FRESENIUS KABI

Product Partnering

Fact Sheet (1)

Fresenius Kabi Product Partnering

Who We Are

Fresenius Kabi Product Partnering is a global leader in the contract development and filling & finishing of sterile pharmaceuticals as well as for the development and supply of medical devices. Being part of Fresenius Kabi, we offer our customers access to the expertise of more than 20 innovation and manufacturing centers. Unparalleled production capabilities, outstanding quality compliance, and an excellent track record in contract manufacturing have made Fresenius Kabi Product Partnering the supplier of choice of an impressive number of pharmaceutical companies.

The integral concept of combining development and production for sterile medicinal products and develop additionally the respective medical devices for your application makes us a one-stop-shop for nearly every kind of project.

Scope at a Glance

Sterile Filling & Finishing

- IV-bags
- Bottles
- Vials
- Ampoules
- Pre-filled syringes
- Customized containers
- Glass
- Plastic
- Solutions
- Emulsions
- Liposomes
- Aseptic filling
- Terminal sterilization
- Lyophilization
- (Potent) APIs
- Biologics
- Clinical supplies
- Full commercial scale
- Worldwide markets

Manufacturing Locations

- Argentina
- Austria
- Brazil
- Chile
- China
- France
- Germany
- India
- Indonesia
- Italy
- Mexico
- Norway
- Poland
- Portugal
- South Africa
- Spain
- Sweden
- USA
- Vietnam

Development Support

- Formulations
- Disposables
- Delivery systems
- Drug improvement
- Process optimization
- QC-methodologyx

Mission

"...to enable our Partners to market their parenterals and medical devices by providing tailor made assistance in the development, registration, and manufacturing of their products ..."

Services & Support

- Laboratory services
- Regulatory
- Shipping & Distribution

Other Products/Services

- Lipids
- Phospholipids
- Lactulose
- Hydroxyethyl Starches
- Secondary packaging
- Ointments, droplets
- Tablet blistering
- Oral Solid Dosage Form

Contacts

Please visit our website

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Fact Sheet (2)

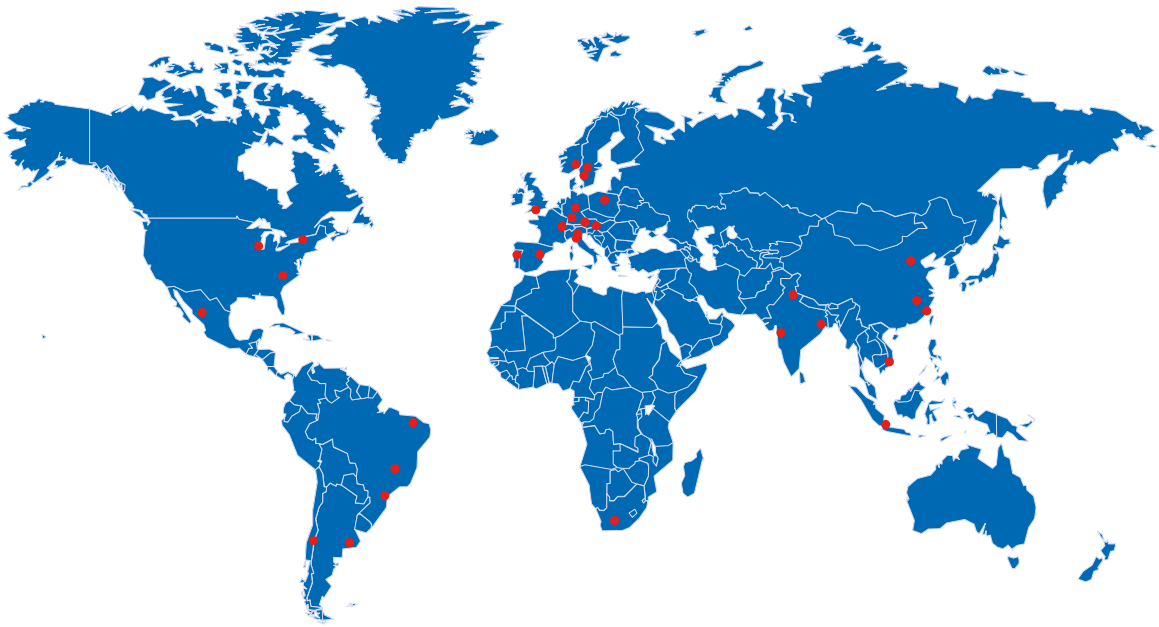
Toll Manufacturing

Fresenius Kabi Product Partnering covers over 20 Fresenius Kabi manufacturing facilities and innovation centers operated in strict conformity with international quality standards (FDA-GMP, EU-GMP, cGAAP, WHO-GMP, Medical Device Regulations). New products are evaluated by means of an initial feasibility study in which the best fit between client (location, required services), product (process requirements, product size, markets), and facility (location, on-site technology and support toolbox) is determined. The development phase and the implementation of commercial manufacturing is supported by a dedicated project team and time-to-market is minimized by an efficient development and qualification program. Validations, stability studies, regulatory support and all other elements relevant to a specific product are brought together in a single project plan in close co-operation with the customer.

Services

- Filling and finishing of IV-bags (large and mini bags), bottles (glass and plastic), vials (glass and plastic), ampoules (glass and plastic), pre-filled syringes (glass and plastic), customized containers
- Aseptic processing, terminal sterilization, lyophilization
- Development and supply of tailor made medical devices
- Processing of solutions and disperse systems such as emulsions and liposomes
- Full analytical, microbiological, pharmaceutical and regulatory assistance
- Worldwide logistic support

Manufacturing Locations



Argentina
Austria
Brazil
Chile
China
France
Germany
India
Indonesia
Italy
Mexico
Norway
Poland
Portugal
South Africa
Spain
Sweden
USA
Vietnam

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Fact Sheet (3)

Medicinal Products Manufacturing / Containers / Support

The business approach of Fresenius Kabi Product Partnering is to provide our customers integral support throughout the life-cycle of their parenteral products: Starting at the early stages through to full commercial scale, covering development as well as filling & finishing, supporting worldwide markets. A focus on continuous improvement and innovation thereby keeps the product tailored to customer demands, regulatory requirements, and market conditions at all times! Also an integral combination of medicinal products and medical devices can be offered to fit your special needs for highest quality products and most convenient application.

Manufacturing Technologies

- Aseptic preparation and filling
- Terminal sterilization
- Emulsion & liposome technology
- Oral solid dosage forms
- Lyophilization
- Oxygen free processing
- State of the art packaging and labelling for all container forms

Container Technologies

Type	Pre-filled syringes	Ampoules	Vials	Bottles	IV-bags	Multi-chamber bags	Specialty Devices
Size	1–50 mL	1–20 mL	1–100 mL	50–1,000 mL	40–5,000 mL	100–5,000 mL	1 mL–200 L
Material	Glass Plastic	Glass Plastic	Glass Plastic	Glass Plastic	Non-PVC PVC	Non-PVC	Various

Support Services

- Laboratory services
- Development & regulatory support
- World wide logistic support

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Fact Sheet (4)

freeflex® THE ART OF INNOVATION

freeflex® is the innovative and flexible container concept from Fresenius Kabi. The bag benefits from the significant improvements made in infusion container technology. It achieves the high ecological and drug-compatibility standard of glass and retains the well accepted characteristics of an infusion bag: Clarity, flexibility, low weight and full collapsibility.

Freeflex® bags are available as single- and multi-chamber-bags offering one or two separate ports, which are also available as safe luer-lock connections.

Freeflex® bags are available in the sizes
50 mL, 100 mL, 250 mL, 500 mL and 1000 mL.

Excellent Drug Compatibility

- Bag consists of multilayer film based on polyolefin (PP)
- Inert material, compatibility with common drugs is comparable to glass
- No plasticizers or adhesives added, hence no migration into the solution
- More than 40 drugs have been tested, showing the same stability as with glass

Easy Handling

- Protective, sterile overwrap with opening aid
- Unique ship shape ports that offers strength to the bag
- Tamper evident and sterile break off caps on both the ports
- Integrated hanger for convenient usage
- Temperature resistant: Can be heated up to 37°C and cooled down up to -22°C
- Tamper evident and sterile ports: No need of disinfection immediately after opening the ports

Enhanced Safety

- Rigid injection port (0,8 mm geometry) to prevent needle stick injuries
- Up to 10 injections possible in the injection port without affecting the resealing property
- Sterile chamber in the injection port to guarantee the closed system whil mixing drugs with a transfer adapte
- Self sealing septum in the infusion port to prevent leakage after removal of the infusion set or syringe
- Sterilized at 121°C within the overwrap to maintain sterility till the bag is opened

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Fact Sheet (5)

Diluents – important "excipients" for modern drugs

Modern drug technology, with a shift from small molecules to big molecules such as peptides and proteins, has created new challenges for the application methods. To keep these molecules chemically and physically stable we need quite different measures than the ones that work for small molecules.

Conventional drug formulations in premixed solutions are in most cases not feasible. The required shelf life can often only be achieved by storing the drug in a solid (powdery) state, sometimes even at low temperatures. Powder filling or lyophilization are common techniques used for such molecules. This makes filling and finishing of these drugs quite different.

All powdery products for IV application have to dissolve before use. The liquid used for reconstitution – the diluent – is a second drug product, one without API. Like the active drug, it has to be registered and approved by health authorities in each country. The most common dissolution solutions are WFI, isotonic sodium chloride and glucose solutions. What kind of product is finally used depends on the formulation and compatibility of the product to be dissolved.

The preferred strategy for providing such a diluent is co-packing. This ensures that the recommended diluent is used and also, it means that the manufacturer of the drug product can assure the optimal container form and volume for the dissolution process.

Fresenius Kabi Product Partnering can offer high quality diluents in a variety of different containers and volumes. Fresenius Kabi is supplying standard salt and glucose solutions in hundreds of million units to customers – mainly hospitals – around the world. At Fresenius Kabi Product Partnering we can offer you tailor-made solutions for diluents according to the needs of your product. We can fill your diluent of choice into glass or plastic containers – ampoules, vials, bottles, bags and pre-filled syringes. The products can be labeled with the artwork you choose, in order to provide an appealing and uniform presentation of drug product and diluent. We can also provide transfer sets for our containers that connect the diluent container with the drug container to enable a smooth transfer and dissolution process. We have several plants around the world that have their focus on the manufacturing of such solutions.

Therefore, we are able to offer the diluents for registration in all major markets with already-available dossiers.

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Fact Sheet (6)

Pre-Filled Syringes

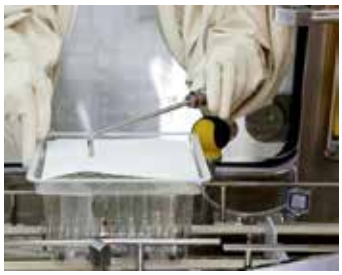
Convenient, safe & efficient

As a way of supplying solutions for injection, pre-filled syringes (PFS) have several advantages over conventional vials. PFS make application of the drug product safer and more convenient for physicians as well as self-administration while enjoying an excellent market acceptance. PFS are also a system of choice for cost-intensive drugs by optimizing product yield. Fresenius Kabi Product Partnering offers you services and expertise for manufacturing your product in PFS and has the flexibility to accommodate the needs of your product.

1) 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

2) 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

3) 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

4) Safety devices

Working with our suppliers, we can implement different safety needle devices that best match your target product profile.

5) Secondary packaging

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

6) Supply for assembly in auto-injectors

For assembly of PFS in auto-injectors at a third party, we can supply PFS as bulk products with PFS placed in tubs.

We have already successfully launched several products and have numerous third-party projects in the pipeline with globally respected customers from the pharmaceutical industry.

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Fact Sheet (7)

Macromolecules with Focus on Carbohydrates

The Fresenius Kabi Austria plant in Linz can point to more than 60 years of experience in the development, manufacturing and analytics of carbohydrates.

cGMP and Contract Manufacturing/ Analytics

Our facility is equipped for production as well as analytics of gram to multi-kilogram quantities, and can supply both simple and complex carbohydrates for any scale from early clinical trials to large-scale production.

Our site complies **with all international regulatory standards.**

Capabilities

- Carbohydrate binding
- Carbohydrate interaction
- Carbohydrate synthesis
- Carbohydrate derivatization
- Carbohydrate tailoring
- Glycosylation
- Fluorescein marking

Technologies

- Lab/pilot scale (up to 200 L / 30 kg)
- Commercial scale (up to tons)
- Multi-purpose & dedicated vessels
- Evaporation (up to 200 L)
- Microfiltration
- Ultrafiltration (up to 1000 L)
- Desalination
- Drying
- Lyophilization bulk/ vials
- Milling (up to 50 kg)
- Packaging

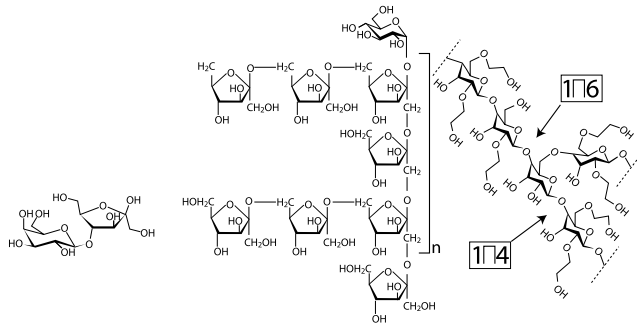
Raw Materials

▼

Innovative Technologies for Carbohydrates

▼

Disaccharide	Oligosaccharide	Polysaccharide
Lactulose	Sinistrine	HES



Our Service

- Synthesis of lab-scale carbohydrates
- Production of pilot-scale carbohydrates, including engineering scale-ups to industrial production processes
- Chemical modification of carbohydrates
- Customizing carbohydrates for narrow polydispersity using membrane separation technology, like ultrafiltration or nanofiltration
- Pilot-scale production of bulk pharmaceutical intermediates and ingredients, as well as APIs based on carbohydrates
- Derivatization of carbohydrates for engineering of physico-chemical properties
- Fluorescein marking for diagnostic applications
- Production of tailor-made linkers for HESylation of Active Pharmaceutical Ingredients
- Analytics like the special HPAEC-PAD as well as routine GPC
- Regulatory support, compilation and support with filing all relevant documentation

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Fact Sheet (8)

Transfer Devices

Fresenius Kabi transfer devices are designed to transfer liquids from one container to another in the safest and easiest way.

Fresenius Kabi offers various spike systems – from simple double-sided plastic spikes, which can be used on a large variety of containers, up to covered needle spikes, which are surrounded by a plastic housing providing a high degree of protection against injuries.

The basic forms are not dedicated to special containers. However, we offer dedicated transfer systems, which provide a fixed and stable snap connection to the bag port or vial/ bottle cap. This feature is especially important for the application of cytotoxic drugs.

Our team of development engineers is ready to take on any challenging development task, such as creating a transfer device tailor-made for your application and the corresponding container, in order to provide the optimum solution for your requirements.

Basic transfer devices	**Dedicated transfer devices for Fresenius Kabi containers**	**Dedicated transfer devices for diverse containers**
Variable usage on many different containers **Examples:** • Basic form with double-sided plastic needle • Micro spike for small vials with needle-free luer lock connection to the syringe	Connection with a dedicated container **Examples:** • KabiPac adapter • Freeflex adapter 	• Connection with a dedicated container and bottle • Customized development

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Fact Sheet (9)

Development & Clinical Trial Supply

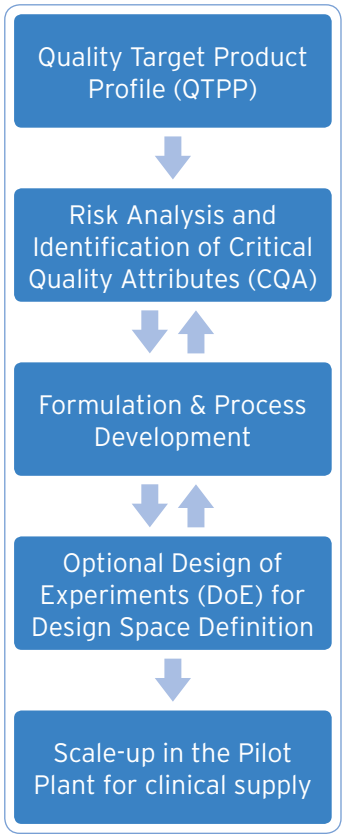
Fresenius Kabi Product Partnering offers services and expertise based on a decades-long track record of successful development of sterile pharmaceuticals.

Our development centers have teams of scientists and engineers with strong academic and industry backgrounds related to all types of sterile pharmaceuticals. By taking advantage of our extensive knowledge on the function of various excipients, we help our customers to transform an idea into a product.

For lipophilic and low-soluble APIs, we build on our knowledge base with emulsions and liposomal formulations to develop safe intravenous administration forms. For lyophilizates, we combine formulation knowledge with cryo-microscopy methods to find a suitable lyophilization process.

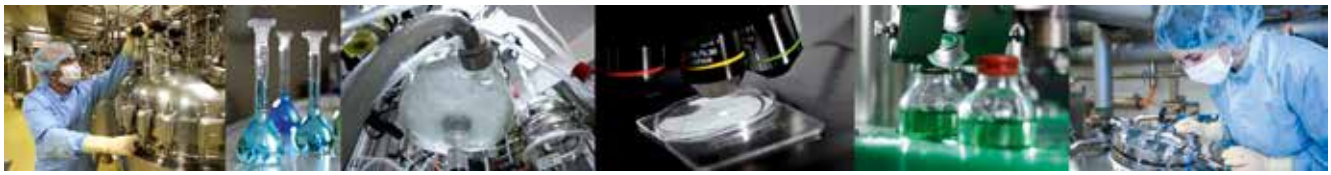
Various compatibility studies allow us to identify the best container closure system, such as ampoules, vials, bottles, pre-filled syringes or bags, to meet the requirements of the product and of the market.

Sophisticated developmental assays help us to optimize process parameters to guarantee a smooth scale-up and consistent product quality following the Quality by Design (QbD) guideline.



Preclinical and Clinical Trial Supply

Our pilot plant in Graz, Austria and our commercial plants are fully compliant with international quality standards (incl. FDA-GMP, EU-GMP), offering supply for preclinical and global clinical studies in various container closure systems. Our plant in Neufahrn, Germany is the ideal partner for aseptic compounding and can also offer blinding of study medication for clinical trials.



Services

Formulation Development for Sterile Pharmaceuticals

- Aqueous solutions
- Aseptic solutions
- Emulsions
- Liposomal formulations
- Suspensions
- Lyophilisates

Formulation and Process Development

- Analytical method development
- Compatibility studies for container closure systems, stainless steel, silicone and Teflon tubing, etc.
- Thermal stability studies
- ICH and ambient photo stability
- Extractables & leachables
- Lyophilization development
- Process optimization by DoE

Clinical Trial Supply for Global Studies

FDA & EMEA approved plants for clinical supply in the US and Europe

cGMP batch sizes: 5 L to 1000 L

Secondary packaging and blinding of study medication for clinical studies

Containers for clinical supply:

- Vials: 10 to 100 mL
- Bottles: 50 to 1000 mL
- Ampoules: 1 to 20 mL
- Pre-filled syringes: 1 to 50 mL
- Bags (PVC free): 50 to 1000 mL

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Fact Sheet (10)

Lyophilization

New Capacities at Fresenius Kabi Austria – Plant Graz

Lyophilization of aqueous solutions and liposomal formulations is a common technology applied for compounds that cannot attain an adequate shelf life in aqueous solution because they are susceptible to hydrolysis, unwanted reactions with other substances or loss of activity for other reasons.

At Fresenius Kabi lyophilization has been a well-established technology for some time. Recently, a new small volume parenteral (SVP) filling line with an integrated freeze dryer has been installed at the Graz plant to add capacity for third-party manufacturing. Fresenius Kabi Product Partnering can now offer services in the development and commercial manufacturing of lyophilized products for aqueous and liposomal formulations.

Development of Formulation and Lyophilization Cycle – I&D Graz

- Formulation development
- Initial analysis using cryo-microscopy to find the collapse temperature
- Development of lyophilization cycle in a small-scale freeze dryer (shelf area: Approx. 0.1 m^2) with temperature sensors in vials
- Scaling-up of the lyophilization cycle to a pilot-scale freeze dryer (shelf area: Approx. 1.0 m^2)
- Evaluation of the formulation and lyophilization cycle based on the shape of the product cake, reconstitution time and analytical endpoints

Commercial manufacture of lyophilized product – Plant Graz

- State-of-the-art aseptic filling line and lyophilization unit, freeze dryers are fully integrated into the aseptic filling line.
- Can work with high-potency and biological APIs
- Able to compound and fill cooled bulk solution
- High-speed SVP line with different dosing systems
- Isolator system
- In-line control of filling volume
- Vials size: 2–30 mL
- Fully-automated transfer of vials from the filling line to the freeze dryer
- Shelf area: Currently 19 m^2 but with extendable lyophilization capacities

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Fact Sheet (11)

Dispersed Systems

Emulsions, Liposomes & Suspension

Fresenius Kabi has decades of experience in developing and manufacturing emulsions for parenteral nutrition and as carriers for drug products. Recently, we have extended our manufacturing capacity for emulsions by installing new state-of-the-art equipment with the ability to process high-potency APIs. Besides emulsions, we offer services for other dispersed systems such as liposomal products. Both, emulsions and liposomes are made with phospholipids extracted and purified at Fresenius Kabi's plant in Brunna, Sweden. As an aseptic competence center, Fresenius Kabi Austria, Plant Graz also provides you with new on-site technology for contract manufacturing suspensions in different packaging materials.

Emulsion – New Capacities

- Vast experience in emulsion formulation and technology
- New preparation unit for processing of high-potency compounds in a weighing isolator
- Oxygen protection in the entire process including the weighing isolator
- Flexible batch sizes
- New high-end filling lines for glass vials and bottles
- Filling into ampoules, bags, and pre-filled syringes also available

Liposomes – New Technology

- Technical experience from emulsions applied for liposomal formulations
- Handling and use of high-potency compounds in the weighing isolator
- Handling of high-potency APIs under oxygen protection
- High-pressure homogenizer
- New high-end filling lines for aseptic filling in glass vials
- Aseptic filling in pre-filled syringes

Suspension – New Technology

- Handling of high-potency compounds in a weighing isolator, with VHP generator for sterile APIs
- Handling of high-potency APIs under oxygen protection
- Implementation of dedicated equipment
- Aseptic filling of suspensions in glass vials and in pre-filled syringes
- Recirculation to maintain suspension while filling

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Fact Sheet (12)

Aseptic filling of bags

Bags are the primary container of choice for parenteral nutrition, as well as for the isotonic buffered infusion solutions that are often used along with injectable drugs. In contrast to glass bottles, bags are more convenient and safer for healthcare professionals and avoid product contact with rubber stopper materials. Most products sold in bags are terminally sterilized due to their nature and composition. However, terminal sterilisation of bags is not compatible with heat-sensitive compounds. Therefore, demand for products in aseptic bags is increasing steadily.

Aseptic manufacturing processes put high demands on the manufacturing plants. Personnel and equipment must comply with stringent guidelines. High standards for engineering, training, monitoring and house-keeping have to be in place at the plant, in order to guarantee stable good performance of aseptic processes.

Fresenius Kabi Product Partnering offers the aseptic competence of Fresenius Kabi plants to its customers.

Selection of Bags for Aseptic Processing

- Pre-printed bags are pre-sterilized before delivery and supplied in overpouches
- Currently, PVC containing bags are used for the aseptic filling process
- Development and implementation of new bag formats and bag materials on demand

Aseptic Filling Line

- Dedicated filling line for aseptic filling of bags
- Inline automated CIP/SIP procedure
- 2-isolator concept (separation isolator and filling isolator)
- Loading and unloading of isolators via mouse holes protected by LAFs
- Filling via filling port
- Welding of the filling port after filling
- Oxygen protection if required (nitrogen gassing, overwrapping, and oxygen scavenger)
- Batch size: Up to several thousand liters
- Extendable capacities available

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