

In the Spotlight: Fresenius Kabi USA, the North American Plants

Our spotlight in this issue is on **APP Pharmaceuticals Inc.**, the newest member of the Fresenius Kabi group. The acquisition of APP in 2008 has given Fresenius Kabi an entry into the U.S. pharmaceutical market and a leading position in the global I.V. generics industry.

APP Pharmaceuticals develops, manufactures and markets injectable pharmaceuticals, with important products in the oncology, anti-infective, anaesthetic / analgesic and critical care fields. The company offers one of the most comprehensive portfolios of products used in hospitals, long-term care facilities, alternate care sites and clinics within North America and manufactures a complete range of dosage formulations.

Integrating the APP plants into the Fresenius Kabi global production network means that the group now has a presence with substantial manufacturing expertise and technical capabilities in North America.



APP operates out of three sites, located in upstate New York, Illinois, and North Carolina. The Grand Island facility is located just a few minutes from the spectacular Niagara Falls, near Buffalo. The site employs approximately 600 people in three buildings. The main building houses aseptic wash and fill (terminal sterilization) manufacturing processes. In the other buildings are offices, laboratories, the warehouse, and a new manufacturing area, with some space for expansion.



Another APP site is located in Melrose Park, Illinois, on the outskirts of Chicago and just 5 miles from O'Hare International Airport. The plant is in a general industrial area and employs approximately 350 people. Besides production, laboratory, office and warehouse facilities the plant also has a state-of-the-art microbiology laboratory, opened in

November 2009. The plant also supports the satellite manufacturing facility in Raleigh, NC.

The Raleigh, NC plant is a satellite facility of Melrose Park



dedicated to lyophilization processes. This site north of Triangle Park was built in 1995. The campus is home to a TL8 filling machine and three commercial lyophilization units.

With the APP platform, Fresenius Kabi is able to market its entire product range in the US, and furthermore through its international marketing and sales network to sell APPs products globally. But the acquisition has not only enlarged Fresenius Kabi's internal capabilities - it has also broadened the possibilities and capabilities of Fresenius Kabi Product Partnering. All the technological capabilities of the APP division (see key facts) are also available for external customers, depending on capacity.

Key data Fresenius Kabi USA - the North American Plants

Facilities:

- Grand Island, NY
- Melrose Park, IL
- Raleigh, NC

Containers:

- PFS: 1mL and 5mL
- Plastic vials: 3, 10, 20, 30 & 50 mL
- Glass vials: 2, 3, 5, 10, 20, 30, 50, 100, 125, & 200 mL

Technologies:

- Lyophilization
- Aseptic liquid filling
- Aseptic SCF syringes
- Terminal sterilization

Markets / Certifications:

- US-FDA

Batch-Sizes:

- PFS: max. 30L
- Plastic Vials: max. 1800L
- Glass Vials: max. 2000L

Services:

- QC Support
- Secondary Packaging
- Stability Studies
- Warehousing & Shipping
- Regulatory Support



Product Partnering

Insight

2010 no. 1

Editorial



Fresenius Kabi Product Partnering (FKPP) - a wide and steady outlook

Dear Readers,

I hope you have had a successful transition to the new decade. We often use a moment like this to recapitulate, review and redefine strategy and to look for new horizons. The buzzwords of the age are "change" and "departure". But after the turmoil of the global economic and financial crisis I also see an urgent need for stability and reliability.

FKPP is entering this new decade as a contract manufacturing partner with more than 40 years of experience in sterile products, a broad customer base and a long track record of successfully managed outsourcing projects. By presenting a whole range of technologies, production facilities and contract services our objective is still the same: to enable our partners to market their sterile dosage forms and medical devices, by giving them tailor-made support in developing and manufacturing their product.

To give you some insights into our technologies and capabilities we will once again highlight some FKPP operations and products.

Firstly, we describe the development of sterile drugs in our R&D centre in Austria. Using a state-of-the-art galenic laboratory and a GMP pilot plant we can develop simple sterile aqueous solutions, highly sophisticated formulation systems like emulsions and liposomes, and highly potent powder products.

Secondly, our medical device team presents Ambix Intraport®, an innovative, metal-free port system for intravenous administration of sterile solutions.

And on the final page in our regular feature "In the Spotlight" you find an article about APP Pharmaceuticals Inc., Fresenius Kabi's most recent acquisition. The description of APP's three manufacturing plants should give you an overview of the technologies FKPP is now able to offer out of the US.

If there's any need for further information or specific discussions, Product Partnering team members are available at several exhibitions worldwide, or are only a telephone call away.

For now, we hope you enjoy reading our latest Insight issue.

Sincerely yours,

Anton Gerdenitsch

Exhibitions

- MEDTEC Europe 2010 (March 23-25, Stuttgart - Germany) Booth 2567, Hall B
- Contract Pharma Table Top (Sep 23, New Brunswick, NJ - USA)
- ICSE 2010 (Oct 5-7, Paris - France) Booth 4E43
- Interphex USA 2010 (April 20-22, New York - USA) Booth B40
- Interphex Japan 2010 (June 30 - July 2, Tokyo - Japan)





High quality formulation development at FKPP

How many drug candidates have failed in clinical trials because of the wrong formulation? It's anyone's guess - but probably more than a few.



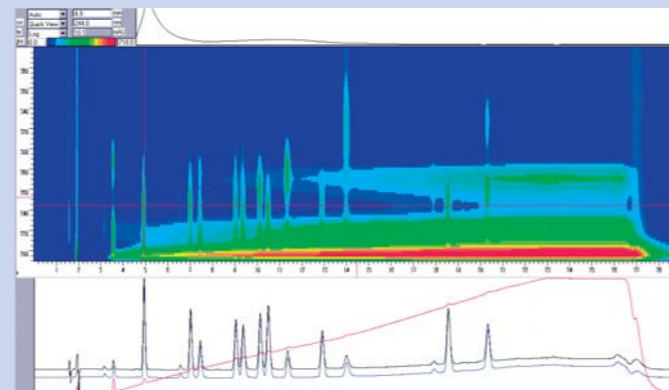
At FKPP, we can help reduce the element of chance with a special formulation development centre at the Fresenius Kabi site in Graz, Austria. The centre is responsible for iv drug development, formulation, manufacturing of clinical batches, and dossier compilation, and is part of our global R&D division, the Kabi Innovation Centre (KIC).

The facility includes both a galenics department, which can manufacture small-scale non-GMP batches, and a pilot plant, which can make GMP and clinical batches from 10L up to 1000L. The combination enables very high quality development work from bench to clinical scale. In the galenics department, we can start with quantities of a few millilitres, allowing us to test multiple formulations for expensive drugs. Later in the development process, bigger batches of the most promising formulations are manufactured and put on accelerated stability, to study all aspects of chemical and physical influences on these formulations. When a promising formulation of the drug product has been worked out, the pilot plant is used to manufacture clinical batches and registration batches under cGMP conditions. These batches are put on ICH stability programmes to deliver all the necessary data for the dossier which is finally submitted to the authorities.

The range of formulation types we can handle includes simple sterile aqueous solutions, highly sophisticated

formulation systems like emulsions and liposomes, and highly potent powder products. These products can be filled in glass vials and bottles (from 5ml up to 1000ml), plastic bags, and pre-filled syringes. All these products have to be sterile at the point of use and we have a versatile hot water spraying autoclave, which we can use to find a sterilization process compatible with the specific product.

When it comes to testing the full spectrum of common analytical methods can be offered (e.g. HPLC, GC). But the centre has also particular competence in analytical methods for emulsions and liposomes. Very good relationships and cooperation with external labs help to circumvent capacity constraints and provide access to highly sophisticated methods like NMR, electron microscopy, and mass spectroscopy.



All these development activities are carried out by a highly motivated team of lab technicians and scientists who have long experience in developing sterile drug formulations. We have proven our flexibility in responding to customer needs many times, e.g. by installing new technology for specific projects.

I hope this article gives you a good overview of the technological capabilities for formulation development at FKPP. Maybe a cooperation with us could give your product a head start in its clinical trials.

Ambix Intraport® - innovative port systems

For more than 25 years, Fresenius Kabi has been developing and producing implantable port systems and cannulae in close cooperation with institutes, users and patients. Our long-term experience and the close collaboration within these relationships have resulted in a sophisticated product range with indication-oriented and trendsetting port technology. Fresenius Kabi offers not only different port systems but also special cannulae for puncturing the port membranes.

In focus: Ambix Intraport® C with metal-free housing

Fresenius Kabi offers the Ambix port system in an aluminium oxide ceramic version. This material has fantastic properties for ports: it is almost as hard as diamond and absolutely scratch-resistant. This eliminates occlusions of port catheters caused by abrasions of the port housing.



Ambix Intraport® C is a venous system which is available with silicone as well as polyurethane catheters.

When choosing a port system, it should be remembered that every single complication may be far more expensive than the port system itself.

For further information on our port systems and special cannulae please visit www.fresenius-kabi.com.



- Bio-inert ceramic, used in millions of hip joint prostheses, is a highly effective electrical insulator. It has no influence on electrochemical processes inside the body and is therefore suitable for long-term application.
- The high-tensile material allows the silicone membrane to be pressed very tightly into the port housing - yet another factor that contributes to the long life-cycle of the port system.
- The ceramic ports cause no problems with medical imaging - artefacts and scattered radiation, troublesome disadvantages of metallic ports, do not occur with ceramic materials.
- The excellent chemical resistance allows the application of drugs that might react with other materials.
- A special bayonet joint makes it easy to see whether the catheter is correctly locked onto the port housing.

