



Boehringer Ingelheim Pharma Chemicals

Integrated Launch Services for Drug Substance and Drug Product



Boehringer
Ingelheim

Integrated End-to-End (E2E) Launch Services for Drug Substance and Drug Product

Putting the spotlight on Boehringer Ingelheim's superior value proposition, we offer our complete range of clinical phase II/III development services for drug substances and drug products to industrial customers.

Our services:

- ▶ cGMP synthesis of new chemical entities (drug substances)
 - Chemical synthesis
 - Plant extraction and purification
- ▶ Manufacturing of a wide array of finished dosage forms (drug products)
 - Solids and liquids
 - Steriles

Our consolidated expertise in handling both complex chemistry and demanding formulation development projects assures our customers of a secure and robust just-in-time supply chain for active pharmaceutical ingredients (APIs) and finished dosage forms.

Boehringer Ingelheim's integrated end-to-end (E2E) launch services for drug substances and drug products offer to industrial customers the following advantages:

- Short time-to-market through optimal project plan integration for drug substance and drug product development
- Dramatically reduced level of complexity of project monitoring
- Dedicated and experienced project management for both API and finished dosage form (E2E services)
- Renowned and unparalleled experience of 125 years in the business, with proven track record for successful worldwide product launches
- Strategic partnership with a financially stable, family-owned company with a long-term view on business
- Access to a network of Western EMEA and FDA-approved cGMP facilities

- Professional consultancy regarding compliance with evolving regulatory requirements in worldwide markets
- Well-established highest quality and safety standards

We understand that innovators strive to develop the optimum processes for the manufacture of drug substances and drug products in the shortest possible time-to-market. In order to support our customers in meeting this challenge, we offer to minimise the level of complexity in the management of projects. This goal is achieved by Boehringer Ingelheim's unique value proposition to provide integrated launch services for both chemical and formulation development projects from clinical phase II onwards.

This superior **end-to-end launch concept** for industrial customers allows for lean and comprehensive coordination of the complete development value chain for both drug substances and drug products. Our integrated approach assures customers of the best possible time-to-market combined with reduced total costs of ownership. And our customer's desire for optimal intellectual property protection has always been respected in our company's 125-year history.

WHY BOEHRINGER INGELHEIM ?

We offer world-class pharma expertise, innovation and service for drug substances and drug products. Our open and honest communication is the foundation of our successful partnership model, as it avoids unexpected costs, mitigates risk of failure and assures short time-to-market. We are committed to support you long-term - for your product's launch success.

Pharma Chemicals presented with USP award

In April 2009, Boehringer Ingelheim Pharma Chemicals was host to an unprecedented visit to the Ingelheim site by Roger L. Williams, M. D., Chief Executive Officer of the world-renowned United States Pharmacopeia (USP), the official public standards-setting authority for all prescription and over-the-counter medicines and other health care products made or sold in the USA.

During his visit, Mr Williams delivered an award to Pharma Chemicals in recognition of its excellent cooperation over many years on product monographs. These detailed descriptions for drug substances and preparations are featured in the USP, as well as monographs for dietary supplements and ingredients. Excipient monographs are contained in the US National Formulary (NF). The USP–NF is published as a three-volume book of public pharmacopeial standards (also available online).

Securing USP approval of monographs forms an important part of the process of gaining US registration for products from the US Food and Drug Administration (FDA), although the FDA is not obliged to accept USP recommendations.

Monographs include the name of the ingredient or preparation, the definition, packaging, storage, and labelling requirements and the specification, which consists of a series of tests, procedures for the tests, and acceptance criteria.

As the USA is the world's leading pharmaceutical market and the largest generator of Boehringer Ingelheim sales, close cooperation with the USP and the US regulatory authorities is vital to the company's commercial success.

Unlike its counterparts in Europe and Japan, the USP, based at Rockville, Maryland, is a non-governmental, non-profit public health body. But it enjoys a quasi-official status and the reference standards it sets, used in more than 130 countries, help to ensure the quality, purity, strength, and consistency of products made for public consumption.

The delegation that visited Ingelheim was led by Mr Williams, CEO of the USP since 2000, and included Richard Wailes, Vice President, Sales and Marketing and Alex Fiechter, Senior International Account Manager, Europe/Middle East/Africa. Representing Pharma Chemicals at talks with the delegation were Dr Joachim Leven, Team Leader, and Dr Andreas Schmidt, Head of API Compliance.

Topics discussed included future active ingredient projects, exchanges with cooperation partners and the development of patent-protected substances. The latest products and projects

being worked on with USP involve homatropine methyl bromide and tropium chloride. The possibility of amending the monograph for epinephrine was also addressed at the Ingelheim meeting.

Dennis Seagle, Head of Global Pharma Chemicals Business, was very pleased to hear that Boehringer Ingelheim received this award. "As a business unit of an ethical pharmaceutical company, we know very well that API's have a significant impact on patients' safety. We therefore view it as our obligation to support the work of the USP; and it is always nice to know that a commitment is recognised."



In Recognition of Boehringer Ingelheim Monograph and Bulk Material Donations, April 2009.

Tropane – Alkaloid Building Block

Boehringer Ingelheim has a long history in tropane alkaloid chemistry. Originally, the company entered the field by extracting and purifying alkaloids from medicinal plant material.

Thanks to its full back-integration with its own plantations, the company actively takes care of customers' supply security and is recognised as a reliable partner in risk management strategies. As a complementary service, the company offers fully synthetic tropane alkaloids and their derivatives, opening new horizons in the variability of substitution patterns.

Based on a bicyclic spine, tropane alkaloids are widely found in the plant kingdom in most parts of the world. The more than 140 naturally occurring tropane alkaloids serve mankind in many different ways.

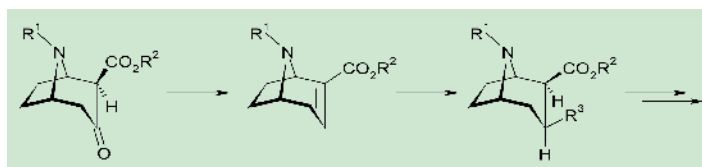
In violent and bloody ancient times, people not only discovered the beneficial aspects of tropane alkaloids, but also their deadly side. For example, over 20,000 years ago, during the European stone age, extracts of *Atropa belladonna* were used as arrow poison and Roman emperors took the very same extract to eliminate their enemies. But, the mydriatic effect of *Atropa belladonna* has also been known since ancient Greece and has been popular down the centuries.

Today, the beneficial aspects of this class of alkaloids dominate by far. Naturally occurring tropane alkaloids and their synthetic derivatives optimised onto their biological target are widely used as therapeutics. These active pharmaceutical ingredients (APIs) are, for example, commonly used in the field of ophthalmology, parkinson, oncology, infectious disease treatment (HIV), microbiological infections, asthma, obstructive lung disease and gastrointestinal treatment. The spasmolytic and anti-emetic effect of tropane alkaloid derivatives are also medically useful.

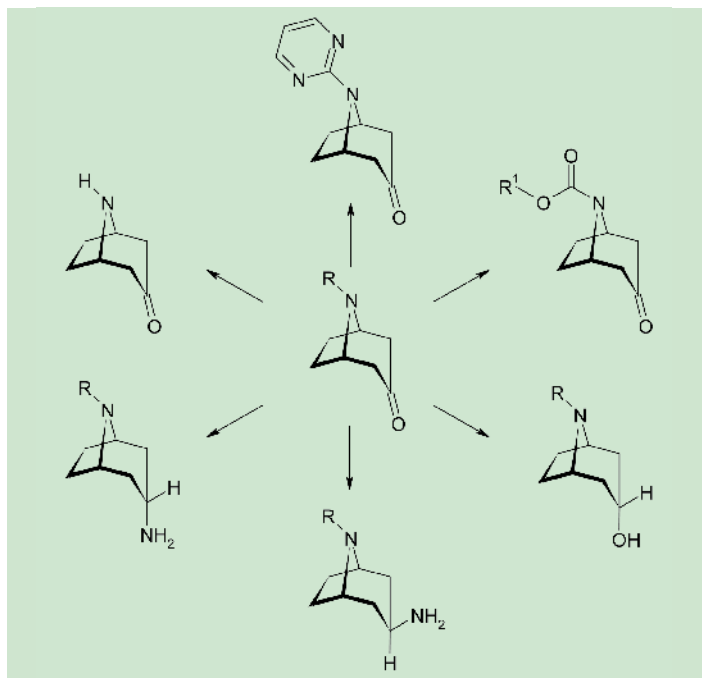
Being well-experienced in the field of tropane alkaloids, Boehringer Ingelheim is the partner of choice for customers



Dr Friedrich Bischoff,
Business Development Manager
Phytochemicals



Scheme 1: Examples for Ecgonin-like tropane alkaloid derivatives



Scheme 2: Examples for Tropine-like tropane alkaloid derivatives

striving for sustainability, best quality, optimum results and high added value to their products.

Boehringer Ingelheim offers

- Excellent tropane alkaloid supply security
- Expert choice of the optimum alkaloid source based on criteria such as economics, follow-up chemistry, impurity profile, residual solvents
- Medicinal plants extraction capacity up to 1000 t/year
- Tropane alkaloid platform based technology tool-box
- Tailor made tropane alkaloid derivatives delivered at short notice
- Up-scaling readiness from kg to ton scale
- Contract manufacturing downstream chemistry services
- Regulatory support
- Experience with import and export restrictions

Boehringer Ingelheim is committed to support its customers long-term. With real commitment, true continuity, process excellence and extraordinary enthusiasm the company contributes every day to customers' success stories.

Methylphenidate Growth Continues Worldwide

Methylphenidate has been a growing and sometimes controversial product since its discovery by Swiss chemist Leandro Panizzon in 1944 and its subsequent launch as a drug product in 1954. Its primary use continues to be treatment of attention deficit hyperactivity disorder (ADHD).

The acceptance of ADHD as a legitimate diagnosis and the use of psychotropic drugs to treat disorders has grown steadily, at first notably in North America, but also in recent years in Europe and more recently in Asia. This growth has prompted the discussion in each society as to whether ADHD is a matter to be treated with pharmaceuticals or is a behavioural issue better handled in other ways.

Boehringer Ingelheim's experience with methylphenidate started in the 1990's when the company decided to build a controlled substance capability at its site in Petersburg, Virginia, USA. Methylphenidate is regulated in the USA by both the Food and Drug Administration (FDA) and the Drug Enforcement Agency (DEA) and is classified by the DEA as a Schedule II compound. Similar regulatory control and product classification for methylphenidate exist around the globe. Boehringer Ingelheim successfully initiated production of methylphenidate active pharmaceutical ingredient (API) in 1999 and it currently is an important product in its Pharma Chemicals business.

As a treatment for ADHD, methylphenidate is now accepted in over 40 countries worldwide. Drug product is available in numerous forms, including tablets, capsules, solutions and patches. Various extended release formulations have been developed



and marketed with the intent of maximising effectiveness and allowing children to take the medicine at home, outside school. Development work on new forms and formulations continues, as does the expansion into new markets, both efforts contributing to a double-digit annual growth rate for methylphenidate.

Boehringer Ingelheim now ranks as one of the world's largest producers of methylphenidate API and has worked with the regulatory agencies of numerous countries gaining approvals for methylphenidate worldwide. Recently, the Japanese Pharmaceutical and Medical Devices Agency (PMDA) completed a successful audit of Pharma Chemicals' Petersburg site specifically for methylphenidate.

While discussion around the suitability of drug treatments for ADHD diagnosis will no doubt continue, it is clear families that try this treatment are frequently satisfied and continue its use. For the foreseeable future, the expectation is that pharmaceutical treatment for ADHD will continue to develop both in drug product forms and in geography.

Boehringer Ingelheim remains committed to this API and the field of controlled substance manufacturing. Recent investments at the Petersburg site bolster the company's capability in this area. Boehringer Ingelheim is proud to contribute its reliable and efficient manufacturing capability to methylphenidate.

AT A GLANCE

Product Name:	Methylphenidate hydrochloride
Manufacturing Site:	Petersburg, Virginia, USA
Manufacturer:	Boehringer Ingelheim Chemicals, Inc.
Grade:	USP
Purity:	Min 98% by HPLC
Water Content:	Below 0.5%
ROI:	NMT 0.1%
Standard Packaging:	50 kg



Ice-cold for new active ingredients

In Synthesis A1 plant at our site at Ingelheim, Germany, a 2.5 m³ reactor has been set up that in test runs has achieved minus 70 centigrade. Initial experience with the new reactor has fulfilled all expectations for the new technology and process.

Dr Thomas Wirth, Head of Synthesis A1, explains that some modern chemistry, like organolithium reactions or asymmetric reductions need to be run at low temperatures to enhance selectivity and reduce side reactions.

The new reactor's capacity will enable Boehringer Ingelheim to produce APIs in large volumes and ensure that market demand is met. The Euro 1.6 million installation will be used to produce several APIs, currently in development, that require extremely low temperatures in the production process.

Modern APIs are increasingly comprised of complex molecules that require increased investment in production. The trend is towards rapid development of the synthesis process and the extremely low-temperature reactor is today an essential part of the tool kit of modern chemistry.

Pharma Chemicals participates at the InformEx 2010 – North America's leading Fair for New Business Development.

Join us in San Francisco, California from February 16–19 at booth 528

Event details are posted at www.informex.com

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