BOSCH
Invented for life

Process Systems for Liquid Pharmaceuticals

Small and Large Volume Parenterals

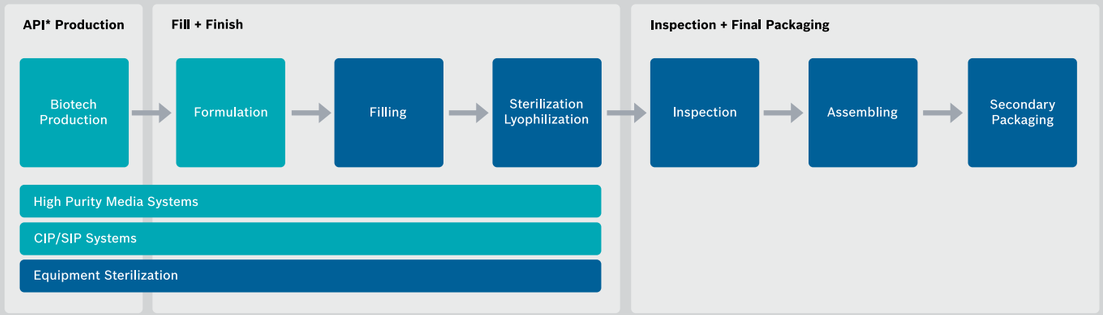
Pharma Specialist at Bosch

At Robert Bosch Packaging Technology GmbH, Pharmatec in Dresden is the competence center for pharmaceutical process systems and plants for the production of liquid active substances or medicinal products. In addition, Pharmatec develops and manufactures complete systems for generation, storage and distribution of high purity media for pharmaceutical use and the biotechnology industry.

Since 1993, Pharmatec has been one of the technology leaders in this segment of plant construction and benefits greatly from the integration in the Bosch family. Its technological expertise and method competence in research, development and project management provide a resilient foundation to meet the requirements of ”Industry 4.0” with all its options.

The enormous advantages of this far-reaching networking and online integration of industrial production processes makes Pharmatec, together with Robert Bosch Packaging Technology GmbH, beneficial to the pharmaceutical and biotech sector – with fully developed and modern solutions for the production, handling, filling and packaging of pharmaceutical active substances or medication.

*API = Active Pharmaceutical Ingredient



Line competence under a single roof: Pharmatec Bosch Packaging Technology

Product life cycle at Bosch

In the interests of its customer companies, Robert Bosch Packaging Technology GmbH has high service requirements: Over the entire product life cycle, we therefore offer all planning and production phases linked together with one another as well as with After Sales Service and Support Offering.

During **consulting and project development**, customer requirements are in the foreground, which are analyzed based on the planned production processes and coordinated with the customer.

Project management is the responsibility of a Pharmatec Project Manager who serves as a central contact person. He synchronizes the activities of all project partners in the framework of scheduling and technical planning.

For the **production process**, Pharmatec engineers implement the detailed plant concept for production. They inspect the design of all system components, coordinate suppliers and service providers until, after the first complete assembly, all functional tests have been completed.

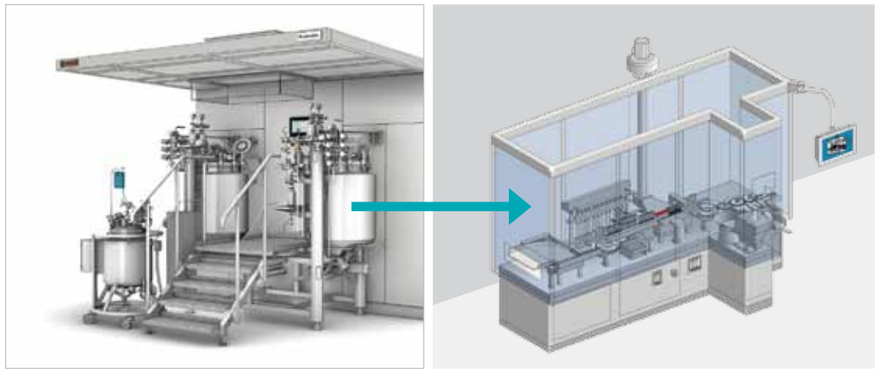
Assembly on-site by highly qualified specialists also includes the integration of the systems in the technical infrastructure as well as repeated extensive testing up to acceptance by the customer.

For **quality assurance**, in each Pharmatec project all work steps from planning up to final inspection are documented extensively and transparently – including endoscopic recordings of the welding seams, test reports, inspection reports and material certificates.

After Sales Services are available to the customer after commissioning for the entire life cycle of his plant. Apart from technical support, this also covers the instruction and advanced training of operating staff and consultation services for operation or conversion of the plant.

Contents

From preparation to filling from a single source



Pre-configured line concepts allow the safe and loss-free transfer of liquid products from the formulation system to the filling machine

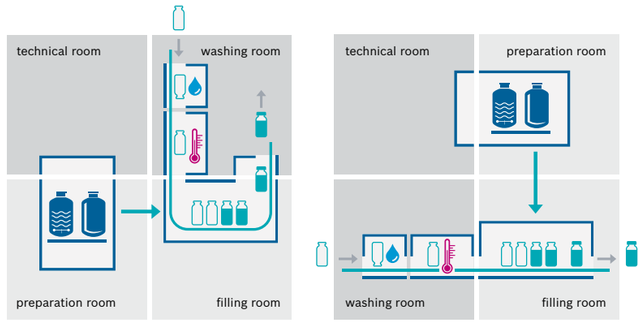
As part of Robert Bosch Packaging Technology GmbH, Pharmatec assumes a key role in product line competence in all areas around liquid pharmaceuticals. This expertise guarantees customer companies in the pharmaceutical and biotech sectors a seamlessly integrated system infrastructure in which even critical interfaces such as those between application system and filling line can be implemented on the highest technological level.

Bio process systems from Pharmatec are thus already used in the development of biopharmaceutical active substances or for blood plasma fractionation. For the **production** of liquid pharmaceuticals, customers can draw on preconfigured lines or make use of the engineering expertise of Bosch specialists, who can design and produce customized process systems. Analogous to this, the supply of **high-purity media** via complete systems for water suitable for pharmaceutical use or pure steam is possible.

Bosch systems for automated filling and packaging of liquids guarantee the trouble-free handling of ampoules, carpoules, vials or presterilized syringes including cleaning, sterilization, depyrogenation and filling.

Bosch‘s system expertise covers a complete production area in the pharmaceutical sector with line solutions tuned to one another. The benefits to the customer are obvious: The flexible design of systems that can be combined with one another seamlessly. This ensures efficient, safe production processes that can be validated across the board.

The clear separation of production area and technical room allow a best possible adaption to different room concepts and line configurations



Reliable quality for pharmaceutical production

Preparation systems for formulation of liquid pharmaceuticals are used, for example, to manufacture parenteral medication and therapeutic agents for oral administration or external application. The highest demands in this area are placed on aseptic production processes in which contamination with microorganisms, particles and pyrogenics must be avoided.

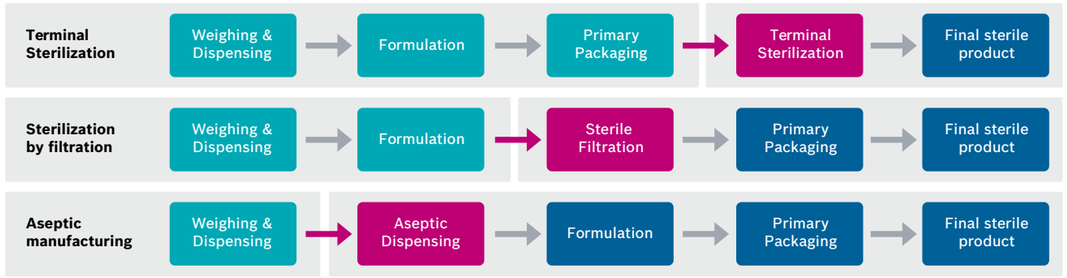
Scalability
Pharmatec designs and supplies custom-made application systems, including systems with complex product requirements, for the pharmaceutical and biopharmaceutical industry. Small two-container configurations for sterile manufacturing processes are as feasible as large volume multi-vessel system for producing insulin, infusions or medical sirup solutions.

Quality
Irrespective of the system size, Pharmatec process systems ensure maximum precision when dosing active substances and excipients. Solids and liquids can be fed into the production process with precision using weighing systems or flow measurement. Flexible control systems and monitoring modules guarantee control over all work steps. Stirring devices that are gentle on the product and different types of temperature control methods guarantee constant product quality. Depending on the manufacturer‘s requirements, different functions such as sterile filters or dosing pumps can be integrated.

Safety and security
Pharmatec designs all of its pharmaceutical production plants in accordance with applicable production and safety standards. Various sterilization options, sterile filtration plants or aseptic manufacturing processes can be integrated as options. Factors such as sterility, cleaning, product transfer and clean room zones alongside all regulatory aspects of pharmaceutical manufacture are taken into consideration.

Including product reliability
All process systems permit sterile product applications and are also configured with different options for thermal or filter-based product sterilization.

The formulation system can be adapted to different production requirements: terminal product sterilization, sterile filtration or aseptic manufacturing



Modular systems for small volume parenterals

The configuration of the modular preparation systems from Pharmatec is designed for maximum flexibility in order to meet all of the customer's requirements as well as possible. The variable plant concept gives the customer a lot of creative leeway with regard to the size and structure of skids, vessels and equipping of various process modules.

Basic configurations
The basis of every SVP process system is formed by the pre-configured skids, the size and structure of which depend on the number and size of vessels and the system configuration. It can therefore be practical to include subsequent extensions to the system already in the design phase.

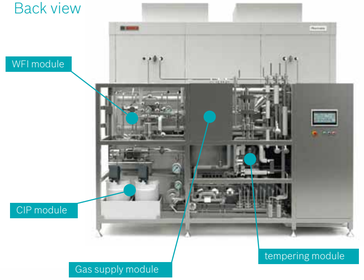
System configurations with up to two preparation and storage vessels respectively can be selected, which, according to the customer's wishes, can either be installed stationery or designed as mobile versions. The six standard vessel sizes hold volumes of between 50 and 1,000 liters. For a perfect connection to a downstream filling line, further vessel sizes can be provided upon customer request. Conically shaped vessel bottoms also enable efficient preparations with low batch volumes and provide maximum flexibility.

Vessel configuration
Depending on the formulation and process requirements, the vessels can be equipped with various monitoring options, sensors or safety devices. Different stirring options and tempering units are available for selection, as well as a gassing module and the integration of venting filters or a sampling location.

Dosing options: The addition of active agents and other substances can take place manually or automatically; several other options are available for powder and liquids. Upon request, the dosing unit can equipped with different scales or, for safeguarding the addition of highly effective or toxic active substances, with containment systems.
Filtration: The product filtration can be designed with different filter options. For example, a two-stage sterile filtration is possible with CIP/SIP-capable filters and an on-site integrity test.

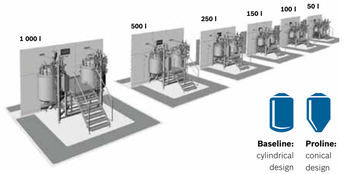
Front view

Back view



Process modules in the technology area (skid)
WFI module for the provision of high pure water for pharmaceutical use which is provided with its own heat exchanger and sampling valve for heat-balancing
Vessel tempering with heating steam or a cooling medium and/or indirectly via a heat exchanger
Gas supply module for compressed, control or sterile air and nitrogen with a device for automatic filter integrity test
Media supply with nitrogen, compressed air, pure steam or water suitable for pharmaceutical use, e.g. for integrated SIP processes for system and filter
CIP module with supply tanks for lye and acid as well as a pump and heat exchanger
Product circulation e.g. for suspensions
Inline mixing unit in various designs, e.g. as homogenizer

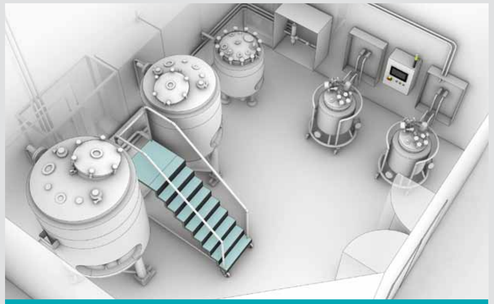
Automation
All SVP systems are controlled via a PLC with touchscreen interface. Its intuitively operated interface visualizes the processes and makes their control during operation and maintenance possible. The process system can be networked via standard interfaces with higher-level production control system and permits batch control and recipe management.



Baseline: cylindrical design
Proline: conical design

Vessel size	50 l	100 l	150 l	250 l	500 l	1 000 l
max. fill volume	50 l	100 l	150 l	250 l	500 l	1 000 l
Baseline (cylindrical), min. fill volume	15 l	30 l	45 l	75 l	150 l	300 l
Proline (conical) min. fill volume	8 l	15 l	20 l	25 l	50 l	100 l

Customized process systems



Factory layout with several formulation systems for different batch volumes with stationery and mobile process vessels

Insulin Plant

For complex production processes that cannot be depicted with the modular process system, the Engineering department of Pharmatec is developing suitable solutions. During insulin production or the production of vaccines, multistep processes with different preliminary applications have to be implemented or a large number of vessels must be integrated. Added to this are options for intermediate storage, the direct supply of high purity media or integrated CIP modules for system cleaning according to specified parameters.

In each case, project-specific planning and design of the system takes place, which can also take future usage changes or extensions into consideration. Upon request, in the case of customer-specific planning the vessel sizes can be provided far beyond SVP scales and reach volumes of several cubic meters.

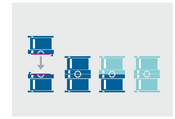
Formulation system for aseptic manufacturing of injection solutions with isolator technology

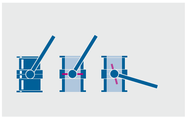
Safety for patients and personnel

Under certain circumstances, the high aseptic standards for formulation and filling of biopharmaceuticals are supplemented by even more stringent requirements. Highly potent products such as cytostatics and antibody conjugates require special safety equipment for formulation and filling to protect operating personnel from any contact with the product or with additives.

Depending on the required protection level, the Pharmatec application systems are integrated in isolators or "Restricted Access Barrier Systems" (RABS). Both designs provide an ergonomic and safe working environment for all employees in contact with correspondingly critical materials.

The product feeding is through sterile or aseptic connections and transfer systems or via high-containment double-flap systems. The barrier systems are equipped with cleaning, sterilization and bio-decontamination systems as required.





High-Containment Butterfly Valve Systems made of stainless steel, as single-use system or hybrid solution

OEB 6	extremly hazardous
OEB 5	very highly hazardous
OEB 4	highly hazardous
OEB 3	hazardous
OEB 2	moderately hazardous
OEB 1	low hazardous

Containment classes

Formulation system with containment isolator

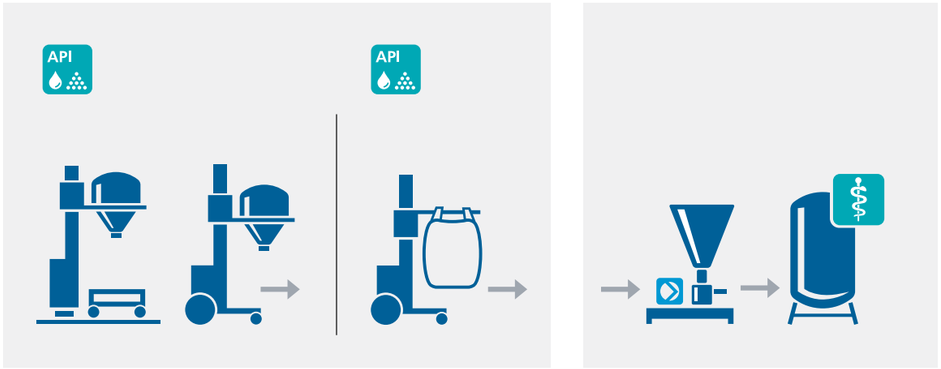
Liquid active substances on a large scale

For the production of large volume parenterals, Pharmatec designs and manufactures LVP process system with container volumes between 1,000 and 20,000 liters. During planning in the LVP area, apart from product reliability the focus is mainly on the handling of large volumes of liquids and solid additives, which should be as uncomplicated as possible. The vessels are therefore equipped with robust functional assemblies that guarantee trouble-free heat-balancing, mixing, monitoring and control during the production processes.

System configurations
Depending on the production requirements, LVP systems can be configured in the simplest **version** as a ”pendulum system”. Two identically equipped containers with the same volume are used alternately as application and storage vessels. Furthermore, more complex systems with further application and storage vessels can be realized. For LVP applications, a **sterile filtration system** is usually used between preparation and storage vessel.

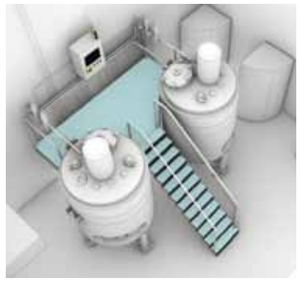
Various options are available for **feeding** the systems with solid and liquid raw materials. Lifting-tilting-swiveling columns are used to handle liquids in barrels, cans and flexible bulk containers; in the case of solids, either vacuum-supported extraction from containers or extraction via tri-blenders is used.

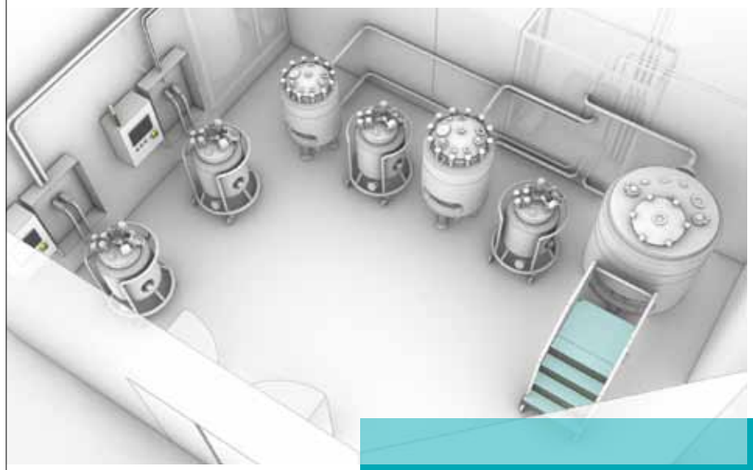
Cleaning and sterilization of all systems is by means of integrated or external CIP/SIP systems using PW, WFI and pure steam. The CIP processes circulate to ensure the efficient use of the cleaning media, or are lost in the last cleaning step with WFI. For low-solubility products, chemical cleaning steps with different solvents are available.



Handling of large quantities of APIs or other substances are carried out via manual or automatic peripherical devices

LVP system with eight storage vessels for manufacturing of infusion solutions





Concept study for planning of a LVP system with stationery and mobile process vessels

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