

**Options for New Production of Fumagillin  
for  
Apiary Use in Alberta**

Prepared for:  
**Alberta Beekeepers Commission**

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**June 2018**



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## Options for New Production of Fumagillin

### Summary

The results of this review of the current supply disruption of Fumagillin-B, an antibiotic that is important for maintain hive health suggest that there is the potential to resume supply during the medium term. The production company, Themis Medicare, has reported that it has resolved its issues and has resumed operating its fumagillin production process. However, the product distribution companies, Medivet and Ceva are no longer interested in maintaining their operations in the fumagillin business.

Therefore primary hurdles facing resumed supply to Canada are:

- a) the regulatory restrictions that prevent changes to pharmaceutical product supply chains.
- b) a new pharmaceutical processing and packaging company needs to be identified and presented with a business case to attempt to assume the Fumagillin-B business.

Details of the technology, market, and longer term supply options relating to the Fumagillin-B business are provided below.

### Background

- Fumagillin-B, the product used by beekeepers, is a white powdered product that contains dicyclohexylammonium salt of fumagillin as the active pharmaceutical ingredient (API). It is sold at 2.1% solid mixture.
- The purpose of the product is its antifungal properties, which are used to prevent *nosema*, which causes bee dysentery.
- The active component, Fumagillin, is produced by *aspergillus fumigatus* via fermentation and extraction.
- The original patents for the production of fumagillin and its isolation as the ammonium salt were issued separately in the 1950s by The Upjohn Chemical Company and by Abbot Laboratories.
- At one point, a Hungarian company, Chinoin, was producing fumagillin, but as an infringement of the existing patents. Through a series of transactions, Sanofi acquired ownership of the production technology. Ceva Animal Health was spun out of Sanofi, and has managed the fumagillin supply since the late 1990s.
- Until early 2018, Ceva Animal Health purchased concentrated fumagillin ammonium salt from Themis Medicare in Mumbai India (or had it produced under contract) and sold the (concentrated product to Medivet. Themis has been the world's only fumagillin manufacturing company.
- Medivet compounded (i.e. mixed with excipients) the final Fumagillin-B product, packaged, and distributed the product. Key regions supplied are Alberta, US, and Korea.

- The size of the business involved importing approximately 500 kg per year of fumagillin as the diclohexylammonium salt, for processing and packaging of 22,500 kg per year of Fumagilin B, with a retail value close to \$3 million.
- The Fumagilin-B brand/product remains as a Health Canada approved product at this time. It is “owned” by Medivet and Ceva. Preliminary indications from Health Canada are that a new supply could be put in place if marketed under the same brand name, although the required documentation needs to be confirmed.

### Supply Status

- Themis has confirmed that they are willing and able to resume production of the fumagillin, the active pharmaceutical ingredient (API). Themis also able to produce the final dosage product (2%) Fumagilin-B, which is the Medivet product.
- Themis is not able to sell the product into Canada since the only product with a DIN and a Health Canada approval is Medivet’s Fumagilin-B. Themis has been advised that their product would be a new supply, new product and would need to go through a 2-3 year approval process.
- Themis is proceeding with supply of fumagillin and/or Fumagilin-B into other markets that do not have the same regulatory restrictions as Canada
- Ceva had provided Themis with a customer list. Themis has made preliminary inquiries about a Canadian company that may be able to fill Medivet’s role to supply Canadian customers.
- Ceva has indicated that they do not have an interest to pursue further fumagillin business. This business has been a niche product with a relatively small market. This position is believed to be precipitated by the Themis supply disruption, and a subsequent decision by Medivet to cease operations.
- Themis Medicare in India remains the only producer of the API.
- Most suppliers of fine chemicals and pharmaceuticals source materials from Asia, and China in particular, but attempts to identify a source with expertise in fumagillin production were unsuccessful. For example, Carbosynth is a fine chemicals company based in the UK that lists Fumagilin-B as an available product. However, they had never sold any. Carbosynth had looked into a fumagillin sourced from China but was unsuccessful. Other companies contacted include Sigma, Toronto Fine Chemicals, and others.

## Technical Information

The following is background information related to a future potential to completely change the supply chain for fumagillin.

- A review of the fumagillin production technology with industry experts in industrial fermentation of veterinary products suggests that starting up a new production point could cost in excess of \$1 million and take more than 12 months.
- Not all facilities are willing to work with *aspergillus fumigatus* due to its classification as a Level 2 Biosafety Hazard (it is a pathogen) and that the organism exhibits sporulation, meaning that it poses challenges for containment.
- Alberta Innovates is unable to work with this organism; University of Alberta's fermentation suite at Agri-Food Discovery Place may be able, but would need to conduct a review. Other potential locations in Canada include SRC/NRC in Saskatoon, and NRC in Montreal.
- The yields of fumagillin reported in the literature are considered marginal in terms of the value of production as compared to industry standard operating costs for fermentation and the solvent extraction processes required to isolate the ammonium salt. Therefore, it is possible and likely that the manufacturing process used by Themis had been optimized considerably over the last 20 years in order to make the supply chain profitable.
- Based on the nature of the beekeeping industry in North America and in several other jurisdictions, it is believed that fumagillin demand will continue. In general, the larger bee colonies along with the practice of moving bees geographically to perform crop pollination creates stress on the bees and can lead to a lack of ability to resist *nosema*.
- There are two fungi that are targeted by fumagillin: *Nosema apis*, and *Nosema ceranae*, although the efficacy against each fungi may be slightly different. There is consensus amongst the scientific community that without *nosema* control, Alberta beekeepers will experience a measurable and consistent increase in losses during overwintering.

## Conclusions

The best option during the near term is to address the product approval issue with Health Canada and assist a Canadian pharmaceutical company to compound, package and market the final product, either by

- acquiring the rights to the existing product (transfer the DIN) or
- by applying pressure for an interim approval for use within the next several months and then following up with a formal approval.

Since the source of the API would continue to be Themis, there is the potential for the process expedited. A process for this will require discussion and agreement with Health Canada.

Other conclusions regarding establishing a new supply chain are as follows.

- a) Fumigillin production is not a simple process that can be simply repeated based on a laboratory procedure. It is a specialized fermentation process, and establishing a new supply chain for fumagillin will require a significant technical effort to demonstrate firstly, technical feasibility and safety, which would then form the basis for developing a business case and demonstrating the financial feasibility.
- b) The cost structure for the production process may necessitate production to remain overseas. Alberta (and Canada) has established offices in Asia and China for assisting with forging new business relationships, and these offices could be valuable resource for establishing new fumagillin supply chain.
- c) Based on the moderate production yields reported in the literature, without access to proprietary in-house expertise held by Themis, any new manufacturer would need to expend considerable resources in order to demonstrate technical and economic feasibility.
- d) There are numerous stakeholders in the beekeeping industry both in Canada and abroad and ABC should establish and/or maintain contact for potential financial support for a fumagillin business development project.
- e) Two candidates initially identified with potential to conduct a fermentation feasibility study (laboratory) are NRC/SRC in Saskatoon, and TerraVerdae operating at Agri-Food Discovery Place in Edmonton. Each may be able to complete fermentation reproducibility studies at 150 – 300 litre fermentation scale (approximately 1/500 of full commercial scale, representing a critical first stage of technical and economic feasibility).

Options to consider for either resuming supply of fumagillin-B at the required scale of 500 kg per year or in other ways address *nosema* in beekeeping are summarized in the Table below.

Option	Key Steps Required	Estimated Timing	Comments
Themis resumes supply of fumagillin ammonium salt	<ol style="list-style-type: none"> <li>1. Identify new local importer and drug compounding facility</li> <li>2. Acquire “rights” to Medivet’s Product approval and DIN</li> </ol>	3 – 6 months	<ul style="list-style-type: none"> <li>- Strathcona Compounding Ltd in Edmonton has limited capacity to import and package</li> <li>- Other options need to be identified and a business proposal developed</li> <li>- Need Health Canada approval expedited</li> </ul>
Themis agrees to transfer its manufacturing expertise to a Canadian third party	<ol style="list-style-type: none"> <li>1. identify new manufacturing company with required fermentation capacity</li> <li>2. facilitate business arrangement with Themis</li> <li>3. transfer manufacturing process technology to new manufacturing company</li> </ol>	<p>6 - 12 months for full scale-up and business feasibility demonstration</p> <p>Timing for Health Canada approval to be determined</p>	<ul style="list-style-type: none"> <li>- need to identify a facility with capacity for contract production for some limited time</li> <li>- scale up/ production demonstration cost could be &gt;\$750,000, cost possible shared between ABC, other beekeeping stakeholder organizations, government funders, and new company.</li> </ul>
ABC and/or CHC leads/facilitates development of new supply chain	<ol style="list-style-type: none"> <li>1. identify new company to reproduce and scale up the manufacturing</li> <li>2. demonstrate technical feasibility</li> <li>3. demonstrate business feasibility</li> </ol>	<p>3 – 6 months for technical feasibility</p> <p>6 - 9 months for full scale-up and business feasibility</p> <p>1 – 2 years process development to achieve required process yields</p>	<ul style="list-style-type: none"> <li>- A range of options exist with expertise and capacity to complete a small scale technical feasibility study, cost estimated at \$120,000</li> <li>- Scaling up studies could cost more than \$700,000.</li> <li>- From this point, the business feasibility can be assessed and a permanent site established</li> <li>- If significant yield improvements are required, costs and timing could easily exceed \$2 million and 2 years.</li> <li>- ABC financial support likely could be matched as high as 3:1 by government programs such as AB Innovates voucher program or AAFC</li> </ul>
Identify alternative product or hive pest control practices	<ol style="list-style-type: none"> <li>1. Initiate an R&amp;D program to investigate options</li> </ol>	3 years	<ul style="list-style-type: none"> <li>- Project has been initiated in Saskatchewan</li> <li>- a good approach to address longer term needs for reduced antibiotic use in food production</li> <li>- fumagillin demand is not expected to diminish based on established honey production practices.</li> </ul>

## Suggested Next Steps

1. Follow up with the potential that Themis production can be imported as previous.
  - a. Identify/develop new Alberta business to import, process, package, and distribute Fumagilin-B.
  - b. Determine documentation required to maintain Health Canada approval of Medivet Fumagilin-B
2. Review current findings with ABC to
  - a. discuss options primarily in reference to risks facing the beekeeping industry.
  - b. Determine as pathway for financing further study into the feasibility of establishing a new fumagillin supply chain, as well as executing a major manufacturing process development project.
  - c. Confirm the potential role for ABC in a project to resource fumagillin.

If ABC concludes that further work is required and can be supported, the following steps are recommended, each with a point where further go/no go decisions can be made.

3. Complete a comprehensive study in order to define the scope of a fumagillin manufacturing project.
  - a. Investigate the potential for other animal health supply companies for interest to lead a program to establish new fumagillin supply
  - b. Establish a project with Themis in order to acquire production process expertise
  - c. Identify and confirm companies, organizations, facilities that are willing to conduct various aspects of the manufacturing process, including lab scale process development, scaled up production, temporary contract manufacturing, and commercial manufacturing, particularly from the perspective of operational safety.
  - d. scope out the options for resuming Medivet's role in product compounding and packaging.
  - e. establish a project financing plan, including gaining support from other industry stakeholders
4. Conduct a thorough review of alternative beekeeping practices that could be implemented in lieu of fumagillin availability during the medium term.