

# Purification of Artemisinin with HFC-134a

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Artemisinin Conference 2011  
2<sup>nd</sup>-3<sup>rd</sup> November in Hanoi

# Current Status

- 2009/10 - Scale up to kilo scale by KTL + ETDL
- 2010/11 – Collaboration with Bionexx and IPCA

EXCELLENT PROGRESS BEING MADE !!

REST IS CONFIDENTIAL

**THAT IS IT**

**Kamtech**



# **Proposed changes to specifications for Artemisinin as an API and a Starting Material**

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**Artemisinin conference 2013**  
**15<sup>th</sup> and 16<sup>th</sup> January 2013, Nairobi**

# Outline of presentation

- Summarise draft specifications circulated by WHO for:
  - ART as a starting material
  - Artemisinin (ART) as an API
- Evaluation of factors influencing the recommendations for ART as a starting material.

# ART as an API

# HISTORY

## [ART as an API]

- April 2012 - Draft document prepared
- May - Discussion
- August - Circulated for comments
- October - WHO Expert committee discussion

**Follow-up actions underway**

# ART as an API

## Current specification

- ART 97/98 -102%
- Artemisitene\* 0.014
- (9-epiART) 0.25
- Single impurity 0.25
- Total impurities 1
- Disregard imp. 0.05

## Proposed changes

- Only 97-102
- 0.15
- 0.3
- 0.15
- Same
- Same

\*After x0.027 correction



# ART as an API

| <u>Current specification</u> | <u>Proposed changes</u> |
|------------------------------|-------------------------|
| • ART 97/98 -102%            | Only 97-102             |
| • Artemisitene* 0.014        | 0.15% ( x10 )           |
| • (9-epiART) 0.25            | 0.3% ( x1.2 )           |
| • Single impurity 0.25       | 0.15%                   |
| • Total impurities 1         | Same                    |
| • Disregard imp 0.05         | Same                    |

Significant increases proposed in artemisitene and 9-epiART levels

# **ART as a Starting Material (Recommendations)**

# HISTORY

[ART as starting material]

- Feb 2010 - Draft document prepared
- March - Circulation of document
- August - Circulation of revised document
- October - Artemisinin conference recommendations
- August 2011 - Circulation of revised draft
- June 2012 - Circulation of revised draft

# ART as Starting Material

|                    | <u>2010 draft*</u> | <u>2011 draft</u> |
|--------------------|--------------------|-------------------|
| • ART              | 95-102%            | Same              |
| • Artemisitene**   | 0.08               | <b>0.15</b>       |
| • 9-epiART         | 1                  | 1                 |
| • Single impurity  | 0.25               | 0.5               |
| • Total impurities | 5                  | <b>3</b>          |
| • Disregard peaks  | <0.05              | 0.1               |

\*Stringham et al 2011 (July)

\*\*After x0.027 correction

# ART as Starting Material

## 2010 draft\*

- ART 95-102%
- Artemisitene\*\* 0.08
- 9-epiART 1
- Single impurity 0.25
- Total impurities 5
- Disregard peaks <0.05

## 2011 draft

- Same
- **0.15** (x1.9)
- 1
- 0.5
- **3**
- 0.1

# WHO recommendations (draft) on ART as Starting Material

|                | <u>2010</u> | <u>2011</u> | <u>2012</u> |
|----------------|-------------|-------------|-------------|
| ART            | 95-102      | Same        | Same        |
| Artemisitene   | 0.08        | <b>0.15</b> | <b>0.2</b>  |
| 9-epiART       | 1           | same        | same        |
| Total impurity | 5           | <b>3</b>    | <b>3</b>    |

**Further increase proposed in artemisitene  
levels**

# SUMMARY

- Both documents are at draft stage.
- Overall effort to simplify documents, especially protocols for HPLC analysis.
- Correction factor (0.027) for artemisitene introduced.
- 9-epiART is a defined impurity.
- Significant increases in impurity levels:
  - x10 for artemisitene
  - x 0.25 for 9-epiAPI

# DISCUSSION

What are the key drivers for relaxing specifications?



# DISCUSSION

- What is the purpose of WHO specifications?
  - ART as an API

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Monograph: Are there any ACTs with  
ART?

# DISCUSSION

- What is the purpose of WHO specifications?
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  - ART a starting material

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- What is the purpose of WHO specifications?
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These are only guidelines/recommendations  
– so why bother

# DISCUSSION

- What is the purpose of WHO specifications?
  - ART as an API
  - ART a starting material

Provide benchmarks for buyers and regulatory authorities??

# DISCUSSION

- What is the purpose of WHO specifications?
  - ART as an API
  - ART a starting material

Is there compelling scientific evidence to justify increased levels of impurity?

# Stringham *et al* (2011)

|                | <u>Current ART</u> | <u>ART as starting material (2011)</u> |
|----------------|--------------------|--|
| ART            | 97-102%            | 95-102                                 |
| Artemisitene   | 0.014              | 0.08                                   |
| 9-epiART       | 0.25               | 1                                      |
| Total impurity | 1                  | 5                                      |

Some justification given in the paper

# Stringham *et al* (2011)

- Specifications should be based on “historical results”
- Use of indirect evidence to postulate fate of impurities e.g. from 9-epiART
- “Given the difficulty in synthesizing the impurities it is apparent that they cannot be used in routine analysis of artemisinin”

Limited hard evidence  
- funding constraints ?



# DISCUSSION

- What is the purpose of WHO specifications?
  - ART as an API
  - ART a starting material

## CONCLUSION:

There is NO compelling scientific evidence to justify increased levels of impurity?

# DISCUSSION

- What is the purpose of WHO specifications?
  - ART as an API
  - ART a starting material

If not science then WHO done it??

ARTE- GATE  
investigation

*Who guided the guidelines?*

# WHO recommendations (draft) on ART as Starting Material

|                | <u>2010</u> | <u>2011</u> | <u>2012</u> |
|----------------|-------------|-------------|-------------|
| ART            | 95-102      | Same        | Same        |
| Artemisitene   | 0.08        | <b>0.15</b> | <b>0.2</b>  |
| 9-epiART       | 1           | same        | same        |
| Total impurity | 5           | <b>3</b>    | <b>3</b>    |

# WHO recommendations (draft) on ART as Starting Material

|                | <u>2010</u> | <u>2011</u> | <u>2012</u> |
|----------------|-------------|-------------|-------------|
| ART            | 95-102      | Same        | Same        |
| Artemisitene   | 0.08        | <b>0.15</b> | <b>0.2</b>  |
| 9-epiART       | 1           | same        | same        |
| Total impurity | 5           | <b>3</b>    | <b>3</b>    |

Artemisitene levels going up, up and up

# WHO recommendations (draft) on ART as Starting Material

|                | <u>2010</u> | <u>2011</u> | <u>2012</u> |
|----------------|-------------|-------------|-------------|
| ART            | 95-102      | Same        | Same        |
| Artemisitene   | 0.08        | <b>0.15</b> | <b>0.2</b>  |
| 9-epiART       | 1           | same        | same        |
| Total impurity | 5           | <b>3</b>    | <b>3</b>    |

9-epiART levels:  
one single hike from 0.25%

# WHO recommendations (draft) on ART as Starting Material

|                | <u>2010</u> | <u>2011</u>  | <u>2012</u> | <u>Semisynthetic<br/>ART 2013</u> |
|----------------|-------------|--------------|-------------|-----------------------------------|
| ART            | 95-102%     | Same         | Same        | Same                              |
| Artemisitene   | 0.08%       | <b>0.15%</b> | <b>0.2%</b> | <b>0.2%</b>                       |
| 9-epiART       | 1%          | same         | same        | same                              |
| Total impurity | 5%          | <b>3%</b>    | <b>3%</b>   | <b>3%</b>                         |

**Spot the trend**

# WANTED

- Definitive work on the fate of pure artemisitene and pure 9-epiART under APIs synthesis conditions.
  - Is this information available?

Major companies claim non-profit involvement in ACTs - so why not disseminate information?



# WANTED

- Definitive work on the fate of pure artemisitene and pure 9-epiART under APIs synthesis conditions.
- Indication that levels of impurity effect yields of API.
- Availability of reference impurities

Bionexx has prepared >50g of pure 9-epiART for this purpose

# WANTED

- Definitive work on the fate of pure artemisitene and pure 9-epiART under APIs synthesis conditions.
- Indication that levels of impurity effect yields of API.
- Availability of reference impurities
- Access to relevant information
  - Having difficulties joining WHO circulation lists??

**Who  
is  
Who  
within  
WHO???**

**It is who you know!!!**

**THANK YOU FOR YOUR  
ATTENTION**