Semi-synthetic Artemisinin Project
RBM/UNITAID/WHO Artemisinin Conference

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Semi-synthetic Artemisinin Project Goals

- Create a complementary source of non-seasonal, high-quality, and affordable artemisinin to supplement the current plant-derived supply.
- Ensure semi-synthetic artemisinin is available to all qualified derivative manufacturers.
- Contribute to stabilizing the price of ACTs to benefit patients and payers.
A 2\textsuperscript{nd} Source to Stabilize the Supply Chain & Price

**Agricultural method**

Cultivation → Extraction → Artemisinin

Lead time from seed to ACT is \( \sim 15 \) months

**Semi-synthetic method**

Fermentation → Photo-Chemistry → Artemisinin

Lead time from lab to ACT is \( \sim 3 \) months

Source: MMV Artemisinin Conference 2010
A Novel Semi-synthetic Route

Glucose → Artemisinic Acid → Artemisinin

Yeast 2.0

Light
Semi-synthetic Artemisinin as an Intermediate

Starting material
Defined specifications

Artemisinic Acid → Artemisinin

Intermediate
Defined specifications

Artesunate
Artemether
Dihydroartemisinin
Arteether
Artelinate

GMP manufacturing

API
Compendial specifications

SANOFI

OneWorld Health, a drug development affiliate of PATH
Semi-synthetic Artemisinin: the Partnership

- **R & D**
  - Discovery of the metabolic pathway and identification of genes from the wormwood plant required to make artemisinic acid
  - Construct biosynthetic artemisinic acid pathway and clone into microbial host
  - Optimize artemisinic acid production

- **MANUFACTURING**
  - Optimize microbial strain
  - Develop scalable processes for manufacture and purification of artemisinin
  - Demonstrate comparability of plant derived versus semi-synthetic artemisinin

- **Fermentation process development**
  - Chemistry process development
  - Develop scalable industrial manufacturing process
  - Production and commercialization

- **Project and alliance Management**
  - Enable adoption of semi-synthetic artemisinin into supply chain
  - Apply WHO sanctioned global health goals to malaria ACTs

Timeline:
- 2005
- 2006
- 2007
- 2008
- 2009
- 2010
- 2011
- 2012
- 2013

We are here
Project Status Update
Fermentation Part - from Pilot to Industrial Scale

- Process development and industrial scale-up completed.
- Facility and equipment are in place.
- Tech transfer to manufacturing site completed.
- Validation completed.
- Routine Production Started.
Artemisinic Acid Production at HuvePharma (BG)

– Production in 2012: 38.7 t of artemisinic acid
  • Facility: 5 fermentors (17 m³)

– Production in 2013: 60 t of artemisinic acid (from 590 t of glucose)
  • Further scale-up in fermentation
  • Extraction, crystallization, isolation remain in same scale and equipment
  • (3 fermentors at 63 m³)
Chemistry Part - from Pilot to Industrial Scale

- Process development and industrial scale-up completed.
- Facility and equipment are in place.
- Tech transfer to manufacturing site completed.
- Validation completed.
- Routine Production Started
**Reaction Schema**

**Step 1**
Artemisinic acid

**Step 2**

**Step 3**
Photooxygenation

**Step 4A reaction**

**Step 4B isolation**

Artemisinin

Artemisinic acid
Equipment Details: Garessio

- 16 reactors of various sizes
- 1 hydrogenator
- 3 photoreactors of 3 lamps each
- 1 centrifuge
- 1 dryer
- 1 packaging room
Current Status

• **2012:** Process validation finished. Regulatory dossiers submitted to WHO and AIFA. Several tons of materials have been produced and are available for testing by potential customers. Please contact Sanofi representatives.

• **2013:** Production goal: 35 tons.

• **From 2014:** Capacity across the value chain adapted to cover production - approximately 50-60 t of artemisinin per year (50% of worldwide annual needs).

• Semi-synthetic artemisinin cost is anticipated to be comparable to high quality field production ($350 - 400 /kg at routine production schedule).
Thank You

National Research Council Canada Plant Biotechnology Institute (NRC-PBI)

Photo: PATH/Laura Newman