

## Boehringer Ingelheim celebrates 100 years of phytochemicals



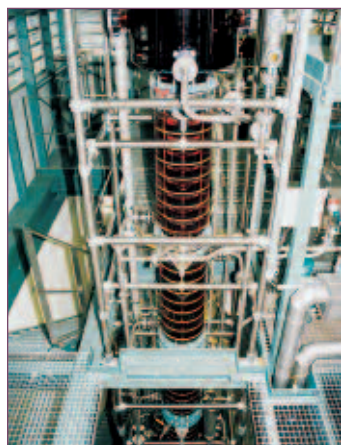
One hundred years ago in 1905, Boehringer Ingelheim built its first manufacturing facility for phytochemicals in Ingelheim, Germany. Phytochemicals are natural products extracted and purified from plants. Some of the first commercially manufactured phytochemicals in BI's facilities were opiates like morphine and codeine.

The Boehringer Ingelheim group of companies is still a world leader in phytochemicals and is actively involved in all facets of phytochemical production, including crop cultivation on company-owned plantations, extraction, derivatization, commercial production and distribution.

"While many pharmaceutical companies around the world have ceased phytochemical production, Boehringer Ingelheim has continued to invest in plantations, horticulture technology, and in recruitment and development of the very best people in this field," said Dr. Manfred Psiorz, Vice President of Technical Operations at

Boehringer Ingelheim Chemicals, Inc. (BICI) in Petersburg, Virginia. Therefore, BICI is able to provide its customers the best technical solution and security of supply along the entire value chain.

Boehringer Ingelheim produces phytochemicals that treat a range of medical conditions, including cancer, heart disease, lung disorders, and digestive system disorders. Boehringer Ingelheim manufactures phytochemicals for



This extraction column isolates the active ingredient digoxin from the plant.

many pharmaceutical companies as well as for its own branded products, Psiorz said.

Boehringer Ingelheim launched its first patent-protected, phytochemical-based medication, Laudanon®, in 1915. The efficacy of this opiate-based painkiller was demonstrated by data from clinical trials. In the following decades, Boehringer Ingelheim introduced other phytochemical-based drugs, including a cough suppressant

called Codyl® Syrup and the respiratory stimulant drug Lobeline.

In 1951, Boehringer Ingelheim launched Buscopan® after 20 years of research on scopolamine derivatives. This spasmolytic drug is still used worldwide for treating the painful spasms related to kidney stones, gallstones and colonic motility disorder, said Dr. Rainer Becker, Boehringer Ingelheim GmbH's product manager for phytochemicals. Further



Dr. Rainer Becker



Dr. Manfred Psiorz

research showed that bronchospasms could also be treated with tropane derivatives so the company developed ipratropium bromide as an active ingredient and launched as Atrovent® (1975) and Combivent® (1994). The newest commercially launched phytochemical-based product is Spiriva®. The drug, which was launched in 2002, uses tiotropium bromide as its active ingredient and is used for treatment of chronic obstructive pulmonary disease (COPD).

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Long-term research in phytochemicals yields high-quality products.



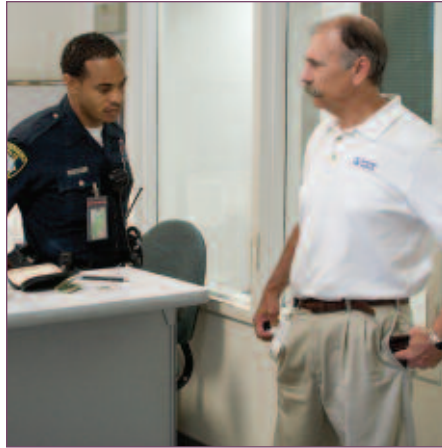
## BICI manages controlled substance quotas through constant communication with DEA and customers

Boehringer Ingelheim Chemicals, Inc.'s (BICI) excellent relationship with the Drug Enforcement Administration (DEA) helps ensure that BICI can consistently fulfill its customers' orders for controlled substances such as methadone and fentanyl.

The DEA regulates the nation's supply of controlled substances, which are divided into five Schedules. Because Schedule I and II substances have the greatest potential for abuse and addiction, the DEA enforces quotas for the quantity of these substances that can be manufactured and sold. BICI manufactures and sells a broad range of controlled substances.

To be responsive to customer needs, BICI stays in constant communication with customers and the DEA to ensure that it has the required regulatory authority to manufacture the appropriate amount of controlled substances, said David McGee, a Marketing Manager for the company.

"In many cases," McGee said, "we coordinate our applications for additional manufacturing quota with our customers' requests for additional procurement quota. This cooperation is really important as the customers' requests for additional quota greatly bolster our request for additional manufacturing quota."



*DEA - trained police officers provide security at BICI*

BICI's excellent relationship with the DEA stems from its continuing effort to strictly adhere to and in many cases exceed the requirements of the Agency's regulations.

"We are very sensitive to our relationship with the DEA to ensure they get everything they need from BICI in a timely and accurate manner and that the DEA understands how committed we are in seeking to be in full compliance with the spirit, not just the letter, of the laws and regulations," said Allyn Carnam, senior division counsel for BICI and a former trial attorney with DEA's office of Chief Counsel.



*Secure vaults protect controlled substances from diversion at BICI*

The goal, he said, is "to do everything we can to ensure our products are not diverted to the illicit market."

BICI exceeds requirements by employing DEA-trained police officers, using a sophisticated video monitoring system, conducting random searches as people exit the manufacturing plant, and conducting extensive background checks and random drug testing of employees and contractors who work on BICI's site.

Currently, BICI manufactures the pain-management medications methadone, fentanyl and dextropropoxyphene, as well as other controlled substances on a custom basis.

*"The goal is to do everything we can to ensure our products are not diverted to the illicit market."*

— Allyn Carnam, Senior Division Counsel for BICI



*Allyn Carnam*

## DEA approves manufacture of dronabinol at BICI

On July 27, 2005, BICI received registration from the Drug Enforcement Administration (DEA) to manufacture tetrahydrocannabinols, a Schedule I controlled substance. Upon receipt of this registration, BICI began development and scale up activities for dronabinol (delta-9 tetrahydrocannabinol). Dronabinol (tradename: Marinol®) has been approved by the FDA for treatment of nausea and vomiting from cancer chemotherapy, for the treatment of anorexia and for weight loss in AIDS patients.

“The DEA aggregate manufacturing quota for tetrahydrocannabinols has grown at over 22% per year over the past five years, driven primarily by increasing demand for dronabinol,” said David McGee, a Marketing Manager for BICI. McGee said, “We look forward to meeting our customers’ growing demand for dronabinol in these critical therapeutic areas.”

BICI’s dronabinol synthesis process is fully synthetic and does not use any DEA controlled raw materials. BICI’s process does not involve extraction from *cannabis sativa* (marijuana) or other plant species.

## BICI’s systematic approach to quality helps ‘conquer the complexity of the business’



Bill Ferguson

Compliance with FDA requirements assures product quality, but Boehringer Ingelheim Chemicals, Inc. (BICI), approaches quality even more comprehensively. It seeks to improve every system and every process in not just manufacturing but also in accounting, information technology, training and every other component of the company. Customers of BICI can expect constant improvement in efficiency and reliability thanks to improvement initiatives already in place.

Notes Bill Ferguson, Director of Business Process Excellence, quality improvement has become instilled and ingrained throughout the BICI organization. At BICI, the study of processes is itself a process, and its mission is to make the company competitive while maintaining the highest possible standards of quality.

“What distinguishes BICI,” he said, “is that the campaign for quality is internally driven, not because a customer directed or required it.”

BICI’s commitment to continuous improvement draws on the *Pareto Principle*, which holds that 20 percent of a situation causes 80 percent of the problems. “Keeping that in mind helps us to set our priorities,” Ferguson said.

BICI’s journey towards competitiveness combined with quality is summarized in the company’s use of the tools of the Lean Six Sigma approach.

- The widely used Six Sigma approach seeks ways to reduce defects by using a variety of tools to eliminate variation by making systems safe, reliable and predictable.

- The Six Sigma tools of quality are combined with “Lean” to improve speed and efficiency and reduce costs; “Lean” focuses on factors that cause congestion and delay and seeks to speed up the process of implementing changes.

Says Ferguson, “Lean Six Sigma allows you to conquer the complexity of the business.”

To measure the effectiveness of the quality systems, BICI’s facility in Petersburg, Va., is evaluated under the ISO 9001:2000 certification process. Ferguson said BICI was one of the first five companies to be certified in the 2000 version of ISO 9001 and that it recently attained re-certification with two commendations and without a single adverse finding. ISO refers to the International Organization for Standardization. An independent external body conducts the certification process.



Bill Ferguson works closely with a supply chain team to streamline BICI’s processes.

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Boehringer Ingelheim is a trusted supplier of phytochemical drug substances to many other pharmaceutical companies, Becker said. Not only are Boehringer Ingelheim's products of the highest quality and purity, as they are manufactured under current Good Manufacturing Processes, but the company also supplies its customers with important documentation to support regulatory filings.

Unlike other phytochemical producers, Boehringer Ingelheim ensures a secure and consistent supply of raw materials by cultivating its own plants. Boehringer Ingelheim owns or contracts with plantations throughout the world to effectively manage harvests in various climates and geographical conditions. By careful planning, BI ensures continuous supply of critical raw materials.

Boehringer Ingelheim is a leading supplier of camptothecin and its derivatives. Several camptothecin-derived anticancer

compounds have been commercialized or are in development, Becker said. The company is also a leading supplier of the world market for digoxin, an active ingredient isolated from foxglove, and a standard treatment for congestive heart failure.

Boehringer Ingelheim is recognized as a competent partner for custom solutions for phytochemicals, which include small scale and up-scaling processes as well as extraction, chemical derivatives and selected total synthesis. Currently several projects on a confidential and exclusive basis are under development, Becker said, and, the company looks forward to continued work in the pharmaceutical industry for custom solutions and manufacturing of phytochemicals in the future.

## Phenylephrine news update

Legislative measures to restrict the sale of cold medicines containing pseudoephedrine, a precursor chemical used to make methamphetamine, continue moving forward. Seventeen states have now put pseudoephedrine-containing products behind the sales counter, and 40 states have enacted some type of restriction. Oregon has moved to require prescriptions for pseudoephedrine-containing medications. Federal legislation restricting pseudoephedrine sales is also moving forward. The U.S. Senate unanimously passed provisions known as the Talent-Feinstein bill on Sept. 9, 2005, and the bill is headed for a Senate-House conference committee.

Boehringer Ingelheim Pharma KG in Germany is the world's largest producer of phenylephrine, an alternative to pseudoephedrine in cold medicines. Boehringer Ingelheim Chemicals, Inc., (BICI) is planning to install capacity at its manufacturing facility in Petersburg, Va., to produce phenylephrine in 2006. Phenylephrine cannot be used to make methamphetamine, and there are no restrictions on the use of phenylephrine.

BICI also offers a hydrogentartrate salt of phenylephrine that has been found to have superior performance in certain formulations. A USP monograph has been submitted to the Food and Drug Administration, where it is under consideration for Generally Recognized as Safe status. This will provide BICI's customers greater flexibility in their formulation development.



*Belgium, site of CPhI Worldwide in 2004.*

## Come see us in Madrid At Hall 10, Stand 10E36

The Boehringer Ingelheim Group will be exhibiting once again at CPhI Worldwide, which will be held November 1-3, 2005, at the Feria de Madrid in Madrid, Spain. Boehringer Ingelheim's booth will be located in Hall 10 at Stand 10E36. This year's show is expected to attract approximately 20,000 leaders in the chemical and pharmaceutical industry from 110 countries. Last year's CPhI show was in Belgium.

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For further information about BICI or any of the products or processes in this newsletter, click on [www.boehringer-ingelheim.com/finechem](http://www.boehringer-ingelheim.com/finechem), or contact Deborah Barnes-Taylor by phone at 804-504-8617 or by email at [solutions@bichemicals.com](mailto:solutions@bichemicals.com).