



## QUALITY REQUIREMENTS FOR ARTEMISININ AS A STARTING MATERIAL IN THE PRODUCTION OF ANTIMALARIAL ACTIVE PHARMACEUTICAL INGREDIENTS (APIs)

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SCHEDULE FOR THE PROPOSED ADOPTION PROCESS OF DOCUMENT QAS/10.349:  
*GUIDELINE FOR ARTEMISININ AS A STARTING MATERIAL IN THE PRODUCTION OF  
ANTIMALARIAL ACTIVE PHARMACEUTICAL INGREDIENTS (APIs)*

Drafting of guideline by group as indicated in Background	January-February 2010
Circulation of document for comments	March-April 2010
Consolidation of comments + Review in informal consultations on: Paediatrics and Generic Guideline Development; and Specifications for Medicines and Quality Control Laboratories	29-30 April 2010 + 10-12 May 2010
Circulation of revised draft for comments, based on additional review of the comments and additional information during a teleconference call composed of a subgroup of experts from the above two meetings	August 2010
Presentation to the forty-fifth WHO Expert Committee on Specifications for Pharmaceutical Preparations	18-22 October 2010
Any further action as required	...

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### BACKGROUND

On various occasions, including workshops organized by WHO and the Medicines for Malaria Venture (MMV), issues relating to the quality control specifications applicable to active substances used not only per se but also as starting materials for their active substances have been discussed. The main challenges identified were that often when used as "starting materials" for derivatives these substances were treated by some national authorities with the same control procedures as if used directly for manufacturing of finished pharmaceutical products (FPPs).

In order to better define these cases the attached text is newly suggested. It was prepared by a small group consisting of: Dr R.W. Stringham, Scientific Director, Drug Access Team, Clinton Health Access Initiative; Ms V. Faillat-Proux, Regulatory Affairs, Access to Medicines, Sanofi-Aventis; Mr I. Bathurst, MMV; in consultation with Dr A.J. van Zyl, Head of Inspections, WHO Prequalification of Medicines Programme.

Comments are welcome on the need for such a guidance text in general, and on the text itself.

## 1. INTRODUCTION

The harmonized good manufacturing practices (GMP) (1) describe requirements for the production of active pharmaceutical ingredients (API). The applicability of these requirements begins with a defined starting material as follows:

“An API starting material is a raw material, intermediate, or an API that is used in the production and that is incorporated as a significant structural fragment into the structure of the API. An API starting material can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement, or produced in-house. API starting materials normally have defined chemical properties and structure.”

The focus of the GMP for APIs is for field inspector use, rather than marketing authorization application (MAA) or new drug application (NDA) review. It defines what may be considered as a starting material and provides guidance on where GMP is applied. The GMP guidelines do not apply to steps prior to the first introduction of the defined starting material. The manufacturer should designate and document the rationale for the point at which production of the API begins. For synthetic process this is known as the point at which the starting materials are entered into processes.

In some national and regional guidelines such as, e.g. the EU guideline on chemistry of new active substance (2) the application of the Directive 2001/83/EEC is addressed with a view to the granting of a marketing authorization (MA) for a new medicinal product. The use of active substance starting materials marks the beginning of the detailed description of the process. The applicant should propose and justify which substance should be considered as the active substance starting material, e.g. incorporated as a significant structural fragment into the structure of the active substance.

In practice the designation of a starting material may be difficult. Generally, at least two synthetic steps are required between the starting material and the API. Since a designated starting material may be obtained from multiple sources it is necessary to have well-defined quality requirements to ensure that produced APIs meet specifications. Establishing these requirements may involve a compromise between a desire for a pure starting material and the impact of this on cost of API production. If impurities present in the starting material do not yield corresponding impurities in the subsequent API their removal at the starting material stage may needlessly add to the cost of API. However, they may impact the yield and consequently the costs.

Artemisinin derivatives used in artemisinin-based combination therapy (ACT) are synthesized from artemisinin in one or two synthetic steps. Artemisinin is typically produced as an isolate from *Artemisia annua* L. Artemisinin complies with the definition of a "starting material", as defined above and described in certain national, regional and international guidelines :

- (a) it is a material used in the production of the active substance that is incorporated into the API as a significant structural element;
- (b) it is commercially available;
- (c) it is a compound whose name, chemical structure, chemical and physical characteristics, properties and impurity profile are well defined; and
- (d) it is obtained by commonly known procedures.

Moreover, prior intermediates are thus not available, making artemisinin the logical designation as a starting material for these derivatives.

In addition, the quality level for a starting material may be debated especially when the considered substance may be used as an API or as a starting material.

There currently exists an *International Pharmacopoeia* monograph for artemisinin used as an API. This usage has largely given way to more bioavailable derivatives. The existence of the artemisinin API monograph may lead to confusion regarding quality requirements for artemisinin used as a starting material.

The artemisinin level of quality should be acceptable for its intended use as starting material for the production of artemisinin derivatives. The specifications presented below take into account an acceptable benefit vs risk between the level of quality for artemisinin as a starting material and the required quality for artemisinin derivatives as API.

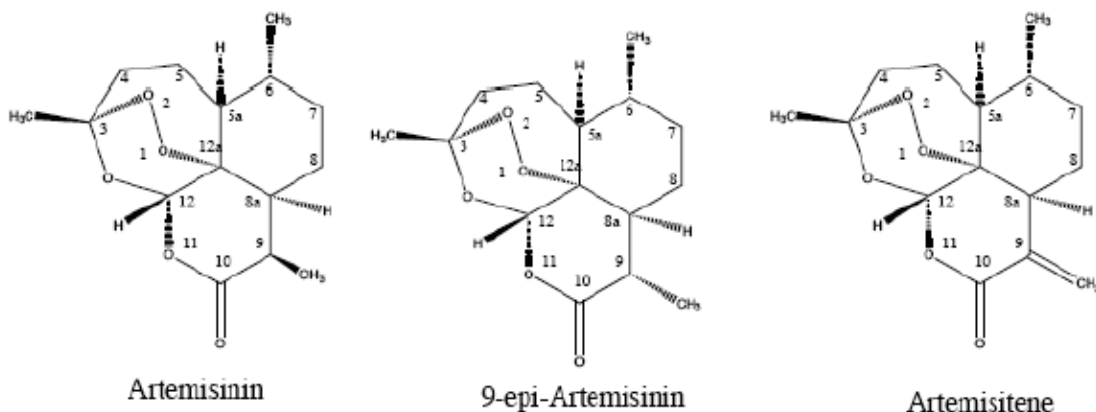
The purpose of this document is to offer a global approach to defining the level of quality of artemisinin when used as a starting material for the production of its API derivatives used in ACT formulations. It does not apply to cases where artemisinin is used as an API. It is intended that the requirements outlined in this document will apply to artemisinin regardless of variations in agricultural considerations or variations in extraction and purification steps. In the eventuality that artemisinin is produced via synthetic chemical approaches these requirements shall still apply.

## 2. CHARACTERIZATION OF ARTEMISININ

Provided that artemisinin intended for use as a starting material has been correctly identified, that major quality concern is the presence and level of impurities with the potential to impact the purity of subsequent API derivatives. Impurities may carry forward from the plant extracts or from synthetic process, or arise from the purification process or from degradation. Recent work (3,4) has contributed a clearer understanding of existing impurities and their analysis.

Different biosynthetic routes may be used at different stages in the plant's development and there are claims of variability between growing regions and environments. Despite a lack of consensus on a single biosynthetic route several potential impurities are common to different routes. These include artemisinic acid, dihydroartemisinic acid, arteannuin B and artemisitene. Of these only artemisitene has been reported in isolated artemisinin.

Examination of a wide variety of artemisinin samples produced in various regions indicated a consistent presence of two impurities. The major impurity is an artemisinin diastereomer with the stereochemistry inverted at C-9. The minor impurity is artemisitene. Observed levels of 9-epi-artemisinin range between 1 and 3% while artemisitene is generally observed below 1% relative to artemisinin. Isolated artemisinin is very stable. Potential degradants proposed based on mechanistic studies do not occur below 100°C. These degradants are not observed in isolated artemisinin.



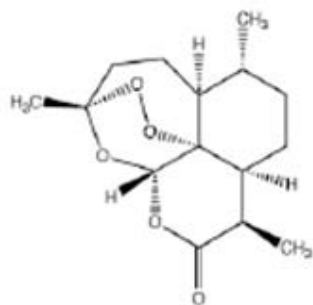
In the chemical conversion of the artemisinin starting material to its API derivatives (e.g. artesunate), the artemisinin diastereomeric impurity will be converted to a corresponding diastereomers at the C-9 position in the API. These resulting diastereomers are not observed in isolated API as they are removed in the crystallization step. The fate of artemisitene is less clear as it may be converted to the same intermediate as artemisinin.

Artemisitene-derived impurities have not been observed in artemisinin derivative APIs. Proposed limits for these impurities are based on historical results. Filings for new artemisinin derivatives should address the fate of these impurities.

These specifications are based on experience with artemether and artesunate. New artemisinin derivate APIs will need to demonstrate the suitability of these specifications for the artemisinin intended use as starting material for their specific synthesis process.

**[Note from the Secretariat: Additional information is being sought on the identification and occurrence of the impurities.]**

### 3. TESTS AND SPECIFICATIONS FOR ARTEMISININ STARTING MATERIAL



$C_{15}H_{22}O_5$

**Relative molecular mass.** 282.3

**Chemical name.** (3*R*,5*aS*,6*R*,8*aS*,9*R*,12*S*,12*aR*)-Octahydro-3,6,9-trimethyl-3,12-epoxy-12*H*-pyrano[4.3-*j*]-1,2-benzodioxepin-10(3*H*)-one; CAS Reg. No. 63968-64-9.

**Description.** Colourless needles or a white to almost white, crystalline powder.

**Category.** Starting material for the synthesis of artemisinin derivative APIs.

## Requirements

Artemisinin contains not less than 95.0% and not more than the equivalent of 102.0% of  $C_{15}H_{22}O_5$  calculated with reference to the dried substance.

## Identity tests

Carry out the examination as described under [1.7 Spectrophotometry in the infrared region](#) of *The International Pharmacopoeia*. The infrared absorption spectrum is concordant with the spectrum obtained from artemisinin RS or with the *reference spectrum* of artemisinin.

**Heavy metals.** Less than 10 ppm.

**Loss on drying.** Dry to constant mass at 80°C; it loses not more than 5.0 mg/g.

## Related substances

Carry out the test as described under 1.14.4 High performance liquid chromatography of *The International Pharmacopoeia*, using the chromatographic conditions and preparing the solutions as described under Assay.

Inject separately 20 µl of solutions (1) and (3). Record the chromatograms for about 1.5 times the retention time of artemisinin.

The impurity peaks are eluted at the following relative retention times with reference to artemisinin (retention time about 5 to 7 min): impurity A about 0.75, impurity B about 0.85.

In the chromatogram obtained with solution (1):

- the area of any peak corresponding to impurity A is not greater than 3 times the area of the peak in the chromatogram obtained with solution (3) (3.0%);
- the area of any other peak, apart from the principal peak, is not greater than 0.5 times the area of the peak in the chromatogram obtained with solution (3) (0.5%); and
- the sum of the areas of all the peaks, apart from the principal peak, is not greater than 5 times the area of the peak obtained with solution (3) (5.0%). Disregard any peak with an area less than 0.1 times the area of the principal peak obtained with solution (3) (0.1%).

## Assay

Carry out the test as described under [1.14.4 High performance liquid chromatography](#) of *The International Pharmacopoeia*, using a stainless steel column (15 cm × 4.6 mm) packed with 5 µM particles of silica gel, the surface of which has been modified with chemically-bonded octadecylsilyl groups. The mobile phase consists of a 50:50 mixture of acetonitrile and water, pumped at a flow rate of 1.0 mL/minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 210 nm.

Prepare the following solutions.

For solution (1) prepare a 5.0 mg/ml solution of the test substance in the mobile phase.

For solution (2) prepare a 5.0 mg/ml solution of artemisinin RS in the mobile phase.

For solution (3) dilute 1 ml of solution (2) to 100 ml with the mobile phase.

Inject separately 20 µl of solutions (1) and (2). Record the chromatograms for about 1.5 times the retention time of artemisinin.

Measure the areas of the peak responses obtained in the chromatograms from solutions (1) and (2), and calculate the content of C<sub>15</sub>H<sub>22</sub>O<sub>5</sub> with reference to the dried substance.

### Impurities

A. 9-epi-artemisinin

B. artemisitene

The identification of the impurities is tentative and based on a publication of Stringham et al. (Journal of Chromatography A, 1216 (2009), 8918-8925). Further investigations into the chemical structures have to be made.

## 4. REFERENCES

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6. The International Pharmacopoeia, fourth edition.  
Volume 1: general notices; monographs for pharmaceutical substances (A–O)  
Volume 2: monographs for pharmaceutical substances (P–Z); monographs for dosage forms and radiopharmaceutical preparations; methods of analysis; reagents, 2006, also

available in CD-ROM format and online

First supplement: general notices; monographs for pharmaceutical substances;  
monographs for dosage forms; general and specific monographs; methods of analysis;  
International Chemical Reference Substances; International Infrared Reference Spectra;  
reagents, test solutions and volumetric solutions (<http://apps.who.int/phint/en/p/docf/>).

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