ARTEMISININ CONFERENCE 2013
Aligning Artemisinin and ACT supplies

Regulatory issues concerning semisynthetic artemisinin for end-users (e.g. API manufacturers)

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1-Regulatory context

Regulatory pathways – In 2009, during the artemisinin conference, we modified the picture…

From one road to artemisinin

To two pathways for artemisinin:

-one for API

-one for Starting Material

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In June 2012…

The guidance related to:

"**Recommendations for quality requirements when artemisinin is used as a starting material in the production of antimalarial active pharmaceutical ingredients "**

was published as **annex 6** of the forty-sixth report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations (see page 38 and 227-235 of the report or 52 and 241-249 of the pdf doc).

http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_970/en/index.html.

Artemisinin as starting material guidance…

The guidance excludes artemisinin produced using synthetic chemical processes or fermentation (especially due to the lack of published data and of information on the quality of the semisynthetic artemisinin)

But it is a good basis for the main characteristics of artemisinin as starting material or intermediate :

Assay: 95.0-102.0%

Artemisiten: NMT 0.2% (corrective factor 0.027)

9-epi: NMT 1.0%

Total: NMT 3.0%

Today, we are at the dawn of well defined standards for…

ARTEMISININ FROM VEGETAL SOURCE

SEMISYNTHETIC ARTEMISININ

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Semisynthetic artemisinin status and next steps

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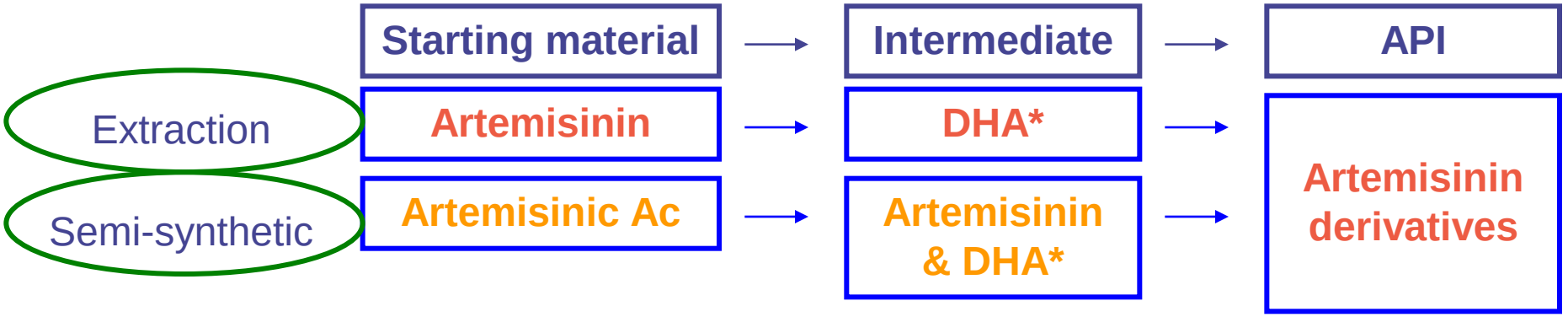
WHO meeting May 2012

For artemisinin derivatives obtained from semisynthetic artemisinin the starting material is considered to be:

ARTEMISINIC ACID

Artemisinin is considered as an *intermediate*.

Dossier content



Brief description, flow chart

Full description, detailled information

Extraction vs semi-synthetic

Additional information from artemisinic acid

Guideline on the chemistry of new active substances CPMP/QWP/130/96 Rev 1

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* DHA could be an API

Semisynthetic Artemisinin current status and next steps

A **Master File** has been submitted to WHO on the **9 October 2012:**

Referenced as APIMF 207

The file was assessed by the WHO-PQ and now requires some peer review but it is not far away.

There will be some questions (not yet received)

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Submitted in parallel to AIFA (Italian Authorities – country of manufacture)

Regulatory key information for end-users of semisynthetic artemisinin

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How to submit an API section in a regulatory dossier ?

It is the choice of the applicant
in accordance with the API manufacturer position…

*APIMF Active Pharmaceutical ingredient Master file or ASMF Active Substance Master File or DMF Drug Master File
**CEP Certificate of Suitability to the monograph of the European Pharmacopoeia (Eu Ph)

***

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How to submit an Artemisinin derivative API section in a regulatory dossier ?

It is the choice of the applicant
in accordance with the API manufacturer position…

No confidential process in Low and middle income countries	No APIMF/ASMF/DMF process in Low and middle income countries	API with great interest for Low and middle income countries but not in EU Ph

*FPP Finished Pharmaceutical Product / **CEP Certificate of Suitability to the monograph of the European Pharmacopoeia (Eu Ph)

***APIMF Active Pharmaceutical ingredient Master file or ASMF Active Substance Master File or DMF Drug Master File

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WHO
API PREQUALIFICATION PROCESS

Responding to:
-The globalization of pharmaceutical production which has led to diversification of API sources
-Confidentiality Risks
-Not in connection with FPP*
-Support for low and middle income countries
-for APIs stated on the Expression of interest list

Process selected by Sanofi for artemisinin and artesunate

*FPP Finished Pharmaceutical Product / ***APIMF Active Pharmaceutical ingredient Master file or ASMF Active Substance Master File or DMF Drug Master File

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Semisynthetic artemisinin dossier management

To facilitate the introduction of semi-synthetic artemisinin the WHO proposed to allow the following exceptions to normal procedure.

- **they will accept the submission and maintenance by Sanofi of a standalone master file for the intermediate semi-synthetic artemisinin.**
- **They will allow API manufacturers, wishing to source this material, to refer to the held master file and only require limited details regarding this material to be submitted by them.**
- **With some notable exceptions, they would exempt API manufacturers from submitting amendments for changes to the preparation and control of semi-synthetic artemisinin.**

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Data provided by sanofi for semisynthetic artemisinin to end-users

Sanofi, as the supplier of semi-synthetic artemisinin, would be responsible for providing to API manufacturers:

- **a letter of access allowing the manufacturer access to the master file held.**
- **an open part of the master file that contains information on:**
  - the sites of manufacture (API starting material and intermediate sites),
  - controls on the quality of the semi-synthetic artemisinin,
  - sufficient information on the preparation, control and stability (possibly) of semi-synthetic artemisinin, commencing from artemisinic acid, to allow the API manufacturer to set and justify their control of this material. Information on the preparation and control of artemisinic acid would not be required to be shared with API manufacturers.

Data to be provided by API manufacturers using semisynthetic artemisinin

API manufacturers (APIMF holders) would be responsible for:

- submitting an APIMF amendment to introduce the supplier of semi-synthetic artemisinin as an API intermediate manufacturer.
- submitting a copy of the letter access allowing them to refer to the master file held for semi-synthetic artemisinin.
- providing a single harmonized set of specifications for the control of artemisinin (regardless of source) and a justification for these specifications.
- providing data verifying that the use of semi-synthetic artemisinin affords the target API of the same quality and does not lead to carryover of unacceptable impurity content.

Could be challenging

REGULATORY PATHWAY EXISTS.
As regulatory perspectives, semisynthetic artemisinin is becoming a reality

A lot of work already performed to provide a file of quality and a lot of efforts to overcome regulatory barriers

Thank you

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