



**FRESENIUS
KABI**

caring for life

Contract Manufacturing Your Partner for Solutions



- At Fresenius Kabi Contract Manufacturing we offer over 50 years of experience in the manufacture and development of sterile pharmaceuticals worldwide.
- As a flexible outsourcing partner, we understand all aspects of pharmaceutical projects from bench to product.
- We balance the need for a rapid time to market with stringent quality and regulatory compliance.
- Challenge us with your requirement - we will provide you with a solution!





Who We Are

Fresenius Kabi Contract Manufacturing 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 Research & Development facilities** worldwide. Unparalleled production capabilities, outstanding quality compliance, and an excellent track record in contract manufacturing have made Fresenius Kabi Contract Manufacturing 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 Fill & Finish Services

- Pre-filled syringes
- IV-bags
- Ampoules
- Bottles
- Vials
- Customized container
- Glass
- Plastic
- Solutions
- Emulsions
- Liposomes
- Aseptic filling
- Terminal sterilization
- Lyophilization
- Potent API (HAPI)
- Biologics
- Clinical supplies
- Full commercial scale
- Track & Trace
- Worldwide markets



Development Support

- Formulations
- Disposables
- Delivery systems
- Drug improvement
- Process optimization
- QC-Methodologies
- Analytical characterization



Services & Support

- Process Scale-up
- Project management
- Analytical testing & stability services
- Regulatory support
- Serialization
- Shipping & Distribution



Manufacturing Locations

- Austria
- China
- Czech Republic
- France
- Germany
- Italy
- Norway
- Poland
- Portugal
- Sweden
- Vietnam
- USA



Other Products/Services

- Lipids
- Sterile Filling & Finishing
- Phospholipids
- Secondary packaging

Mission

“...to enable our Partners to market their sterile pharmaceuticals and medical devices by providing tailor made assistance in the development, registration, and manufacturing of their products ...”



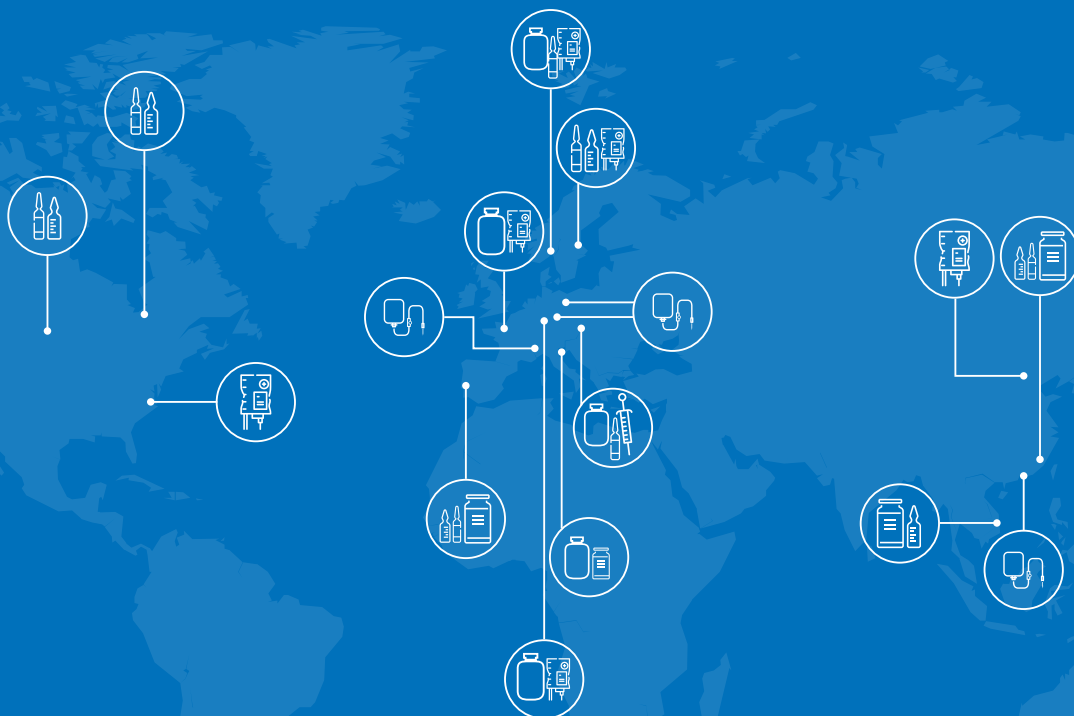


Fresenius Kabi Contract Manufacturing offers access to over 20 Fresenius Kabi manufacturing facilities and Research & Development centres worldwide operated in strict conformity with international quality standards (FDA-GMP, EU-GMP, cGAAP, WHO-GMP, Medical Device Regulations). New products are evaluated 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

- Fill & finish services for pre-filled syringes (glass and plastic), IV-bags (single and multichamber), ampoules (glass and plastic), vials (glass and plastic), bottles (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 microparticles, emulsions, suspensions and liposomes
- Full analytical, microbiological, pharmaceutical and regulatory assistance
- Worldwide logistic support

Manufacturing Locations





Fresenius Kabi Contract Manufacturing business approach is to provide our customers integral support throughout the life-cycle of their sterile pharmaceuticals 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!

In addition, 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
- Lyophilization
- Oxygen free processing
- State of the art packaging and labeling for all container forms



Container Technologies



Size	1-50 mL	1-20 mL	1-100 mL	50-1,000 mL	40-5,000 mL
Material	Glass, Plastic	Glass, Plastic	Glass, Plastic	Glass, Plastic	Non-PVC, PVC
Type	Pre-filled syringes	Ampoules	Vials	Bottles	IV-bags



Support Services



Laboratory services



Development & regulatory support



Worldwide logistic support





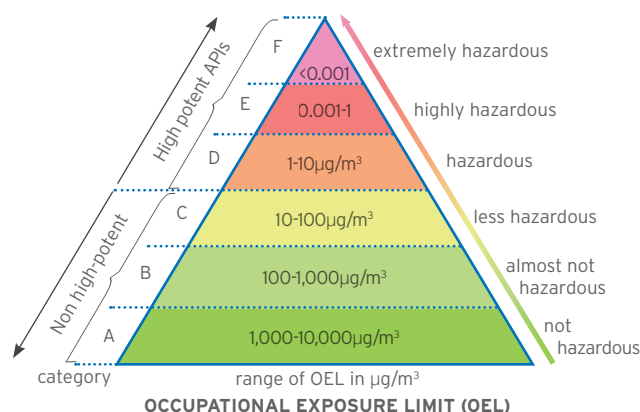
Fresenius Kabi has decades of experience in developing and manufacturing solutions and emulsions used as carriers for lipophilic drug substances. Our state-of-the-art manufacturing capacity also allows to produce complex formulations, such as emulsions, suspension and the ability to process high-potency active pharmaceutical ingredients (HAPIs).

HAPIs such as steroids, hormones and prostaglandins, work at doses of 10 mg or lower with biological activity at $\sim 150 \mu\text{g}/\text{m}^3$. More effective drugs are good news for patients, but also create new challenges for drug manufacturers.

At our Fresenius Kabi facilities in the US and Austria we:

- Handle HAPIs down to an OEL of $0.1 \mu\text{g}/\text{m}^3$ including hormones, antibiotics (excl. beta-lactams)
- Rate (environmental) risks based on European Medicines Agency (EMA) guidelines
- Have compounding containment facility connected to dedicated tanks and disposable bags
- Established a process flow for risk management and process definition by dedicated HAPIs team
- Possess filling lines equipped with dedicated or disposable filling equipment
- Train our employees on how to safely handle HAPIs

Potent Compound:
A drug substance with an OEL of $10 \mu\text{g}/\text{m}^3$ or lower



Manipulation of highly active substances

- Mobile vessels connected to isolator
- HAPIs transfer into isolator
- Weighing of HAPIs
- HAPIs transfer into mobile vessel
- Cleaning procedure



Manipulation of sterile substances

- Mobile vessels connected to isolator
- Isolator sterilization via hydrogen peroxide (VHP)
- API-container is connected aseptically (via port system)
- Weighing of sterile API
- Transfer of sterile API into mobile vessel
- Cleaning





Fresenius Kabi Contract Manufacturing offers high quality diluents in a variety of different containers and volumes. At Fresenius Kabi Contract Manufacturing 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, 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 offer the diluents for registration in all major markets with already-available dossiers.

Infusion Solutions

Infusion solutions can be used as diluents and have small molecules that flow easily from the bloodstream into cells and tissues.



freeflex®
50-1,000 mL



Plastic Ampoules
5-20 mL



KabiPac
50-1,000 mL



Bottles
50-1,000 mL



Irrigation Solutions

Irrigation solutions are customized for patients treatments in different medical fields such as urology, gynecology, oncology...



Careflex duo
1,500-5,000 mL



Plastipur
250-1,000 mL



KabiContainer
10 L





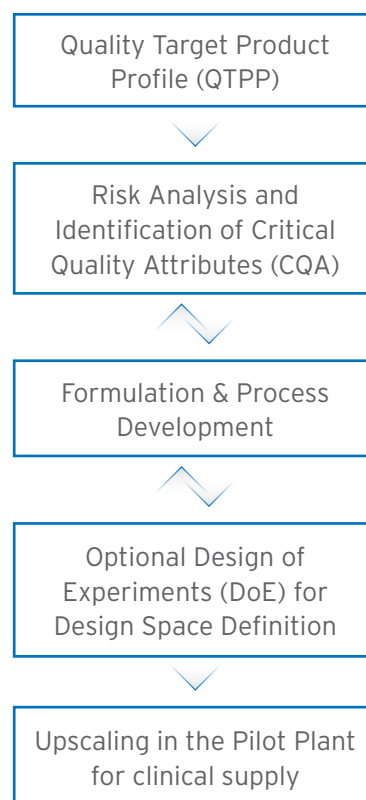
Fresenius Kabi Contract Manufacturing offers services and expertise based on a decades-long track record of successful development of sterile pharmaceuticals.

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 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.

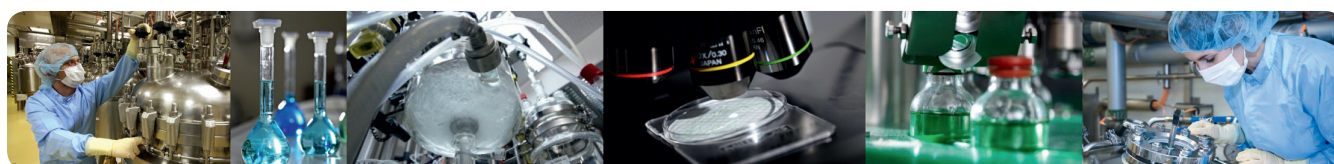
Various compatibility studies allow us to identify the best container closure system, such as ampoules, vials, pre-filled syringes or bags, thus meeting the requirements of the product and market.

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

For pre-clinical and global clinical studies, we offer the supply of sterile pharmaceuticals in various container closure systems out of our pilot- and commercial plants, all fully compliant with international quality standards (incl. FDA-GMP, EU-GMP).



Services

Formulation Development for Sterile Pharmaceuticals

- Aqueous solutions
- Aseptic solutions
- Emulsions
- Liposomal formulations
- Suspensions
- Lyophilizates
- PLGA-based microparticles

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: 5-1,000 L
- Secondary packaging and blinding of study medication for clinical studies
- Containers for clinical supply:
 - Vials: 10-100 mL
 - Bottles: 250-1,000 mL
 - Ampoules: 1-20 mL
 - Pre-filled syringes: 1-50 mL
 - Bags (PVC free): 50-1,000 mL



Dispersed Systems I

Suspension & PLGA macroparticles



Fresenius Kabi provides tailor-made contract manufacturing solutions with modern on-site technologies such as suspensions and PLGA microparticles in different packaging materials.

Biodegradable poly (lactic-co-glycolic) acid (PLGA) based microspheres of 10-125 μm size are used as novel prolonged-release drug-delivery systems.

Suspensions are obtained through aseptic compounding and filling is performed with carboy recirculation to maintain suspensions during the manufacturing process.



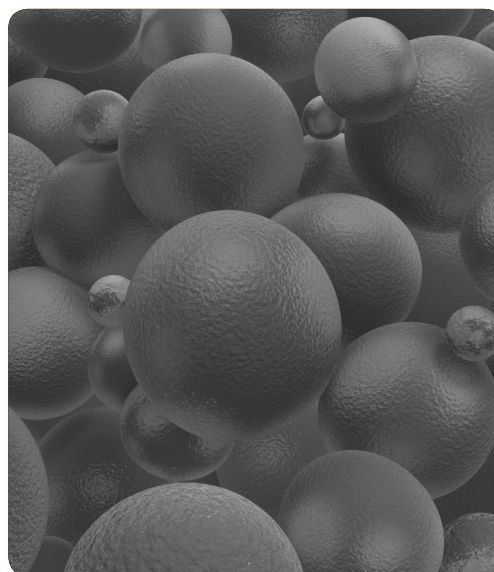
Suspension - Technology & Capabilities

- Handling of high-potency compounds in a weighing isolator, with vaporized hydrogen peroxide (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



PLGA Microparticles - Technology & Capabilities

- Complex release mechanism defined by a variety of critical process parameters
 - H_2O permeability and solubility (hydrophilicity /-phobicity)
 - Additives (acidic, basic, solvents, drugs)
 - Morphology (crystalline, amorphous)
 - Depot dimensions (size, shape, surface-to-volume ratio)
 - Porosity
 - Glass transition temperature (glassy, rubbery)
 - Molecular weight and molecular weight distribution
- Process & manufacturing set-up for development activities available up to 100 g



Dispersed Systems II

Emulsions & Liposomes



Fresenius Kabi has decades of experience in developing and manufacturing emulsions for parenteral nutrition and as drug carriers for lipophilic drug substances. Our emulsions are produced in state-of-the-art equipment under full cGMP compliance, batch sizes ranging from 5 to 6,000 L.

We achieve emulsification with fully-automated high-pressure homogenizers. 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.



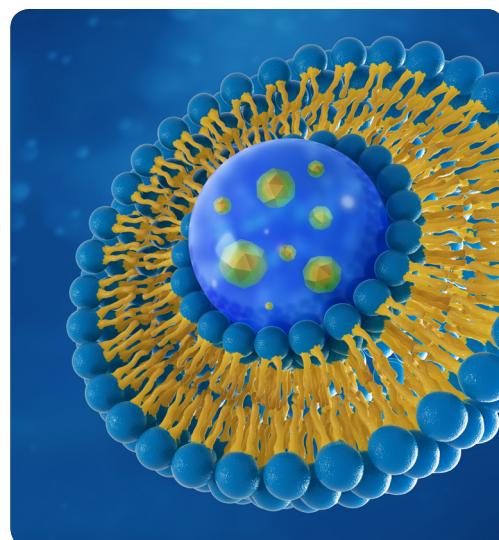
Emulsion - Capacities

- Vast experience in emulsion formulation and technology
- 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
- High-end filling lines for glass vials and bottles
- Filling into ampoules, bags, and pre-filled syringes also available



Liposomes - Technology

- Technical experience from emulsions applied for complex formulations containing all kinds of lipid vehicles for drug transport / delivery
- Handling and use of high-potency compounds in the weighing isolator
- Handling of high-potency active pharmaceutical ingredients under oxygen protection
- High-pressure homogenizer
- New high-end filling lines for aseptic filling in glass vials
- Aseptic filling in pre-filled syringes
- Subsequent liposome lyophilization possibilities internally available, e.g. to increase shelf life of the products





Lyophilization of aqueous solutions and liposomal formulations are common technologies 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 our Fresenius Kabi production facilities in Austria, USA and China, lyophilization is a well-established technology. Fresenius Kabi Contract Manufacturing supports with the development and commercial manufacturing of lyophilized products for both aqueous and liposomal formulations filled in vials.

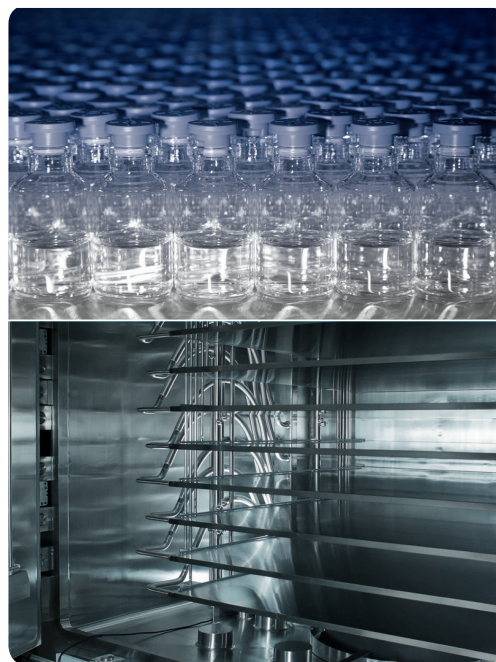
Development of Formulation and Lyophilization Cycle

- 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 m²) with temperature sensors in vials
- Scaling-up of the lyophilization cycle to a pilot-scale freeze dryer (shelf area: approx. 0.1 m²)
- 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

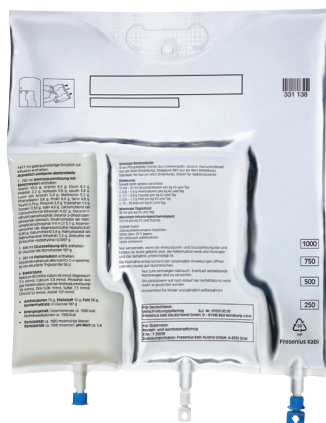
- State-of-the-art aseptic filling line and lyophilization unit, freeze dryers are fully integrated into the aseptic filling line
- Capability to handle high-potency and biological active pharmaceutical ingredients
- Able to compound and fill cooled bulk solution
- High-speed vial line with different 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 m² but with extendable lyophilization capacities



freeflex® - Fresenius Kabi IV-bag



freeflex® - Fresenius Kabi IV-bag 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® THE ART OF INNOVATION

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 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 while mixing drugs with a transfer adapter
- 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 until opening the bag

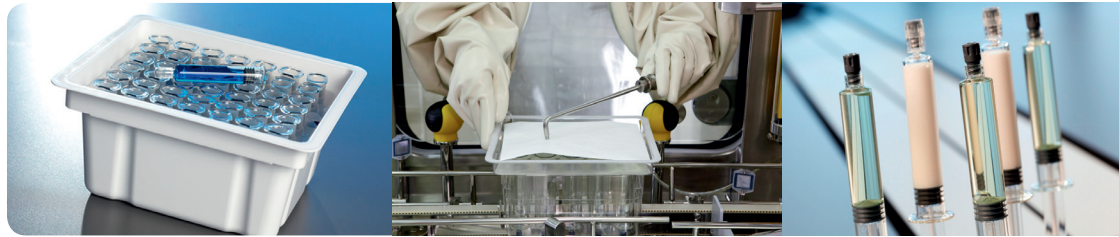


Pre-Filled Syringes

Convenient, safe & efficient



As a way of supplying solutions for injection, pre-filled syringes (PFS) offer advantages over conventional vials to both healthcare personnel and patients. PFS make application of the drug product safer and more convenient for physicians as well as self-administration with reduced contamination risk and risk of errors. PFS are a system of choice for cost-intensive drugs by optimizing product yield. Fresenius Kabi Contract Manufacturing 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
- 0.5-50 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 Restricted Access Barrier System (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.

Successful track-record of the development and launch of several PFS products for global supply.



Transfer Devices



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

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 fix and stable snap connection to the bag port or vial/ bottle cap. This feature is especially important when it comes to the application of cytotoxic drugs.

Our team of development engineers is ready to take on any challenging development task by creating a tailor-made transfer device for your application and the corresponding container – thus providing the optimal solution for your requirements.

Basic transfer devices

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

Dedicated transfer devices for Fresenius Kabi containers

Connection with a dedicated container

Examples:

- KabiPac adapter
- freeflex® adapter

Dedicated transfer devices for diverse containers

• Connection with a dedicated container and bottle

- Customized development



Manufacturing Locations

Austria
China
Czech Republic

France
Germany
Italy

Norway
Poland
Portugal

Sweden
USA
Vietnam

