Dossier and data requirements for an application for participation in the pilot of the Quality Assurance Mechanism for Modified Mosquito Production

Parent Document

This parent document has been developed to support the pilot of the proposed procedures presented in the document "Procedures for the Pilot of the WHO programme for Quality Assurance of Modified Mosquito Production."

This document identifies the data requirements and technical considerations which are applicable to the submission of an application within the context of the pilot of Quality Assurance Mechanism for Modified Mosquito Production (QAM).

It will be supported by implementation guidance documents which provide further technical considerations and guidance for data generation as well as provide forms/templates for the compilation of the dossier.

This document is being published the purpose of the public comment period open from 28 August 2026 to 30 October 2026.

The WHO pilot of this programme and should not be considered as WHO recommendations to Member States or other interested parties.

PARENT DOCUMENT

1. Introduction

In recent years there have been significant advancements in the field of mosquito modification aimed to prevent or interrupt the transmission of mosquito-borne diseases. A variety of intentional modifications have been developed resulting in such examples as mosquitoes which carry a bacterial infection, sterilized mosquitoes, and those mosquitoes which carry alterations of their genetic code.

Considering the spectrum of potential products, some of which may require continuous/seasonal releases to those which could result in complete population replacement or eradication from a single release, there is an inherent need for WHO to consider an approach that would enable assessment of the quality of products in advance of establishment of the potential epidemiological impact. Member states will look to WHO for guidance well in advance of epidemiological data and full WHO recommendations becoming available.

2. Purpose of this document

The purpose of this document is to present the identified data requirements and technical considerations which would be applicable in implementing a quality assurance mechanism for modified mosquitoes. This document is supported by **implementation guidance** documents which provide information and considerations for ***how*** applicants would approach the generation of supporting information.

This document should only be referred to within the context of the "Procedures for the Pilot of the WHO programme for Quality Assurance of Modified Mosquito Production." These procedures establish the pilot programme for the WHO Quality Assurance Mechanism for Modified Mosquito Production (QAM).

> The purpose of the QAM is to independently establish that:
>
> - the product is clearly defined, including all potential presentations/packaging configurations
> - the manufacturing process is clearly defined, and the product can be consistently produced, conforming with the product specific relevant specifications
> - the integrated modification can be identified and measured with validated methods in the finished product, and post-deployment as applicable
> - the finished product is supported by data demonstrating the entomological capability for performance

The entirety of the information within this document has been developed within the guiding principles and framework for the activities of WHO Special Prequalification Programmes (PQT/SPP).

The document is intended to:

- Describe the requirements for an assessment of quality of modified mosquito products within the context of a quality assurance mechanism;

- Describe approaches for consistent and reliable data generation for inclusion in submissions;
- Allow for flexibility to incorporate the future evolution of product designs/types, methods and analysis as well as deviations from standardized guidance when justified

The proposal is not intended to:

- Convey any impression that WHO has determined that it will implement such a programme nor recommend the implementation of such a programme to member states
- Be a guide for academic research
- Be a literature review of modified mosquito products and related methodology
- Establish best practices and recommendations for the use of modified mosquito products
- Address potential local, national or regional biosafety requirements applicable to either the research or generation of data for modified mosquitoes
- Provide guidance for use of unsubstantiated, unproven, and unvalidated information or methods
- Provide guidance on requirements or processes for the development of WHO recommendations through the technical units responsible for vector-borne disease guidelines.

3. Characteristics of modified mosquito products

A modified mosquito is a mosquito (regardless of life stage) that has undergone intentional alteration to change an intrinsic characteristic of the organism, e.g. fertility status, bacterial infection or genetic modification.

In the context of public health pesticides, the term **modified mosquito product (MMP)** refers to a class of products that are designed to mitigate or reduce a target vector population through the introduction of mosquitoes that have been intentionally altered to carry specific characteristics. MMPs may encompass a variety of:

- modifications, e.g. *Wolbachia spp.* infection, intentional genetic alterations, sterilization through irradiation, etc.
- life stages of mosquitoes, e.g. eggs, larvae, pupae or adult
- designs and formulations including “packaging”
- release strategies, for example, continuous, periodic or one-off
- intended impacts, for example, population replacement or population suppression.

Accordingly, other documents may refer to modified mosquitoes using the specific terminology related to the modification, e.g. genetically-modified mosquitoes.

The information presented in this document is primarily considered within the context of the use of modified mosquitoes as interventions for malaria and dengue. However, many of the concepts, principles, and requirements can be relied upon with minimal augmentation for consideration in the use of modified mosquitoes as interventions for other vector borne diseases.

3.1. Intended approaches for impact of modified mosquito products

3.1.1. *Mosquito Population replacement*

The intent of population replacement is to release mosquitoes (regardless of life stage) to modify wild vector populations in a self-perpetuating manner which reduces the transmission of disease by mitigating the mosquito and/or life cycle of the vector-borne pathogen. Examples of modified mosquitoes that may be used in population replacement strategies are *Wolbachia spp*.-infected female mosquitoes for introgression into the wild population, and gene drive mosquitoes carrying effectors which prevent the pathogen from developing/being transmitted.

Population replacement may also be referred to as population modification/alteration/conversion [2].

3.1.2. *Mosquito Population suppression*

The intent of population suppression is to release mosquitoes (regardless of life stage) to suppress (or even eliminate) the wild population, i.e., to decrease the vector density and, in doing so, limit the transmission of vector borne diseases through reductions in human-vector interactions. Examples of modified mosquitoes that may be used in population suppression strategies are *Wolbachia spp*.-infected male mosquitoes, sterile insect technique and self-limiting genetic modification.

Population suppression may also be referred to as population reduction [2].

3.2. Defining the modified mosquito product

An MMP is defined by the manufacturer based on the declared form/life stage of the mosquito, the deployment methods, the inputs/rearing processes which contribute to its production, and the characteristics which enable the intended performance of the MMP.

3.3. Rearing, manufacture, packaging, and release of modified mosquito products

For the quality assurance mechanism, the manufacturing process includes the receipt of raw and/or formulated materials and ends with the release of the product(s) to a third party.

The legal manufacturer of the MMP is responsible for all aspects of the manufacturing process. The manufacturing process may be implemented in whole by the legal manufacturer, by toll manufacturer(s), or a combination.

3.4. Deployment

The deployment of modified mosquitoes, including the size and periodicity of releases, heavily depends upon the intent of the product (e.g. suppression vs**.** replacement) and environmental, vector population, temporal and sociological factors. In most cases, the deployment of modified mosquitoes is expected to take place in coordination and cooperation with national and local partners which may include official government programmes and third-party implementers. In each situation, the release scheme is expected to be tailored to the necessary requirements of the intent and situation in which the modified mosquitoes are to be deployed. The applicant is responsible for documenting the key factors which need to be considered for operational deployment.

4. Indicators of modified mosquito capability of performance

In the context of the QAM pilot, the product performance is demonstrated by the declared product's capability to impart the intended effect of the modification. This is referred to as the capability for performance. This should be demonstrated within a contained free-flight or release study setting which includes deployment of the product in its intended final form. Performance should be substantiated using the final product.

5. Quality assurance of modified mosquito products

The application and assessment of a dossier complied based on this document will follow the process, terms and conditions presented in the document "Procedures for the Pilot of the WHO programme for Quality Assurance of Modified Mosquito Production."

The assessment of applications submitted within the pilot QAM relies on the following criteria:

- Quality – Assess product definition and formulation, rearing/manufacturing process and critical characteristics of the product that can be tested, e.g. infection prevalence, transfer of genetic material from adults to eggs, heritability of characteristics, e.g. modified genetic material
    - Appropriate, validated methods to identify and/or quantify critical characteristics must be developed.
    - A quality management system must be established to control the manufacturing process from the receipt of raw and/or formulated materials through to the release of the product(s) to a third party.
- Capability for performance – Assess information substantiating the capability for performance of the MMP on the target vector population(s) in conditions/settings applicable to the intended use of the product, including characterisation of the samples used in various performance studies according to the declared critical characteristics.

The QAM pilot will also include the inspection of the declared manufacturing site(s).

6. Dossier format and purpose of each module

6.1. Administrative Module

- **Statement of intent**
  - The intent of the Administrative Module is for manufacturers to provide information which demonstrates:
    - Establishment of the responsible company as the legal manufacturer/owner of the proposed product;
    - Identification of authorized contacts;
    - Formal request for assessment;
    - Table of contents of all documents included within the application;
    - Applicable label content to support the assessment of the product.
- **Description of requirements**
  - Cover letter
  - Application form
  - Table of contents
  - Declaration of labelling/operational manual

6.2. Quality Module

6.2.1. *Product definition and manufacturing*

- **Statement of intent**
  - The intent of the Quality Module is for manufacturers to provide information and data which demonstrate:
    - the definition of the product that is being commercialised to ensure:
      - clarity on the intended life stage of release, e.g. eggs or adult mosquitoes
      - definition of those identifying or critical characteristics which can be tested, e.g.
        - infection prevalence of *Wolbachia spp*. infection
        - reliability of transfer of genetic material through mosquito generations
        - modified mosquito fitness, e.g. fecundity, longevity, hatch rate
      - appropriate methods for testing critical characteristics are, developed, validated, and in place
    - the "formulation" or inputs required to produce the product which may include water characteristics, nutrients/feeds, packaging materials and their sources.

- the manufacturing details of the modified mosquito product and the consistency of the production process
    - manufacturing details include rearing processes in addition to product production process, e.g. encapsulation of mosquito eggs and larval diet into the final product formulation
    - applicants must establish a quality management system to control the rearing of the defined product
- stability of the modified mosquito product formulation during storage and transport

- **Description of data requirements**
    - Product summary – description of the product, components/equipment for deployment, intended use pattern/deployment strategy and justification for the claim of duration of impact (as applicable)
    - Multi-batch/production study which demonstrates the defining entomological characteristics and the presence of the modification to characterize the potential variability for those defining characteristics (including those present in the manufacturing release specifications)
    - Identifying information about product samples used in testing – includes batch/partition IDs, formulation codes and manufacturing process for all product samples used in data generation and the corresponding studies.
    - The complete product composition and purpose of all formulants/inputs required for the rearing and packaging of the finished product
    - The complete product manufacturing details including:
        - Declaration of manufacturing Sites (DMS)
        - Control of starting materials
        - Batch delineation and formula (or other form of production division/identification)
        - Description and control of manufacturing Process (DMP)
            - Note: A key difference between the manufacturing details in the Quality Module and the information required in Sites Master Files for the Inspection Module is that the description of manufacturing process defines all equipment, settings/ranges, speeds, temperatures which must be followed in order to produce the product as intended. The QMS, as presented in the SMF, is the system by which a manufacturer ensures that the declared process is followed.
    - Declaration of product sampling - defined sampling procedures from individual products and batches as relevant to the definition of the product and final packaging/presentation for the purposes of critical and physical characteristics analysis.

- The physical characteristics of any packaging/presentation components, e.g., capsules, containers for holding adult mosquitoes, in the finished product
- Storage and transport stability – critical characteristics data generated on product samples having been subjected to real-time storage and transport
- Manufacturing release specification, including methods and notes
- Other related information as determined necessary based on the characteristics and design of the product.

6.2.2. *Capability for Performance*

- **Statement of intent**

  - The intent of the Capability for Performance requirement is for manufacturers to provide information and data which demonstrate the product's capability to impart the intended action of the modification, thereby indicating the potential of the product to produce the intended entomological effect within the target vector population, for example,
    - Population replacement strategies: the ability of the product to achieve a defined lower threshold of introgression within the target vector population in multiple contexts, for example, urban/suburban/rural, environmental/climate.
    - Population suppression: the ability of the product to achieve a defined lower threshold of reduction in the density of the target vector population in multiple contexts, for example, urban/suburban/rural, environmental/climate.
  - Care is required in sampling strategies to ensure:
    - that the impact and spread of the product/modification is accurately quantified
    - the biological and manufacturing consistency of the product used in such studies, e.g. compliance with the manufacturing release specification.

- **Description of Data Requirements**

  - Contained outdoor free-flight studies
    - Must be designed to allow for normal interaction of the modified mosquito with target vector population (colonised or otherwise), and to collect data on the endpoints relevant to the demonstration of the capability of the MMP, e.g. rate of introgression and time to reach specified lower threshold;
    - Are conducted in closed system contained outdoor facilities. Contained outdoor facilities are considered to generate data that are closest to what may occur when a modified mosquito product is deployed, whilst still maintaining controlled conditions.

  or,

- Release studies
  - Must be designed to allow for release of the product under routine conditions, with interim time points to demonstrate the endpoints relevant to the demonstration of the capability of the MMP, e.g. percentage introgression into wild population.
- The batches of all product samples used in contained free-flight or release studies must be fully characterized and demonstrate compliance with the declared manufacturing release specification.
- Further information to include in the assessment of the product and its potential performance in various settings.

6.3. Inspection Module

- **Statement of intent**
  - The intent of the Inspection Module for modified mosquito products is for manufacturers to provide information which demonstrates:
    - The existence and implementation of an appropriate quality management system, for example, Good Manufacturing Practices (GMP), ISO 9001 or equivalent

- **Description of Data Requirements**
  - SMFs must be submitted for all manufacturing sites identified in the Declaration of Manufacturing Sites form.

7. Importance of tolerance set for manufacturing release specifications and critical criteria for mosquito fitness

Ideally, all data generated for inclusion in the dossier should rely on the final product formulation and optimized manufacturing process, as compared to product prototypes or versions for research. If data are generated on prototype formulations, a scientific rationale for inclusion of these data in support of the final product is necessary.

In order to assess the capability for performance, complete information on the batches used in data generation must be submitted.

A baseline understanding for controlling and assessing the quality of future production batches is established through the correlation of physical and entomological characteristics and the analysis of intra- and inter-batch variability of the batches used in the testing.

8. Requirement for generation of data in compliance with GLP

All studies submitted to address dossier requirements must be conducted in compliance with GLP, or equivalent standard, where applicable. Studies conducted outside of GLP may be submitted; these will be considered as supplementary evidence in support of the submitted GLP studies.