

Artemisinin & Synthetic Biology

A Case Study



About 100,000 farmers currently grow *Artemisia annua*. Novartis AG

Product: Artemisinin, the key ingredient in the world's most effective anti-malarial drug, is extracted from *Artemisia annua*, an ancient medicinal plant commonly known as sweet wormwood. Artemisinin is incorporated into WHO-authorized antimalarial cocktail drugs called ACTS (Artemisinin Combination Therapies).

Status: Supported by funds from the US Gates Foundation, Synthetic biologists at California-based Amyris, Inc. engineered yeast to produce artemisinic acid, a precursor to artemisinin. Pharmaceutical giant Sanofi Aventis has now scaled up commercial production of between 35-60 MT of what is marketed as Semi-Synthetic Artemisinin (SSA). Amyris founder Jay Keasling has indicated interest in having SSA take over full global production.

Affected Country/

Region: Until 2013 natural artemisinin was sourced entirely from an estimated 100,000 small farmers in Asia and Africa, as well as wild harvesters of the crop in China. Currently 80% of all artemisinin derived from *Artemisia* crops is produced in China. Vietnam is a distant second (around 10%), with the remainder coming from Madagascar, Kenya, Tanzania and Uganda. A small amount is grown in India. Farmers have also been growing trial crops of *Artemisia* in Zimbabwe, South Africa and Nigeria. The average crop area per farmer in China and Africa is around 0.2 hectares. The introduction of SSA coincided with a dramatic fall in artemisinin prices in 2013. Subsequently 2014 plantings of *Artemisia* are at only a third of previous production levels and commercial operations are at a standstill.

Market: Current market demand for artemisinin is about 150-180 metric tonnes (MT). The major buyers are a handful of approved pharmaceutical companies making ACT drugs.

Commercialization: Already commercialized. In 2013 Sanofi produced 35 MT of SSA with production rising to 50-60 MT in the coming years. Although advocates claim synthetic biology will make anti-malarial drugs cheaper, in fact the current production-run of SSA is priced at between \$370-\$400 per kg, significantly above the price of naturally-derived artemisinin, which sells for around \$250-\$270 per kg. Natural artemisinin producers further charge that its impossible to know the true costs structure of SSA since it has received extensive philanthropic subsidies. As the last step before being put on the market an intermediate version of the

synthetic artemisinin has been approved by the

Synthetic Biology Artemisinin Commercialisation:

- 2013 - Production goal 35 MT – for Sanofi use.
- 2014 – Production capacity 50-60MT.
- Cost estimate is \$350 – \$400/kg (not-for-profit price).



Plant-Derived Pharmaceutical Ingredients and Synthetic Biology

A New and Emerging Issue for CBD

Developments in synthetic biology could disrupt the livelihoods of thousands of small farmers who cultivate *Artemisia* for the plant's anti-malarial compounds. These developments impact land use that supports biodiversity and fair and equitable sharing of benefits from the genetic resources that produce natural plant products.

If biosynthesis of artemisinin can be successfully scaled up, the pharmaceutical industry will source future supplies of artemisinin from a handful of microbial cell factories instead of over 100,000 farmers in Asia and Africa. Artemisinin is just one example of a raw material that may be affected; it is conservatively estimated that at least 50% of today's commercial pharmaceutical compounds are derived from plants, animals and microorganisms. Seven of the ten largest pharmaceutical companies are now partnering with synthetic biology companies to develop synthetic biology production routes for pharmaceuticals previously processed from botanical sources.

Artemisia is just one of hundreds of economically important natural plant compounds whose production may be switched to synthetic biology production in a very short time frame. No inter-governmental body is addressing the potential impacts of synthetic biology on the conservation and use of biodiversity and on the livelihoods of those who depend on agricultural export commodities (including high-value flavors, fragrances, essential oils, etc). The Convention on Biological Diversity is the most appropriate forum to address this new and emerging issue.

WHO for the preparation of approved artemisinin derivatives (such as artesunate).

About Artemisinin

The key ingredient in the world's most effective drug treatment for malaria – artemisinin – is extracted from an ancient medicinal plant, *Artemisia annua*, commonly known as sweet wormwood. According to the WHO, artemisinin-based combination therapies (ACTs) provide the most effective treatment against malaria. The pharmaceutical industry sources natural artemisinin from thousands of small farmers who grow *Artemisia annua*, primarily in China, Vietnam, Kenya, Tanzania, Uganda, Madagascar and India.

Origins of Semi-Synthetic Artemisinin

In 2006, Professor Jay Keasling of the University of California-Berkeley and 14 collaborators announced they had successfully engineered a yeast strain to produce artemisinic acid, a precursor to the production of artemisinin. Supported a \$53.3 million grant from the Bill & Melinda Gates

Foundation, the researchers achieved the complex feat of engineering the metabolic pathway, which comprised 12 new synthetic genetic parts. Inserted into yeast, the engineered pathway makes the yeast produce artemisinic acid. A chemical process is then used to convert artemisinic acid to artemisinin. In 2008, Amyris granted a royalty-free license for its synthetic yeast to Sanofi for the manufacture and commercialization of artemisinin-based drugs, with a goal of market availability by 2013. Aiming to be efficient and fast, the production of artificial Artemisinic acid is supposed to take less than three months. Sanofi built a new facility for the chemical conversion of artemisinic acid in Italy and began the world's first commercial production of synthetic microbe-derived artemisinin in April 2013.

Sanofi initially produced 35 metric tonnes (MT) in its first 2013 batch. It has indicated plans to annually produce enough semi-synthetic Artemisinin to meet between a third and a half the global demand. Sanofi says it will ensure its distribution under the "no profit, no loss" principle. The key researcher associated with the Synthetic Artemisinin project is

synthetic biologist Jay Keasling, founder of Amyris and professor at the University of California at Berkeley.

Sanofi's production is slated to increase to 60 MT per year. Keasling has publicly stated that the goal is now to fully replace the botanical version. Keasling is rumoured to be in discussions with other Pharmaceutical companies to provide a process for synthetic biology-derived artemisinin different than that licensed to Sanofi.

Impacts of Semi-Synthetic Artemisinin

A 2006 report from the Netherlands-based Royal Tropical Institute predicted the effects of synthetic sources of artemisinin: "pharmaceutical companies will accumulate control and power over the production process; Artemisia producers will lose a source of income; and local production, extraction and (possibly) manufacturing of ACT in regions where malaria is prevalent will shift to the main production sites of Western pharmaceutical companies."

The report warned that the prospect of synthetic artemisinin production could further destabilise a very young market for natural Artemisia, undermining the security of farmers just beginning to plant it for the first time: "Growing Artemisia plants is risky and will not be profitable for long because of the synthetic production that is expected to begin in the near future."

Fueling the Boom-bust Cycle?

According to the Royal Tropical Institute's analysis, sufficient supplies of Artemisia could be met solely by increasing cultivation of sweet wormwood. The report estimated that between 17,000-27,000 hectares of Artemisia annua would be required to



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satisfy global demand for ACTs, which could be grown by farmers in suitable areas of the developing world. Indeed, subsequent to the Royal Tropical Institute's report, farmers planted tens of thousands of additional hectares and in 2007 the artemisinin market became saturated with supply.

"Early on, it was not about replacing the agricultural form... and now I think it's nearly inevitable that it will shift over."

- Jay Keasling

Prices crashed from more than \$1,100 per kilogram to around \$200 per kilogram driving 80 processors and many small farmers out of business. As a result, availability once again dropped below demand. Though poorly managed, the 2007 production spike demonstrated the feasibility of meeting world demand for artemisinin with botanical supplies.

The international drug-purchasing facility, UNITAID, subsequently established the Assured Artemisinin Supply System (A2S2) initiative to provide loans and supply chain investment to increase the Artemisia harvest to sustainable high levels. In

2011, artemisinin production from harvested crops was estimated at between 150-170 tonnes, close to 2007 levels.

The creation of the A2S2 was largely successful in calming the swings in price and ensuring stable botanical supply to meet medicinal needs. Sanofi claimed that introducing limited amounts of synthetic biology-derived artemisinin would also help calm these price spikes. However, its introduction instead appears to have been followed by increased volatility. Experts had warned that a badly-managed introduction of synthetic artemisinin could instead cause further instability and lead farmers to refrain from planting in the face of competition from synthetic microbes.

“If it’s brought in too fast it could create huge shortages, because people will stop producing the natural stuff,” says Malcolm Cutler, technical adviser to the Assured Artemisinin Supply System initiative, which organized the Nairobi conference.

This may be what is happening now. 2014 prices of botanical artemisinin have dropped to a decade low and plantings are down by 2/3rds. If the prices of artemisinin rise quickly again because of the reduced plantings, SSA may undercut natural production cost in some markets (eg China). Far from calming market volatility, SSA may have helped fuel it.

Natural producers fear that the competition is unfair if SSA is marketed at a “not for profit price” based on large subsidies from the Gates Foundation. They point out that the real costs of SSA have been hidden by philanthropic support <http://www.a2s2.org/market-data/a2s2-market-update-aug13.html>



Intellectual Property related to Biosynthesis of Artemisinic Acid:

US8101399: Artemisinic epoxide and methods for producing same. Assignee: The Regents of the Univ. of California. Published: 24 Jan 2012

US7622282: Biosynthesis of isopentenyl pyrophosphate. Assignee: The Regents of the University of California. Published: 24 Nov 2009

US7192751: Biosynthesis of amorpha-4,11-diene. Assignee: The Regents of the University of California. Published: 20 March 2007

US7172886: Biosynthesis of isopentenyl pyrophosphate. Assignee: The Regents of the University of California. Published: 6 Feb 2007

For More Information

ETC Group has published several documents explaining and analyzing the impact of Synthetic Biology on biodiversity and livelihoods including Extreme Genetic Engineering - An introduction to Synthetic Biology, The New Biomasters - Synthetic Biology and the Next Assault on Biodiversity and Livelihoods and The Principles for the Oversight of Synthetic Biology available on our website http://www.etcgroup.org/en/issues/synthetic_biology

The Potential Impacts of Synthetic Biology on the Conservation & Sustainable Use of Biodiversity: A Submission to the Convention on Biological Diversity’s Subsidiary Body on Scientific, Technical & Technological Advice (A Submission from Civil Society)

References

References

For references, email info@etcgroup.org.