Artemisinin as starting material

Walter Cabri
EURARTESIM®

TWO APIs

PIPERAQUINE TETRAPOSPHATE TETRAHYDRATE

DIHYDROARTEMISININ
Eurartesim registration strategy
Sigma-tau/MMV

Stringent regulatory authority approval
WHO prequalification
Endemic countries filing

EMA centralized procedure

public

private
Total Quality

- Preclinical Development
  - GLP

- Clinical Development
  - Phase III
  - QTC
  - Food Interaction
  - GCP

- DS/DP
  - cGMP
  - EH&S
  - GREEN CHEMISTRY
  - Social care
Some key topics covered in the CMC section

- Artemisin as starting material
- Specification of starting materials, DS & DP
- Mass balance & shelf life. DS & DP
- Full toxicological qualification of impurities
- Genotoxic impurities are undetectable
From Artemisin to DHA is a short process, therefore the quality of the starting material is directly affecting the quality of the API.

1. Artemisin coming from different continent has an identical profile?
2. Justification of the specs.
3. Validation of analytical methods for impurities and OVI.
4. Definition of dry leave specs.
5. Seed control.
6. Farmers control……
7. Pesticides.
8. Different processes?
Artemisinin

We are selecting suppliers based on the following requirements:

1. Artemisinin suppliers information:
   A. Declaration on the use of pesticides.
   B. Declaration BSE/TSE.
   C. Declaration on the use of fumigants.
   D. Declaration on the source of seeds.
   E. Declaration on the cultivation procedure.
   F. Specification of dry leaves.
   G. Declaration on the solvents used.
   H. Inspection of the facility.

2. The batches must comply with our specifications.

3. Three validation batches of the DHA
## Artemisinin specs

### Specifications

<table>
<thead>
<tr>
<th>TEST</th>
<th>SPECIFICATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appearance</td>
<td>Colourless needles or a white crystalline powder</td>
</tr>
<tr>
<td>Identity IR, HPLC</td>
<td>Conforms to the ref. std.</td>
</tr>
<tr>
<td>Melting range</td>
<td>151-154°C</td>
</tr>
<tr>
<td>Specific rotation</td>
<td>+75°/ +78°</td>
</tr>
<tr>
<td>Sulphated ash</td>
<td>0.10%</td>
</tr>
<tr>
<td>Heavy metals</td>
<td>See later</td>
</tr>
<tr>
<td>Loss on drying</td>
<td>≤ 0.50%</td>
</tr>
<tr>
<td>Solvents</td>
<td>ICH, no class I contamination</td>
</tr>
<tr>
<td>Assay</td>
<td>97.0% -102.0%</td>
</tr>
<tr>
<td>Impurities:</td>
<td></td>
</tr>
<tr>
<td>Artemisitene</td>
<td>≤ 0.15%</td>
</tr>
<tr>
<td>Epi-artemisinin</td>
<td>≤ 0.50%</td>
</tr>
<tr>
<td>Each unknown impurity</td>
<td>≤ 0.20%</td>
</tr>
<tr>
<td>Total impurities</td>
<td>≤ 1.0%</td>
</tr>
</tbody>
</table>

### Optimization of WHO method to increase selectivity/sharp peaks.

### Impurity calculation are considering response factors
We need to establish general specification considering that some producers are not able to control the farmers.

Soil contamination  Contamination by other plants
### Artemisinin additional specs

<table>
<thead>
<tr>
<th>METAL</th>
<th>SPECIFICATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pb</td>
<td>≤ 1 ppm</td>
</tr>
<tr>
<td>Cd</td>
<td>≤ 0.2 ppm</td>
</tr>
<tr>
<td>Hg</td>
<td>≤ 0.1 ppm</td>
</tr>
<tr>
<td>As</td>
<td>≤ 1.5 ppm</td>
</tr>
<tr>
<td>Fe</td>
<td>≤ 10 ppm</td>
</tr>
<tr>
<td>Cu</td>
<td>≤ 10 ppm</td>
</tr>
<tr>
<td>Ni</td>
<td>≤ 10 ppm</td>
</tr>
<tr>
<td>Zn</td>
<td>≤ 10 ppm</td>
</tr>
</tbody>
</table>
Forecasts optimizations

Million of treatments
Age/weight distribution
Market distribution
Artemisinin process efficiency

Also the kg artemisinin to get 1kg of API in the DP must be optimised
These yields were presented at the Mumbai 2009 conference by Jacques Pilloy.
Based on literature data and lab/industrial experience the yields calculated in ST are the one reported on the right.

**API production and price**

- **Main APIs**

<table>
<thead>
<tr>
<th>API</th>
<th>Artemisinin need per kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>DHA</td>
<td>1.24 kg if API</td>
</tr>
<tr>
<td></td>
<td>1.12 kg if interm.</td>
</tr>
<tr>
<td>Artesunate</td>
<td>0.98 kg</td>
</tr>
<tr>
<td>Artemether</td>
<td>1.67 kg</td>
</tr>
</tbody>
</table>

1.25
0.90
1.42
An Improved Manufacturing Process for the Antimalaria Drug Coartem. Part I

Matthias Boehm, Peter C. Fuenfschilling, Matthias Krieger, Ernst Kuesters, and Fritz Struber

Novartis Pharma AG, Chemical and Analytical Development and Chemical Operations, CH-4002 Basel, Switzerland.

Abstract:
Artemisinin and its derivatives, such as artemether, are highly sensitive compounds, which require careful optimized production processes for their manufacture. Due to robustness issues, the manufacturing procedure of the reduction of artemisinin with potassium borohydride to dihydroartemisinin was reinvestigated. The most important factor for obtaining optimal yields is to ensure low levels of contamination of potassium hydroxide in potassium borohydride. Application of a lower reaction temperature, fast addition rate of potassium borohydride, and careful control of the pH during the quench with acid are further important parameters in guaranteeing a robust process. In the redesign of the conversion of dihydroartemisinin to artemether, the yield was increased, and dichloromethane was replaced by the ecologically friendlier methyl acetate. A robust manufacturing process for artemether is now at hand, allowing the production of this important medicine reliably and in good quality and yield.

Figure 1. The active ingredients for Coartem: artemether 1 and lumefantrine 2.

nonprofit basis to health authorities in malaria-endemic developing nations since 2001. Production of Coartem, the leading artemisinin-based combination therapy, has increased from 100,000 treatments in 2002 to up to 65 million in 2006.

In view of the fast-growing demand, the improvement of the manufacturing processes for both active ingredients, the semi-natural product 1 and the fully synthetic tricyclic compound 2 (Figure 1), were urgently needed. In this paper,
Italy: Eradication of Malaria

Deaths x million

State Quinine distribution education

Agro Pontino reclamation

DDT

Alberto Coluzzi, 1961
Malaria map (1882) by sen. Luigi Torelli

The map was developed to verify the health and hygienic conditions along the railway lines.

About 8331 kilometers of railways, 3762 were well in malarial areas.
Eurartesim CMC Team

~50% coming from the Agro Pontino