Exclusive Manufacturing Solutions
Helsinn Advanced Synthesis SA

Making the difference with highest quality manufacturing facilities, expertise, investments and commitment
# Index of Contents

**Building better todays for people with cancer**  
Riccardo Braglia, Helsinn Group Vice Chairman and CEO  
Page 4

**Helsinn Advanced Synthesis, always at the forefront**  
Waldo Mossi, Local General Manager, Chemical Business, Helsinn Advanced Synthesis  
Page 5

**State-of-the-art Manufacturing**  
Page 7

**R&D Development Capabilities**  
Page 9

**Drug Substance Manufacturing**  
Page 11

**Highly Potent APIs (HPAPIs)**  
Page 13

**Anticancer Compounds**  
Page 17

**Analytical – R&D and QC**  
Page 19

**Regulatory & Compliance**  
Page 21

**Contact Information**  
Page 22
Helsinn’s manufacturing operation is one of the most-respected contract manufacturing organisations globally. Our quality is demonstrated through our work on a daily basis: through our rigorous commitment to compliance with global regulations, our state of the art technology and the fact that we are regularly rewarded for our efforts by our peers in industry awards.

Our manufacturing operations are based on decades of experience and expertise and this, combined with our constant commitment to invest in our technology and our staff, has earned us a valuable position of trust within the industry.

As Helsinn evolves to keep pace with the changing needs of the cancer care community, so our manufacturing operations must also adapt. We announced recently a plan for a major upgrade to our manufacturing plant in Biasca, Switzerland, to allow us to respond to a greater need for manufacturing of cancer therapeutics.

In order to support the growing demand from customers wanting cancer care therapeutics, Helsinn will invest CHF 15 million to build new laboratories and a new production unit focused on the development, analysis and production of anticancer drugs. The development of the new facility will be completed by the end of 2018. This is a great example of how Helsinn is constantly moving forward to keep pace with the needs and demands of the industry.

At heart, Helsinn is a family company based on three core values, quality, integrity and respect and, as we move forward with the constant innovation that we need to drive our company forward, we are committed to work by these values.

Riccardo Braglia
Helsinn Group
Vice Chairman and CEO
Quality is one of Helsinn’s core values and underpins all of our activities. Nowhere is quality more important than in our manufacturing activities. Our 30 years’ experience in manufacturing classic Active Pharmaceutical Ingredients (APIs), and, more recently, 15 years’ experience in manufacturing High Potency Active Ingredients (HPAPIs), puts us in a unique position of trust with the global pharma industry.

Throughout Helsinn’s 40 plus year history we have put a premium on continuing investment in our facilities to make sure they are able to maintain the highest-possible levels of production quality and safety. To make sure we retain our leading position, we are reviewing our systems against our own exacting standards as well as industry developments. Our two plants, Helsinn Advanced Synthesis and Helsinn Birex are constantly upgraded and maintained to remain fully compliant with global regulations as established by the FDA, EMA, Swissmedic, Japanese PMDA and PIC requirements.

Our commitment to quality is increasingly recognised by our peers, leading us to be a trusted partner for many of the best-known names in the drug development industry. In 2016, our efforts were recognised, for the second year running, with several awards at the CMO Leadership Awards, which recognize the highest quality contract manufacturing organizations as chosen by real customers.

In early 2017 we announced a plan for a major upgrade to the manufacturing and development footprint for Helsinn Advanced Synthesis in Biasca, Switzerland, to reflect the growing demand for anticancer therapies. Due to these upgrades in our technological capability, Helsinn Advanced Synthesis’s capacity will be significantly increased and we look forward to working with several new customers. The development of the new facility will be completed by the end of 2018.

At Helsinn we have built one of the highest-quality manufacturing facilities in the world and we are committed to maintaining our focus on quality the next years ahead. We look forward to meeting and working with you, our customers and stakeholders, to respond to your needs and to innovate to maintain our industry-leading position.

Waldo Mossi
Local General Manager
Chemical Business
Helsinn Advanced Synthesis
Helsinn Advanced Synthesis SA (HAS) develops and manufactures Active Pharmaceutical Ingredients (APIs), Advanced Intermediates, High Potency Active Pharmaceutical Ingredients (HPAPIs), and most recently anticancer compounds for third parties under cGMP on an exclusive basis.

Our production plants, located in Biasca, Switzerland, were first established in 1983 and have gone through continuous expansions and renovations to keep up with the latest technology trends.

Holding a GMP certificate since 1984, production has been completely dedicated to products requiring cGMP, with a clear focus on resources for the Pharmaceutical Industry. Furthermore, HAS has placed a high level of focus to our internationally recognized Quality System. Since early 2000 our plants have been ISO 14001 certified, confirming Helsinn’s commitment towards International environmental protection. The continuous work on Health, Safety & Environment (HSE) also led to the OHSAS 18001 certification in 2005; we were one of the first chemical plants in Switzerland to achieve this status.

The “Helsinn Advanced Synthesis Sustainability Report” was approved and issued in 2012 by GRI (Global Reporting Initiative). Helsinn Group’s first Sustainability Report, issued and approved by GRI in December 2015, provides an updated situation of its production facilities at HAS.

For API and cGMP Advanced Intermediates, production scale ranges from kilograms to tens of tons for clinical and commercial use. For HPAPIs, production scale is from grams to hundreds of kilograms. For anticancer compounds, production scale is from grams up to tens of kilograms. HAS is constantly making large investments to increase production capacity and more importantly add new technologies to increase production flexibility.

Our values of respect, integrity and quality are reflected in everything we do.
R&D Development Capabilities

Contract manufacturing for the development and manufacturing of New Chemical Entities (NCE) is based on confidentiality and full trust of your manufacturing partner.

Our reputation and quality record allows our client to feel complete confidence in HAS as their partner of choice.

Process Evaluation

After signing a Confidentiality Agreement and the Request for Proposal and the technical package have been received, Helsinn’s R&D Group together with Business Development and Logistics put together a project proposal. The supply chain experts are involved from the beginning to ensure optimization of the costs and quality of starting materials. Before submitting the project offer, discussions with our client will clarify the possible registration strategy with the support of our regulatory experts. This allows us to fine tune the project timeline needs and optimize global project costs by including the necessary activities to reach the end goal, which in many cases is the filing of an NDA. The quotation submitted to our partner therefore not only includes cost and timelines but also a mix of several services to be considered in order to successfully support the critical clinical phases as forecasted with high quality material and documentation.

Technology Transfer (TT)

The Technology Transfer (TT) phase forms a crucial part of the execution of any project involving transfer of know-how on the process as well as analytical procedures and documentation. Helsinn’s long-term experience with over 100 projects successfully transferred over the past 30 years and the procedures in place will ensure a smooth transfer from the laboratory to production. Each Project will be assigned a Project Team during the TT.

R&D Development Capabilities

During the Laboratory Implementation phase, we ran multiple laboratory trials to gain familiarity with the process. Depending on our client’s needs, optimization activities may occur to increase yield and develop a robust process that will be ready for scale up.

The Project Team gains confidence and know-how with the process prior to scale up activities. Below is a summary of activities performed during this phase:

- Glass reactors ranging from 250 mL to 5 L are used to conduct laboratory trials and produce laboratory samples for process familiarization prior to scale up
  - Process implementation at laboratory scale
  - Confirm robustness/repeatability of the process
  - Process ready for scale-up in cGMP manufacturing plant

- Flow Reactor technology available
- Flexy Lab Systag System to study process parameters in order to determine which parameters are critical
  - 4 x 250 mL reactors in parallel
- Process risk analysis to ensure that the process is safe and ready for scale up
- DOE approach to establish a design space
- Preparative HPLC to isolate impurities
- Process development and optimization
  - Adaptation of the process to HAS facility
  - Evaluation of the possibility to increase yields
  - Improvement and industrialization of the laboratory process
cGMP APIs and Intermediates

Helsinn has a large flexibility in reactor sizes for small molecule classical APIs. All reactors have their corresponding receivers. The chart below gives a good cross section of where we provide services based on the phase of drug development you are in.

**cGMP Process Scale-up**
- kg quantities in our cGMP scale-up plant (100 and 250 L reactors)
- Stainless steel, glass-lined reactors
- Process verification and fine tuning

**Production**
- Flexible range of 1’000, 2’500, 4’000, and 6’300 L reactors including a (−80 °C) reactor for metallorganic chemistry
- Stainless steel, glass-lined & Hastelloy

**Isolation**
- Horizontal peeler centrifuges
- Basket centrifuges
- Pressure filter

**Drying Unit**
- The final processing step in API manufacturing fulfils the conditions of final dosage form production
- Biconical rotary vacuum dryer (2000 L and 4000 L reactors) ISO 8

---

**HAS: API Development & Manufacturing | Services Overview**

<table>
<thead>
<tr>
<th>Market</th>
<th>Commercial Supply</th>
<th>Yearly Report Audit</th>
<th>Ongoing Stability Program</th>
</tr>
</thead>
<tbody>
<tr>
<td>NDA</td>
<td>Process Validation</td>
<td>NDA Submission</td>
<td></td>
</tr>
<tr>
<td>Phase III</td>
<td>Production of 3 Registration Batches</td>
<td>Audit DMF</td>
<td>Stability Program for DMF Submission Powder Flowability</td>
</tr>
<tr>
<td>Phase II</td>
<td>Scale-up and Supply of API for Next Phase</td>
<td>Methods Validation</td>
<td>CMC Updates &amp; Agency Interaction</td>
</tr>
<tr>
<td>Phase I</td>
<td>Synthetic Route Optimization Kg Quantities</td>
<td>Finalize Methods Definition of all Specifications</td>
<td>CMC Preparation &amp; IND Submission</td>
</tr>
<tr>
<td>Pre-clinical</td>
<td>Synthetic Route Mapping Grams Quantities</td>
<td>Methods Finding</td>
<td>Stability Program for Supportive Data Polymorphism Program</td>
</tr>
</tbody>
</table>

**Additional Services**
- Salt and Polymorphism Screening and Selection Patent Services
Highly Potent APIs (HPAPIs)

High Therapeutic Activity - Potent Low Dose Compounds require product handling in containment facilities which provide the necessary protection for personnel, the environment and for the product itself.

Helsinn’s expertise and reputation in this highly specialized area has been recognized world-wide by customers and agencies alike across the US, Europe, and Japan. Several HPAPIs have already been successfully produced in our multi-purpose production plant. With over 15 years of experience handling highly potent molecules, our highly skilled team has produced numerous HPAPIs in therapeutic areas including: CNS, Cardiovascular, Respiratory, Dermatology, and Cancer Supportive Care.

In terms of manufacturing, we can offer three levels of production dedicated to HPAPIs.

- The Pilot Scale HPAPI Production Center, in operation since 2006, with 25 and 30 L reactors producing ~ 50 to 500 grams of material, process dependent
- The Small Scale HPAPI Production Center, in operation since 1999, is a multipurpose facility with 100 and 250 L reactors producing ~ 1 to 7 kg, process dependent
- The Large Scale HPAPI Production Center with 4000 L reactors is able to produce from ~ 25 kg up to hundreds of kgs, process dependent.

The chart below is the banding system that we have adopted. When working with highly potent and anticancer compounds, the first step is to define the containment level based on product characteristics.

### Control Banding System | Categorization

- 3a - Capable of handling material OEL ≥ 1 µg/m³
- 3b - Capable of handling material OEL ≥ .05 µg/m³ or 50 ng/m³

### Occupational Exposure Limit (OEL) µg/m³

<table>
<thead>
<tr>
<th>[&gt;500]</th>
<th>[500 - 10]</th>
<th>[10 - 0.03]</th>
<th>[&gt;0.03]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

*Note HAS 3b goes down to .05 µg/m³ whereas Safebridge 3 goes down to .03 µg/m³*
Categorization
Tools used to categorize molecules and define whether the project is HPAPI or anticancer include:

- Mode of action
- Toxicological data
- Literature
- MSDS

We have taken the Safebridge system and further defined Category 3 [Occupational Exposure Limits (OELs) range from 30 ng/m³ to 10 µg/m³] into two sections: 3a and 3b. Our 3a Category includes highly active materials with an OEL > 1 µg/m³ and our 3b Category includes highly active materials with an OEL > 50 ng/m³.

Containment
The primary containment used at HAS for both highly potent and anticancer compounds is the glovebox technology which has the following attributes:

- Air exhaust of the glove box passes through HEPA filters
- Operators can’t directly access compound
- Dangerous substances can’t be released in the environment
- Cleaning verification measurable
- Must be equipped with alarm in case of malfunction

The secondary containment is an airlock system which limits the powders released. This allows the material to be contained in the limit of the bay and the system enables decontamination. The pressure cascade regime is set up and maintained using airlocks. The Bubble kind airlock avoids cross contamination through high pressure on the inside of the airlock with lower pressure on both outer sides.
Anticancer Compounds

We have built a dedicated anticancer plant exclusively for the development, analysis and manufacturing of clinical and commercial anticancer APIs. The design of HAS facility offers complete independence from existing API and highly potent API areas to segregate production and anticipate pharmaceutical trends and future regulatory restrictions.

Laboratories

New dedicated laboratories have been constructed exclusively for R&D trials, design of experiment, initial process development, as well as QC activities.

cGMP Production

The anticancer Plant is segmented into three levels of production. Each production area is designed using state-of-the-art closed system equipment with variable air pressure and engineering controls designed to protect HAS employees, the environment and the integrity of your product.

In terms of manufacturing, we can offer three levels of production dedicated to anticancer compounds.

• The Pilot Scale anticancer Production Center with 20 and 30 L reactors can produce ~200 grams to 3 kg of material, process dependent
• The Medium Scale anticancer Production Center with 250 and 400 L reactors can produce ~3 to 20 kg, process dependent
• The Large Scale anticancer Production Center with 630 and 800 L reactors can produce up to ~30 kg, process dependent

Facility Design Highlights

• Temperature range: -80 °C up to +150 °C
• Pressure range: Up to 6 Bar
• Specific design and equipment to meet stringent OEL limits down to 50 ng/m³
• Additional safety measures for superior Health Safety & Environment (HSE) protection
• Closed system from raw material
When transferring a new project to HAS, you will be assigned an Analytical Lead. Depending on our client’s needs we can develop methods, transfer a method already in place or improve the method that is transferred.

Once it moves from R&D to QC we can validate the method, if requested.

Data Management Tools

- **LIMS** (Laboratory Information Management System): Sample Manager (Thermo)
- **CDS** (Chromatography Data System): Empower (Waters) and ChemPlus (Agilent)
- **LaPIS** (Laboratory Paperless System) using SDMS and Vision Publisher (Waters)
- **EDMS**: Electronic Document Management System

Stability

We have stability chambers available and will customize its program to meet our client’s requirements.
After successful technology transfer and subsequent production of either clinical batches, registration batches, or validation batches, the documentation is prepared for the following purposes: filing an IND, end of Phase II meeting, NDA submissions, DMFs in eCTD format, etc.

The HAS Regulatory Group has supported our partners in product registrations over the past 30 years. Therefore we possess expertise and know-how that few of our competitors meet.

FDA inspections, the most recent of which was in April 2014, have not resulted in any 483s. This is highly valuable to our partners who recognize and appreciate the smooth review and approval of submissions, saving both time and money.

**Quality**

The Quality Division at Helsinn is staffed with highly qualified individuals with a vast knowledge of the pharmaceutical industry.

Our Quality system is based on cGMP and fully complies with the requirements of 21 CFR part 211, 21 CFR part 212, 21 CFR part 11 and ICH Q7.

Besides the customer and regulatory audits, internal audits are performed by QA and Corporate QA to ensure the compliance of our Quality system is exceptional.

**Sustainability**

The Helsinn Advanced Synthesis Sustainability Report was approved by GRI (Global Reporting Initiative) in 2012.

Helsinn Group’s first Sustainability Report, issued and approved by GRI in December 2015, provides an updated situation of its production facilities at HAS.

### Inspections

<table>
<thead>
<tr>
<th>Agency</th>
<th>Date</th>
<th>483s</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA PAI Inspections</td>
<td>Jun-03</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Sep-07</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Apr-12</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Apr-14</td>
<td>0</td>
</tr>
<tr>
<td>Swissmedic</td>
<td>Nov-08</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Nov-10</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Jan-13</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Feb-15</td>
<td>0</td>
</tr>
<tr>
<td>KFDA (Korea)</td>
<td>2005</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Jun-11</td>
<td>0</td>
</tr>
<tr>
<td>PMDA (Japan)</td>
<td>2010</td>
<td>0</td>
</tr>
</tbody>
</table>

**ISO 14001**

All Manufacturing sites operate in accordance with Environmental Management System and operate under a Safety Management System.

**OHSAS 18001**

We have been awarded the Occupational Health and Safety Assessment Series (OHSAS) 18001 certification since May 2005. HAS was one of the first Swiss chemical manufacturing sites to achieve this certification.
Contact Information

Helsinn Advanced Synthesis S.A.
Via Industria 24
6710 Biasca – Switzerland
tel. +41 (0) 91 873 94 00 – fax +41 (0) 91 873 01 11

Registered Office as above.
Registered in Lugano, Switzerland No. CH-514.3.003.432-4

For contract manufacturing services
and inquiries please contact:
Phone +41 (0) 91 873 94 00
Fax +41 (0) 91 873 01 11
Email: manufacturing@helsinn.com
www.helsinn.com