, the applicant submits a letter of intent to the NRA together with the application form, which should contain the following information:

* Name, designation and contact details of applicant
* Evidence that the sponsor is in agreement with the use of the IMP as being applied for
* Name (INN, study code if applicable), dosage form, manufacturer details and country of origin of the IMP/Therapeutic intervention
* Quality, Safety and Efficacy information as agreed (during NRA and EC consultations)
* Quantity to be imported, dose to be administered and duration
* Estimated date of import
* Cohort of patients description, number, gender distribution, and other relevant details
* Diagnosis of the condition, with due consideration of the range of disease (mild to severe)
* Justification for the application appropriate to the spectrum of use envisioned.
* Evidence that the patients are aware of and have agreed to use the IMP
* The applicant/physician responsible for administering the therapy to the patients, commits to inform the NRA and EC of the outcome of therapy

• Any other relevant information

The NRA should confirm that the quality, safety and efficacy information available justifies the use of the IMP for the group of patients.

The application for compassionate use should include information required for EC assessment. The applicant should provide the following:

•The proposed daily dose, route, and frequency of administration, duration of planned treatment, criteria for discontinuation of treatment, and planned monitoring for adverse events;

•The key details of the patients’ collective histories, including diagnosis and summary of prior therapy (including response to such therapy), as well as information regarding the distribution of patients’ relevant clinical characteristics (such as comorbid conditions and concomitant medications) that are necessary to assess the potential for increased risks of the group during therapy;

•A summary of known risks of the IMP/ un-registered novel product

•For pediatric patients, evidence of age-appropriate assent from the child, and written permission from the parents or guardians should be submitted.

**It should be clear that a careful benefit/risk assessment of all options has been made in recommending compassionate access for the group. The information provided should justify why compassionate access to the IMP/un-registered novel medicine for the patient group is the only appropriate route in the current public health scenario.**

The EC should confirm that the primary purpose of the group CUA is to diagnose, monitor, or treat the patients’ disease or condition, rather than to generate scientific information on the safety and efficacy.

In approving the use of the IMP/ unregistered medicinal product for use by a group of patients, NRAs and ECs should clearly state in the approval letter the conditions and context of the permission in accordance with national laws. Conditions should include but are not limited to the following:

* The approval is for the use of the IMP/un-registered novel product within the context requested for and for the described group of patients only, unless otherwise justified.
* The outcome of the use is the responsibility of the physician or public health official responsible for and supervising the use of the IMP.
* The physician or public health official should submit a safety report on the use of the IMP/un-registered novel product to the NRA and EC.
* If an import permit is issued it should be specified that the permit is for a single import of the stated quantity only, unless otherwise justified. The import permit validity should also be stated, valid for 6 months from date of issue.

For emergency group of patients CUAs, the applicant is required to notify the NRA about the intent to import. An emergency import permit should be provided by the relevant agency within 24 hours, if required by national legislature and import control regulations. The emergency compassionate use import permit should be specific for the group of patients and IMP or un-registered medicinal product.

The quantity that may be imported should be limited to a quantity that can be safely and reasonably administered for the desired duration to the group of patients to achieve therapeutic or prophylactic goals, taking into account the known safety profile of the IMP. Additional quantities beyond this may be justified as time progresses. In general, a reassessment of the clinical scenario should occur at least every 6 months.

The outcome of the use of the product for the group of patients is under the direct responsibility of the applicant (Minister for Health) and responsible physician. All relevant national public health laws apply.

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# 8.0 Plans for Compassionate Use Application Processing by NRAs and ECs

NRAs and ECs should have appropriate plans and policies in place, for regulatory and ethics review to address CUAs for individual patients and groups of patients in non-emergency and emergency situations. Review during public health emergencies may follow modified procedures and practices specifically designed for such situations.

Through their plans, NRAs and ECsneed to anticipate the pressures, time constraints, priorities and logistical challenges that may arise to ensure quality, timely, proportionate and appropriate regulatory and ethics review. The plan should be piloted in advance of an actual emergency.

A regulatory outcome of an approval or denial, in response to a group CUA should take no more than 24 hours during public health emergencies.

# 9.0 Marketing Authorization Options for Compassionate Use in Public Health Emergencies

In the interest of public health, applicants may be granted a conditional marketing authorization for such an IMP /un-registered novel product or un-registered therapeutic intervention, where the benefit of immediate availability outweighs the risk of less comprehensive data than normally required, based on the scope and criteria defined in this guideline and in accordance with local laws. In all cases, however, the manufacturer is obliged to conduct all required studies to inform the safety (and potentially efficacy) of the product.

For products intended for use in emergency situations, less comprehensive pharmaceutical and non-clinical data may also be acceptable if a positive benefit –risk assessment exists. A conditional marketing authorization may be granted for an IMP/ un-registered novel medicinal product or unregistered therapeutic intervention if the responsible authority /NRA finds that all the following requirements are met:

* the benefit-risk balance of the product is positive;
* it is likely that the applicant will be able to provide additional comprehensive data;
* unmet medical needs will be fulfilled;
* the benefit to public health of the medicinal product's immediate availability on the market outweighs the risks due to incomplete data.

The conditional marketing authorization should be valid for a limited time-period (12 months), with an option for a single renewal. Further renewal is at the discretion of the responsible authority. The NRA will assess the application and determine the conditions of issuance of the conditional marketing authorization aimed at providing further comprehensive data confirming that the benefit-risk balance is positive. The applicant is required to satisfy the requirements of the conditional approval, which are usually requirements of comprehensive data and other specific obligations.

Once comprehensive data on the product has been obtained, and specific obligations satisfied, the marketing authorization may be changed to a standard marketing authorization. The validity of the marketing authorization will depend on national laws and regulations.

# 10.0 Fees for Compassionate Use

Each country should charge the relevant fees according to their government approved fees schedule. Some countries may decide that there should be no fees payable for processing of CUAs.

Where the procedure is to benefit an individual named patient- the recommendation is that the minimum possible administrative fee is charged so as not to burden the patient or health system. Where the procedure is applied within the context of a group of patients’ application or to address a public health emergency, any fees charged should be deductible from the fees payable for an application for marketing authorization for the same medicinal product, submitted by the same applicant.

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1. <https://www.afro.who.int/publications/african-vaccine-regulatory-forum-avaref-strategy-and-guidance-emergency-preparedness> [↑](#footnote-ref-2)