Clarification on the Process for Introducing a Supplier of Non-plant-derived-artemisinin

1. BACKGROUND

Artemisinin is the key chemical compound used in the preparation of several important active pharmaceutical ingredients(APIs) exhibiting anti-malarial properties, including artemether and artesunate.

Artemisinin is traditionally obtained by extraction from the plant *Artemisia annua*, also known as sweet wormwood plant, or "quinghao". However, recent synthetic biology developments now offer the possibility of obtaining artemisinin by semi-synthetic means.

The challenge presented by non-plant-derived-artemisinin is to ensure that such material is comparable to plant-derived-artemisinin. Primarily, this means ensuring that non-plant-derived-artemisinin contains neither new impurities (including undesired diastereomers), nor existing impurities at levels that might compromise the quality of resulting APIs. Secondly, ensuring that non-plant-derived-artemisinin is produced in a manufacturing environment that adheres to good manufacturing practice since its synthesis is dependent on an artificial rather than a natural process.

Since in many cases information pertaining to the preparation of non-plant-derived-artemisinin is includes protected information, and to ensure the regulatory burden on API manufacturers wishing to use this material is minimized, the following procedure has been introduced.

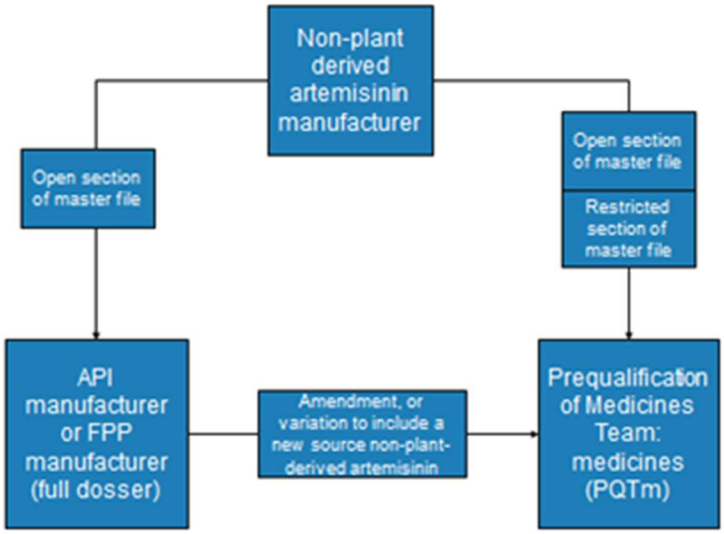
2. PROCEDURE OVERVIEW

Manufacturers of non-plant-derived-artemisinin are invited to submit a stand-alone master file (open and restricted parts) for their material to WHO. This master file should outline artemisinin's manufacture from simpler molecules; how the quality of the material is controlled; and the stability of the material upon storage. Such manufacturers should maintain the accuracy of this information as per standard API master file (APIMF) amendment procedures.

Manufacturers wishing to use this artemisinin may request that WHO refer to the confidential sections of the master file (with the permission of the artemisinin supplier) and only need include within their regulatory documents limited details regarding this material.

Manufacturers will be exempted from submitting amendments or variations for changes to the preparation and control of non-plant-derived artemisinin with the following exception: changes to the manufacturing site of artemisinin; changes to the specifications for the control of artemisinin, or major changes to its preparation.

Figure 1 **Overview of the procedure to register a source of non-plant-derived-artemisinin**



3. RESPONSIBILITIES

The holder of the master file for non-plant-derived-artemisinin (typically the manufacturer), will be responsible for:

a. submitting a master file outlining the preparation, control and stability of non-plant-derived-artemisinin.

b. maintaining the on-going accuracy of this information as per standard APIMF amendment procedures.

c. providing to the API manufacturer or finished pharmaceutical product (FPP) manufacturer[1] a letter of access permitting WHO to refer to the held master file.

d. providing to the API manufacturers or FPP manufacturers an open part of the master file that contains:

- information on the sites of manufacture
- sufficient information on the preparation, control and stability of non-plant-derived-artemisinin commencing from simpler molecules, to allow the API manufacturer to determine and justify its their control of this material.

e. providing on-going updates to the API manufacturer regarding any major changes to the manufacturing process of non-plant-derived artemisinin or sites of manufacture, or changes that may affect the specifications of non-plant-derived-artemisinin.

API manufacturers or FPP manufacturers[2] will be responsible for:

[1] In the case of an FPP prequalified using API information submitted through the "full dossier" these responsibilities are undertaken by the FPP manufacturer.
[2] In the case of an FPP prequalified using API information submitted through the "full dossier" these actions are undertaken by the FPP manufacturer.

a. submitting an APIMF amendment or FPP variation to introduce the supplier of non-plant-derived-artemisinin, together with the specified supporting information.

b. providing amendments or FPP variations relating to non-plant-derived-artemisinin when any changes are made to sites of manufacture or specifications or when major changes are made to its preparation.

c. revising their regulatory documentation to include the new supplier.

Despite being considered in principle an API intermediate, it is suggested that information on this substance be included in the CTD document[3] section 3.2.S.2.3 (and applicable annexes), as expected for the inclusion of an additional API starting material supplier. The suggestion that this information be included in section 3.2.S.2.3 rather than in section 3.2.S.2.4 is made in recognition of the advantages of maintaining information on all sources of artemisinin in one place within the regulatory dossier.

4. PROCESS FOR REGISTERING A SOURCE OF NON-PLANT-DERIVED-ARTEMISININ

API manufacturer or FPP manufacturers wishing to introduce a source of non-plant-derived-artemisinin should use one of the following procedures. They should submit either:

- An APIMF amendment, if the resulting API is participating in the API Prequalification procedure or APIMF procedure, or
- An FPP variation if the API source was accepted through the full dossier route at the time of FPP prequalification.

[3] www.ich.org/products/ctd.html