FRESENIUS KABI
caring for life

CONTRACT MANUFACTURING

M( )RE IN AMERICA

INSIGHT

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Contract Manufacturing in the U.S.

IN THIS ISSUE

EDITORIAL

Dear Valued Readers,

We're writing to update you with the exciting news that in the last year, we've successfully commercialized several more customer products in our U.S. sites.

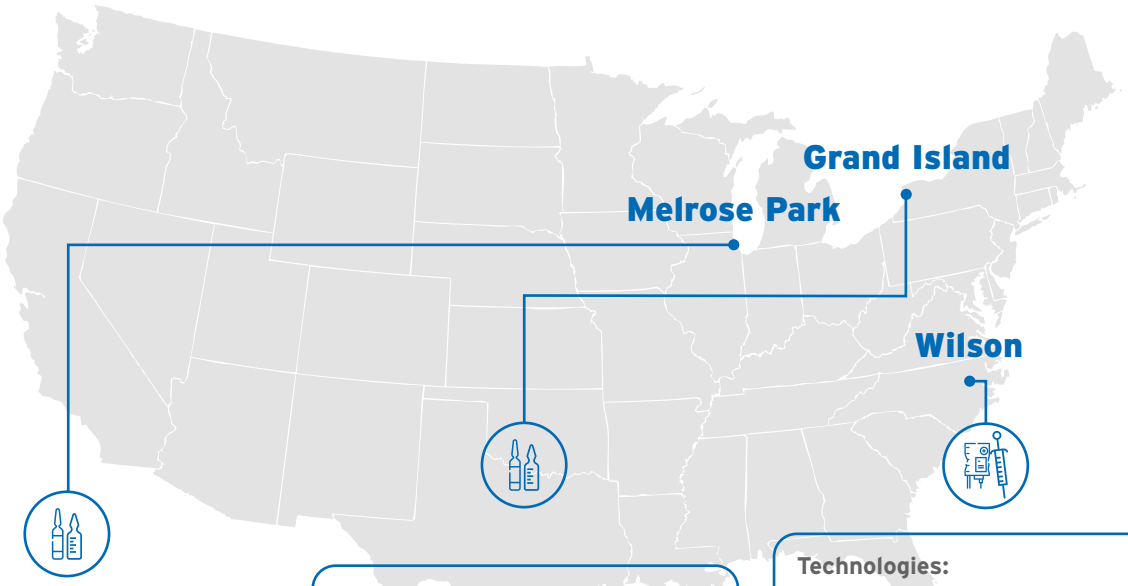
In the future, we're looking to take advantage of the nearly $1 B in advanced manufacturing technology investments at our U.S. sites for your sterile injectable! These investments drive quality through automated, closed systems, reducing the number of interventions required. At the same time, they also drive cost efficiency via high throughput and allow us to offer capacities in the tens of millions of units annually to our customers. Our isolators have positioned us well for European and eventually, global supply, as this technology is a basic requirement for distribution into those regions.

Our technical teams support process modernization, optimization, and scale-up, delivering the highest levels of safety and efficiency for your products. Our processes and manufacturing equipment enable us to handle a variety of different sterile products, such as a diluent, controlled substance, colloidal formulations, biosimilars, and high potent or cytotoxic drugs, using both mobile and fixed tank systems to achieve a variety of batch sizes. Our sites offer a variety of different packaging containers, dedicated equipment, and lyophilization based on product requirements.

Our project management team's technical background is an asset during your product launch, as it allows you to focus on regulatory approval while we implement a robust manufacturing process. We look forward to working together on your next product launch!

Sincerely,
Your Fresenius Kabi Contract Manufacturing Team

MANUFACTURING LOCATIONS | USA



Technologies:
- Aseptic liquid filling
- Lyophilization
- Terminal sterilization
- Isolator contained dispensing; disposable product path (SUS)
- Cold filling
- Highly Oxygen sensitive products
- Cytotoxic line
- High Potency capabilities

Products:
- Anesthetic/analgesic
- Oncolytic
- Critical care

Glass: Vials (2-200 mL)

Plastic: -

Certificates:
- US-FDA
- Canada-Health Canada

Technologies:
- Aseptic filling
- Lyophilization
- Terminal sterilization
- Glass and plastic vial capabilities
- Oxygen sensitive products

Products:
- Anti-infectives
- Standard solutions
- DEA schedule II and IV-controlled drugs
- Critical care
- Anesthetic/analgesic
- Oncologic

Glass: Vials (2-200 mL)

Plastic: Vials (3-200 mL)

Certificates:
- US-FDA
- Canada-Health Canada
- DEA

Technologies:
- Aseptic filling with in-line E-beam decontamination
- Formulation available in 100% Single-use-system, fixed and/or mobile tanks with CIP/SIP
- Terminal sterilization
- Automated inspection of product filled syringes, stopper/plunger, tip cap

Products:
- Anesthetic/analgesic
- Diluents/standard solutions
- DEA schedule II and IV-controlled drugs
- Critical care

Glass: Pre-filled syringes (0.5-3 mL)

Plastic: Pre-filled syringes (5-10 mL)

Certificates:
- US-FDA
- Canada-Health Canada
- DEA

IN THE SPOTLIGHT: PRE-FILLED SYRINGES

As a safe, effective and convenient way to administer injectable medications, pre-filled syringes (PFS) have become the injection system of choice for a growing number of drugs.

PFS allow healthcare professionals to easily handle syringes, reduce waste and save time by providing a ready-to-use container, while also allowing them to precisely dose and minimize overfill.

PFS are also the system of choice for cost-intensive drugs, as they optimize product yield. Fresenius Kabi Contract Manufacturing offers PFS expertise and service at our manufacturing sites in Graz, Austria and Wilson, USA. These sites have significant experience with PFS and therefore, have the flexibility to accommodate the needs of your product.

Advantages of glass and polymer-based pre-filled syringes:

Pre-Filled Syringes	Polymer	Glass
Absence of heavy metals	✓	
Breakage resistance	✓	
Design space / customizing	✓	
Oxygen protection		✓
Integrated luer-lock/needle	✓	
Long term experience		✓
Multiple sources	✓	✓
Tight tolerances	✓	

From customer need to commercial manufacturing

We accompany our partners from the early stages of development through commercial manufacturing and offer pre-filled syringes from formats of 0.5 mL – 50 mL, can do high volumes, and both low and high complexity products via customized adaptations.

In order to find the right product for our customers, we evaluate drug specific, manufacturing specific, and user specific requirements. The Fresenius Kabi Contract Manufacturing team offers you services and expertise for manufacturing PFS and has the flexibility to accommodate the needs of your product.

Filling process

- Use of sterile primary packaging components
- Nested syringes, ready-to-fill
- Closed RABS
- Stoppering with vacuum or positioning pipe
- Option for aseptic and non-aseptic filling of all formats available
- Use of dedicated equipment if required

Formats

- Glass and plastic PFS
- Depending on materials and size, PFS can be supplied with Luer cone, Luer Lock, or staked needle
- 0.5 mL–50 mL PFS
- Qualified suppliers

Secondary packaging

- Cardboard boxes
- Pouches with/without oxygen protection
- Blisters with/without oxygen absorber
- As bulk product in tubs
- Serialization to be implemented

Critical quality attributes of your product

- Oxygen sensitive
- High viscosity
- Light sensitive
- Water-based solutions and water-free products
- Emulsions and suspensions
- Biological products, hormones
- Small molecules
- High-potency compounds

IN THE SPOTLIGHT: free*flex*® IV bags

Fresenius Kabi builds on its broad range of expertise in flexible container technologies for infusion and clinical nutrition therapy.

As the originator of many container technologies that include the IV bag platform **free***flex*®, we wish to highlight the characteristics and advantages we offer to our partners to fill & finish their products in our PVC-free bags.

IV bags are widely used in hospitals and health-care clinics all over the world. Plastic is preferred over glass as a packaging material for many types of pharmaceutical dosage forms due to its unbreakable, lightweight, and leak-resistant characteristics. Furthermore, plastic containers are chemically inert and corrosion resistant. They are additionally collapsible and can be easily molded or remolded. [1-3]

Fresenius Kabi's IV bag technology is the **free***flex*® container system. These IV bags are made of polyolefinen, an inert plastic material consisting of polypropylene (PP) and thermoplastic elastomer, free of PVC and latex. **free***flex*® bags are approved for various infusion solutions and are compatible with more than 140 drugs based on internal Fresenius Kabi studies and published data based on containers with comparable polyolefinen materials. [4-7]

free*flex*® are available in the size range of 50 to 1,000 mL with one or more separate ship-shaped ports made of PP. Their arrow and color coding facilitate the identification of the injection and infusion ports, and the tamper-evident flip-off covers protect them from external contamination. Tests have shown that the infusion port is compatible with all IV sets commonly available on the market. The container concept of **free***flex*® offers a strictly closed system for drug reconstitution to guarantee maximum sterility while ensuring intuitive and safe handling. [8-10]

The package concept of **free***flex*® bags consists of a primary bag to hold the solution and a secondary bag as physical sterile protection. The secondary PVC-free film is clear and flexible; it protects the primary bag mechanically and against water loss through vaporing. The overwrap is easy to open and has excellent transparency to allow visual inspection. **free***flex*® bags are sterilized in their overwraps at 121°C.

Leading independent hospital physicians and pharmacists in France have awarded free*flex*® the top accolade for innovation. It is representing Fresenius Kabi's solution to the increasing complexity of drug handling and infusion protocols.

It is designed to simplify user handling and maximize patient safety. From the crystal-clear, non-PVC, phthalate-free bag and patented leak-resistant technology to the easy-to-handle bag design, every element of this innovative and flexible container system makes **free***flex*® the perfect choice for safe infusions.

free*flex*® bags are produced by Fresenius Kabi in many facilities around the world, including Fresenius Kabi Norge AS in Halden, which is a competence center for the filling of IV drugs in bags based on decades of experience and state-of-the-art technologies.

The advantages of using free*flex*® bags include:

Easy handling:

The shape of **free***flex*® is optimized for both strength and convenience and has soft edges that will not cut hands or gloves.

Excellent drug compatibility:

free*flex*® bags demonstrate high drug compatibility standards and have been tested with more than 140 drugs including antibiotics and cancer drugs. [11]

Environmentally friendly:

free*flex*® bags can be recycled to minimize the environmental impact through the product life cycle.

LYOPHILIZATION AND DILUENTS

With more than 30 percent of the FDA-approved parenteral drugs and a steady increase in injectables requiring lyophilization, the Fresenius Kabi Contract Manufacturing organization is dedicated to support both our new and existing partners' drug product portfolios. Our U.S. based state-of-the-art facilities offer lyophilization and sterile diluents for reconstitution in various containments and volumes.

Lyophilization, defined as the freeze-drying process of a liquid product after it is frozen and placed under a vacuum, has three interdependent processes; freezing, sublimation (primary drying), and desorption (secondary drying). The process simplifies aseptic product handling while enhancing the stability of the product in a dry state through the removal of water without excessive heat. Products with instability in solution are manufactured as a lyophilized form. There are a multitude of lyophilized product advantages including extended shelf life (typically two to five years) while maintaining drug potency, room temperature storage conditions and ease of transport due to the reduced weight and volume of the finished product.

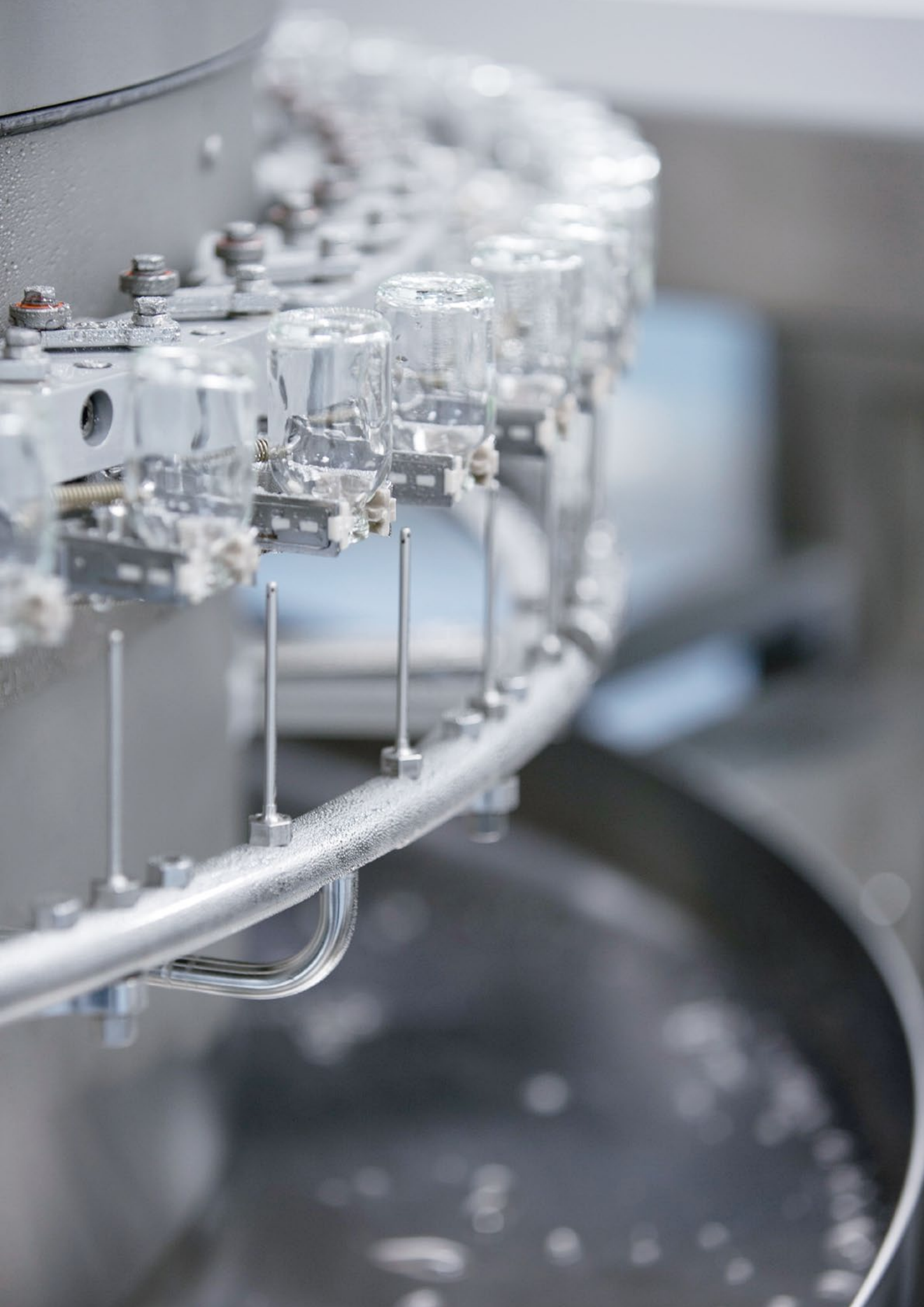
As lyophilized drug products require diluent for reconstitution, Fresenius Kabi Contract Manufacturing is proud to provide sterile diluent to our partners in both pre-filled syringe and vial formats through our plants in Wilson,Grand Island and Melrose Park.

In addition to PFS, we offer sterile diluents in a variety of vial formats and volumes.

We offer manufacture of diluents in 1-10mL pre-filled syringes (PFS) and vials, as well as larger volumes upon request.

Choosing the right partner is critical to the success of your product development and commercialization. When your complex formulation cannot be sterile filtered or terminally sterilized, let our aseptic fill & finish, lyophilization, and sterile diluents (filled in PFS out of Wilson and vials filled out of Grand Island and Melrose Park) contract manufacturing services provide you with the solution.

Taken together, we can combine large-scale fill & finish services for both complex lyophilized parenterals and their associated simple diluents, making us the ideal one-stop-shop for your next outsourcing project for these complex sterile pharmaceuticals.



WILSON, NC

Our Fresenius Kabi U.S. center of excellence for prefilled syringes (PFS) is in Wilson, which is located in the eastern part of North Carolina. The Wilson site is a world-class facility with state-of-the-art, fully automated syringe technologies that are focused on the production and distribution of complex and critical drugs in ready-to-administer delivery systems and diluents, both for Fresenius Kabi and contract manufacturing partners.

The Wilson site specializes in the formulation, syringe filling, and packaging of aseptic and terminally sterilized drug products and diluents with the advantage of being able to offer large-scale quantities and flexibility in the syringe portfolio and sizes. PFS drug products and diluents are produced on fully automated manufacturing, inspection, and packaging lines in a continuous process under controlled conditions. This highly automated and state-of-the-art manufacturing facility, half of which is dedicated to prefilled syringe production, has a unique capability and capacity to launch additional tens of millions of new and existing commercial PFS drug products including biologics, highly active compounds and products (maximum OEL = 0.1 µg/m^3), and products that are sensitive to temperature, light, and/or oxygen.

Highly active compounds and products and biologics are able to be formulated and filled using disposable single-use system technologies with completely disposable and/or dedicated product contact parts for reduced exposure levels. Products sensitive to oxygen can undergo nitrogen-filling technologies with light-protected palletization to achieve maximum shelf life and market value.

The site in Wilson has the capacity to fill and finish more than 100 million units of ready-to-administer product in PFS anually

including anesthetic, analgesic, antiemetic, anti-inflammatory, and a host of modifier and inhibitor therapeutic classes. These pharmaceuticals are filled in various configurations of syringes (Luer lock and/or staked needle), and are inspected and packed in various configurations such as nested syringes of unlabeled bulk, as labelled and blistered (singles and/or sheets), cartoned as cases, and/or are kitted with additional product(s).

This manufacturing facility is implementing additional automated state-of-the-art PFS manufacturing lines, suitable also for larger PFS formats up to 10 mL, flow-wrapped packaging, as well as IV bags and standard solution bags based on Fresenius Kabi's **free***flex*® platform. These implementations will create a unique possibility to launch products across multiple platforms specific to various product and customer requirements.

To support you with a global supply of your product, our Wilson plant has been inspected by domestic and international agencies

and will be capable of serving the worldwide market in the future, including key markets like the EU and China.

We are proud to offer our partners the possibility of filling their solutions into syringes and **free***flex*® bags in Wilson, North Carolina. Please get in touch with us to find the perfect solution for your formulation and filling and finishing needs.

GRAND ISLAND, NY

The Grand Island site is located just over ten miles from Buffalo, NY and a few minutes from the spectacular Niagara Falls. Buffalo is in the Western New York region of the northeast U.S. The Grand Island plant has been under Fresenius Kabi ownership for the last 12 years. Only recently, Fresenius Kabi has invested more than $ 200 million in its Grand Island plant to extend its overall manufacturing capacity.

The site currently holds the capacity of more than 200 million units anually, embodying the company's commitment to „caring for life" with each patient dose.

At this time, the main markets are the U.S. and Canada with projects to expand to the European market ongoing. The vials shipped from here include both plastic and glass containers and range in size from as small as 2 mL to as large as 200 mL. The site's products include mostly critical care and anesthetic and analgesic medications.

Today, the plant consists of two production facilities that manufacture IV drugs and one newly developed production facility that is dedicated to monobactam products.

The site's production facilities hold approx. 300.000 ft^2 including for advanced technologies with restricted access barrier systems, handling and filling of controlled substances, and a dedicated area for monobactams.

The site focuses on controlled substance production and logistics, lyophilization, and sterilization.

Lastly, the fully automated monobactam facility in development contains 19,000 ft^2 (1,765 m^2) of manufacturing space with one lyophilization line and isolator technology.

As can be seen, the site can offer significant capability for customers when it comes to sterile diluents and lyophilization. The site has also invested in the infrastructure and processes needed for controlled substance production and logistics.

With a cross-functional team of more than 800 employees across five shifts, the plant is constantly improving and advancing. Examples include the addition of larger formulation tanks to scale up batch size, automatic cleaning processes for equipment, in-line depyrogenation tunnels, automated visual inspection recipes, and packaging serialization. The site has also assembled a team which continues improvements such as the planned implementation of an electronic batch records aid in the batch release process occurring at the highest level of compliance.

We are committed to sustainable production, which is evidenced by all three U.S. plants obtaining the ISO 14001:2015 Environmental Management Certificate and ISO 50001:2018 Energy Management Certificate.

The Grand Island team's collaboration and passion are vital to the product launch process. We embrace the opportunity to learn and grow our technical capabilities together and look forward to partnering with you for your contract manufacturing needs!

MELROSE PARK, IL

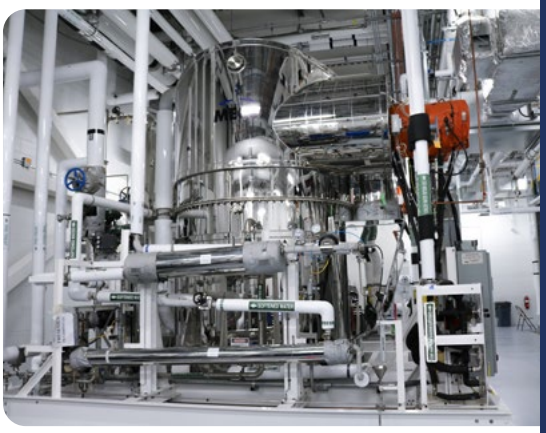
Do you have a developed parenteral injectable product in glass vials (2-200 mL), and are you looking for a high throughput facility to partner with for Phase 3 and/or commercialization? Then, the Fresenius Kabi Melrose Park site is for you. Melrose Park is a suburb of Chicago and is located five miles away from the O'Hare International Airport. The facility has more than 12 years history within Fresenius Kabi, and currently produces a wide range (250 finished products) of parenteral injectable medicines for the treatment of critically and chronically ill patients.

The new facility is equipped with a state-of-the-art urban manufacturing campus, fully-automated aseptic filling lines and advanced isolator technology, as well as expanded lyophilization capabilities and formulation areas.

Fresenius Kabi is currently completing a $ 250 million investment project to expand capacities at its Melrose Park site with annual capacities in future of more than 250 million units.

Multiple integrated aseptic filling lines in connection with lyophilizers with automated loading are being installed in the expansion, including one cytotoxic line, one highpotent/ hormone line and multiple general product lines to increase overall manufacturing capacities. This additional capacitity will significantly enhance the annual output as of today, with multiple aseptic lines and lyophilizers in place in the existing site for the supply of life-saving drugs filled in vials for distribution in the U.S. and Canada.

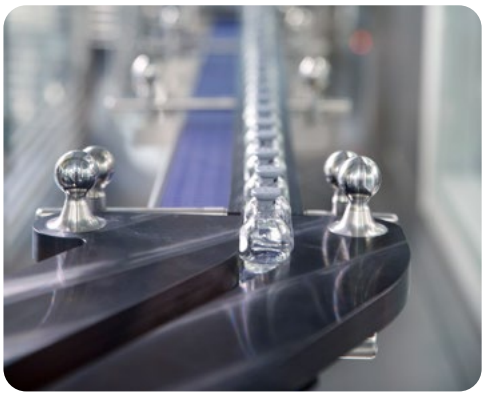
We offer also filling and finishing services for highly potent products in a multiproduct facility using effective separation with smart HVAC and architecture design and new disposable single-use system technologies with fully disposable and/or dedicated product contact parts for the reduced risk of cross contamination.



Additionally, we offer technologies required for filling advanced complex parenterals such as emulsion processing, cold filling, oxygen reduction, metal-sensitive, and other sophisticated technologies.

The site is also home to GMP compliant semi-automated and automated inspection processes, and five packaging lines, two of which are fully automated, and all are installed with serialization and aggregation equipment to meet DSCSA requirements.

The Melrose Park team is passionate about our "caring for life" philosophy and bringing value to our customers and their patients through high-quality products. We are excited to learn about your contract manufacturing needs and be *Your Partner for Solutions!*



FIND OUT MORE ABOUT OUR CAPABILITIES

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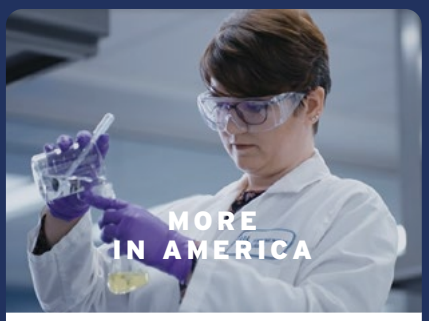

Find out more:
https://www.fresenius-kabi.com/us/company/more-in-america

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Fresenius Kabi Contract Manufacturing is the contract manufacturing platform of Fresenius Kabi, providing partners easy access to the expertise of more than 20 manufacturing sites worldwide. Capabilities include the fill/finish of sterile pharmaceuticals in a wide variety of containers, as well as sterile devices and APIs. Insight is a publication of Fresenius Kabi Contract Manufacturing. The content of Insight is offered in good faith, believed that it is accurate and correct. Fresenius Kabi Contract Manufacturing expressly disclaims any liability for errors or omissions in such information.